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Review

Estro-Progestins and Pain Relief in Endometriosis

Libera Troìa [1] and Stefano Luisi [2,*]

[1] Obstetrics and Gynecology Department, San Donato Hospital, 52100 Arezzo, Italy; libera.17@hotmail.it
[2] Obstetrics and Gynecology, Department of Molecular and Developmental Medicine, University of Siena, Policlinico "Le Scotte" Viale Bracci, 53100 Siena, Italy
* Correspondence: stefano.luisi@unisi.it; Tel.: +39-0577-586-641; Fax: +39-0577-233-454

Abstract: Endometriosis is a benign, hormone-responsive chronic disease that affects women of reproductive age; long-term treatment to balance satisfactory tolerability with clinical efficacy is necessary for these patients. The first-line therapy for endometriosis is predominantly medical treatment, in order to improve symptoms or prevent post-surgical disease recurrence. Multiple factors including age and women preference, pain severity, and endometriosis stage must be considered in the choice of the most suitable therapy. Estrogen-progestogins are generally used as first-line hormone therapies among different medical options currently effective for endometriosis management. Several studies have shown that they are able to improve pain symptoms in most patients, are well tolerated, and are inexpensive. Combined hormonal contraception treatment, administered cyclically or continuously, with different types of hormones and route of administration, results in clinically noticeable decrease in dysmenorrhea, noncyclic pelvic pain, dyspareunia, and recurrence rate after surgery, and also in quality of life improvement.

Keywords: endometriosis; pain relief; estro-progestins; combined oral contraceptive; combined hormonal contraception; medical treatment

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1. Introduction

Endometriosis is a chronic disease in which endometrial tissue grows outside the uterus. Endometriotic implants most commonly occurs in the pelvis, involving ovaries, peritoneum, uterosacral ligaments, rectovaginal septum and vesico-uterine fold, but less frequently they can appear in another site in the body such as umbilicus, diaphragm, bowel, pleura and pericardium. An estimated 5–10% of reproductive-age women, or approximately 176 million women worldwide, are affected by this disease. Although some women do not experience symptoms associated with endometriosis, the disease is more commonly responsible for painful symptoms (such as dysmenorrhea, non-menstrual pelvic pain, dyspareunia, dysuria, dyschezia) and infertility [1]. Pain negatively impacts sexual activity, energy work, social life and overall quality of life (QoL), representing the most debilitating symptom in women with endometriosis. Many societies including the American Society for Reproductive Medicine (ASRM) and the American College of Obstetricians and Gynecologists (ACOG) suggest empiric treatment before definitive surgical diagnosis [2,3]. In spite of surgical procedures for the treatment of endometriosis that significantly improve pain symptoms, they can be associated with complications [4] and the pain relapse rate after surgery is not negligible [5]. Furthermore, the risk of damage to the ovarian reserve must be considered when ovarian endometriomas are treated surgically [6]. Accordingly, medical treatment plays a key role in long-time management of this disease [7,8]. The ongoing hormonal therapies are not able to improve infertility associated with endometriosis, but they can only ameliorate painful symptoms [7]. Endometriosis cannot be resolutely eliminated with hormonal therapy, as it persists and even progresses in spite of the effectiveness of drugs in improving symptoms [9]. Indeed, pain generally recurs when patients discontinue therapy due to the onset of adverse effects or the desire

for pregnancy. Hormone treatments available for symptomatic endometriosis work by suppressing ovulation and uterine blood flow, and by reducing serum estradiol levels, thus resulting in a estrogen-deficiency state [9]. Combined oral contraceptives (COCs) and progestins are the drugs of choice for treating symptoms related to endometriosis. Careful diagnostic examination of women with endometriosis should be performed before opting for second-line hormonal therapies, including gonadotropin-releasing hormone analogs (GnRH-as) or aromatase inhibitors (AI). Furthermore, different new molecules have been studied in vitro and in animal models of disease since the knowledge of the molecular pathways underlying endometriosis' pathogenesis has increased [10]. Pain control is the main goal of endometriosis treatment because this is accompanied by an improvement in the QoL and the burden of disease. Moreover, drugs find their application in decreasing surgical interventions, improving postoperative pain control and even achieve disease remission. Since endometriosis is a benign but chronic disease it is of the utmost importance to select pharmacotherapies that maximize benefits and minimize side effects. The aim of this review is to examine evidence on the efficacy of COCs as first-line hormone therapies in patients with endometriosis to improve disease-associated symptoms and prevent postoperative clinical recurrence.

2. Methods

A literature search was performed using MEDLINE and Scopus databases for identification of relevant articles published from inception to 31 May 2021. Identified studies were selected by the authors based on information from the title and abstract according to selection criteria. Disagreements were resolved through discussion. Study selection and criteria: all RCTs and cohorts conducted in human beings were included if they met all the following criteria: studied in patients with endometriosis (ultrasound and clinically diagnosed or surgically diagnosed); compared any estro-progestins interventions regardless of dosage, duration of treatment and drug discontinuation with each other and with other types of hormonal treatments. The outcomes related to pain relief and pelvic pain recurrence were analyzed. Studies were excluded if they provided insufficient data for analysis.

3. Endometriosis-Related Pain

The pelvis is highly innervated and vascularized, which allows pain impulses to be processed and sent from this region to the brain [11]. This, along with many other factors, supports the painful syndrome associated with endometriosis. High levels of nerve growth factors that promote neurogenesis have been found in the peritoneal fluid of patients with endometriosis; the ratio of sympathetic to sensory nerve fibers is significantly altered within endometriotic lesions and the nerve density within endometriotic nodules is increased [12,13]. Additionally, prostaglandins and cytokines released by inflammatory cells appealed to ectopic endometrial-like tissue can activate nerve fibers and nearby cells to produce inflammatory molecules [11]. Entrapment of nerve fibers within endometriotic tissues also contributes to the genesis of pain [11]. Cyclic sciatic pain, sensory loss, and weakness can result from endometriotic entrapment of the lumbosacral, femoral, and sciatic nerve roots. There are several cases of sacral radiculopathy occurring in patients with endometriosis and there are even descriptions of women in wheelchairs who become fully ambulatory after treatment of deep infiltrating endometriosis [14]. Another mechanism that promotes endometriosis-related pain is the central sensitization. Women become highly sensitive to subsequent painful stimuli due to endometriosis-induced neuroplastic changes in the descending pathways that modulate pain perception. In response to a subsequent insult (i.e., nephrolithiasis or pelvic organ injury), patients may experience endometriosis-like pain due to the inability to trigger descending pathways of inhibition [15].

4. Medical Management: An Overview

There are several current medical options for the management of endometriosis-associated symptoms. Medical therapy is not able to eradicate the disease and increase fertility or solve infiltrative lesions or endometriomas, and implants and symptoms commonly reappear upon discontinuation of therapy. The primary goal of medical management is to prevent relapses and reduce symptoms, thereby eliminating the need for repeat surgery or extending the time between surgeries [16,17]. Therefore, all hormonal treatments should be considered suppressive rather than curative. Since the effectiveness of medical options for improving symptoms is comparable, the choice of medication depends on several factors, including patient's age and preferences, pain severity and degree of the disease, and the desire for pregnancy. Additional factors to consider are the costs and expected duration, as well as risks, side effects, and accessibility of treatments (Figure 1). Endometriosis is an estrogen-dependent disease and medical therapies have focused on creating a hypoestrogenic or hyperprogestin environment. COCs contain estrogen plus progestin capable of causing central inhibition of gonadotropin release, inhibiting ovulation and overall decreasing serum estrogen levels. They can determine a hyperprogestogenic milieu, leading to decidualization and consequent atrophy of the ectopic endometrium (Figure 1) [18]. Evidence supports the effectiveness of COCs for endometriosis-related pain [19], and amenorrhea is the most beneficial effect of COCs in women with dysmenorrhea, with better results obtained with continuous rather than cyclic administration [16]. At present, COCs are prescribed as a first-line treatment choice for long-term therapy, even though they are prescribed off-license for the indication of endometriosis [1]. Similar to COCs, progestin-only pills (POPs) or other progestins induce atrophy of endometriotic lesions [18]. Evidence supports the efficacy of norethisterone acetate, medroxyprogesterone acetate, [20] and dienogest [21] and they are generally prescribed for patients with contraindications to COCs or as first-line therapy [22]. The levonorgestrel-releasing intrauterine system (LNG-IUS) is effective in improving dysmenorrhea [23]. Gonadotropin-releasing hormone (GnRH) agonists are also able to reduce pain by suppressing pituitary function and thus inducing a hypoestrogenic milieu [24]. Nevertheless, the onset of adverse effects, including loss of bone mineral density and vasomotor symptoms, such as night sweats and hot flashes, limit long-time administration of these drugs [25]. Since discontinuation of GnRH agonists causes relapse of symptoms, "add-back" therapy (addition of low levels of estrogen and progestin) has been recommended to extend the duration of GnRH agonists administration [26]. However, GnRH agonist plus add-back therapy is expensive and is only recommended in selected patients who are unresponsive to first-line therapy or in high-risk surgical candidates [1]. Oral GnRH antagonist elagolix has also been shown to be effective for endometriosis-related symptoms [27]. Amongst drugs currently under investigation, GnRh antagonists have achieved promising results. These molecules induce a hypoestrogenic state by inhibiting gonadotropin secretion; however, unlike GnRH agonists, they have the advantage of causing a rapid decline in estrogen, thus avoiding the initial increase in FSH and luteinizing hormone secretion (so-called flare effect of GnRH agonists). AI should be recommended for symptomatic patients refractory to other hormonal therapies, only in a research setting, as few data on long-term safety and efficacy are available. The large availability of several better tolerated hormonal drugs has limited the use of danazol in the treatment of endometriosis [1]. Hormone treatment is often accompanied by the use of analgesics such as NSAIDs, acetaminophen or opioids. Since the available treatment options for endometriosis are not curative, research into new drugs represents a major challenge and several new molecules are currently being tested in vitro, in animal models of endometriosis or in preliminary clinical studies. Selective progesterone (or estrogen) receptor modulators, immunomodulators and antiangiogenic agents represent therapeutic options under investigation [28]. However, further studies are needed to conclude whether these treatments could be useful for treating endometriosis.

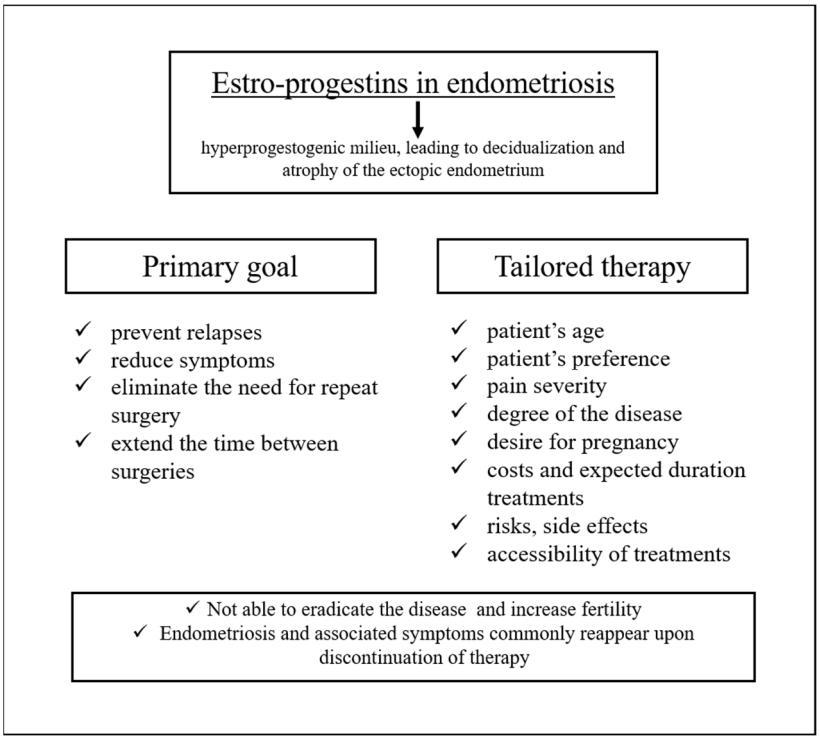

Figure 1. Overview of medical management of endometriosis with estro-progestins. COCs contain estrogen plus progestin capable of causing central inhibition of gonadotropin release, inhibiting ovulation and overall decreasing serum estrogen levels. They can determine a hyperprogestogenic milieu. The primary goal of medical management is to prevent relapses and reduce symptoms, thereby eliminating the need for repeat surgery or extending the time between surgeries. Therefore, all hormonal treatments should be considered suppressive rather than curative. The choice of medication depends on several factors including patient's age and preferences, pain severity and degree of the disease, and the desire for pregnancy. Additional factors to consider are the costs and expected duration, as well as risks, side effects, and accessibility of treatments.

5. Estro-Progestins and Endometriosis

Since ovulation and menstruation play an important role in the pathogenesis of endometriosis, the therapeutic key for the control of the disease and associated symptoms would be hormonal treatment, leading to suppression of both conditions. Combined hormonal contraceptives (CHCs) are indeed an efficacious therapeutic option for the management of endometriosis-related symptoms in patients who also require effective contraception. Over the last 60 years COCs have undergone notable changes: starting from exclusive use of synthetic estrogen ethinylestradiol (EE) at progressively lower doses, to introduction of estradiol (E2)—valerate or micronized—a natural estrogen produced by granulosa cells of the ovaries [29]. On the other hand, several generations of progestins were combined with the estrogenic component and different molecules of progestins have been tested with the aim of obtaining tailoring contraceptive options that could meet the different needs of patients. The introduction of alternative routes of administration to the oral one, such as intravaginal, transdermal, subdermal, intrauterine and injectable represented another considerable step in the technology of hormonal contraceptives (Figure 2) [29]. The guidelines of European Society of Human Reproduction and Embryology [16] recommend treating women with hormonal contraceptives to improve endometriosis-related symptoms. However, there is no clear evidence on which specific preparation, among the numerous combinations of CHCs available, should be utilized based on endometriosis stage and type, and woman's age to obtain a targeted treatment. When analyzing studies on estro-progestins for the treatment of symptoms related to endometriosis the results should be

interpreted considering also the main methodological differences related to eligibility requirements, treatment assignment, and outcome assessments. Some studies required a surgical diagnosis of disease, others used radiological criteria or both methods. The study methods are manifold: there are randomized controlled trials (RCTs) (double-blind or open-label) or observational studies; among the latter some did not have a comparison group so they compared post-therapy scores with the baseline ones, while other observational studies used a comparative design. Furthermore, most observational comparative studies applied a patient preference design in which each participant could decide which treatment group to belong to. Visual analogue scale (VAS) or verbal rating scale (0–10 cm or 0–100 mm) based on Andersch and Milsom or Biberoglu and Behrman scales are the most frequently used pain assessment tools. A difference in pain score ≥10 mm on a 100 mm VAS may be considered clinically significant, although a greater difference is required if consistent differences emerge between the treatments compared [30].

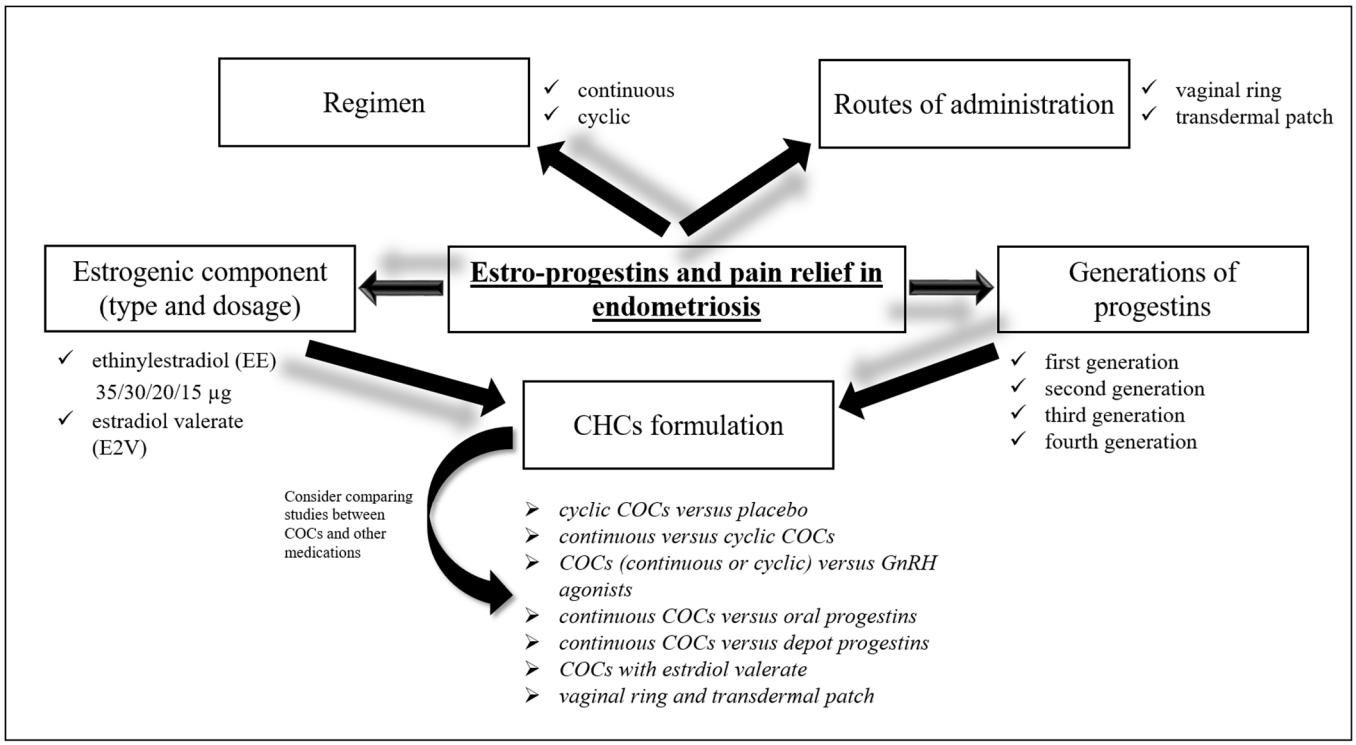

Figure 2. Estro-progestints in endometriosis. CHCs are an efficacious therapeutic option for the management of endometriosis-related symptoms. The different routes of administration (oral, vaginal, transdermal), the regimen (continuous versus cyclic), and the estrogenic and progestin component should be considered to obtain a targeted treatment. However, there is no clear evidence on which specific preparation, among the numerous combinations of COCs available, should be utilized based on endometriosis stage and type, and woman's age. There is no strong evidence to establish the comprehensive superiority of COC therapy and its benefits over other approaches. A step-by-step approach based on the use of COCs as the first line, progestogens (including POPs) as the second step, and GnRH agonists and antagonists as the third step was recommended. CHCs: combined hormonal contraceptives. COCs: combined oral contraceptives.

Unlike the VAS scale, which allows for an accurate and well-validated measurement of endometriosis-associated pain, neither the Biberoglu and Behrman scales nor the Andersch and Milsom scales have been validated, leading to confusion and methodological limitations [30]. Differences in clinical practice and in the characteristics of enrolled patient populations also represent study limitations. Others relevant concerns such as duration of

therapy, COCs formulation and regimen (continuous or cyclic), and the route of administration should be considered when comparing studies (Figure 2).

5.1. Cyclic COCs vs. Placebo

Harada et al. in two different studies used a double-blind placebo-controlled design to evaluate COCs effectiveness in Japanese patients suffering from pain associated with endometriosis. In the first study, one hundred patients with endometriosis-related dysmenorrhea were randomly assigned to receive four cycles of either monophasic COC (EE 35 μg plus norethisterone 1 mg) or placebo [19]. Total dysmenorrhea scores assessed by a verbal rating scale significantly decreased at the end of treatment in both the COCs and placebo groups. Nevertheless, dysmenorrhea VAS scores reduction exceeded the minimum clinically significant threshold only among COCs users (31.1 mm), with three-fold greater reduction compared to the placebo group (difference of 9.6 mm). This statistically significant difference between groups was recorded from the first course of treatment and continued until the end of treatment. There was no clinically significant reduction in non-menstrual pain in COCs users [19]. Endometriomas larger than 3 cm in diameter significantly reduced their volume in the COCs group, but not in the placebo group [19]. Almost all of the patients (approximately 95%) had endometriomas diagnosed only by ultrasound in the absence of a surgical diagnosis, representing a study limitation. This could hide a higher percentage of more advanced disease in the population enrolled than is usually observed in clinical practice. Safety and efficacy of EE 20 μg plus drospirenone 3 mg were evaluated in another double-blind, placebo-controlled, parallel-group study by Harada and colleagues; an extended flexible regimen versus placebo for the treatment of pelvic pain associated with endometriosis was investigated [31]. A total of 312 Japanese patients with endometriomas predominantly diagnosed by ultrasound were randomized to a flexible extended regimen, placebo, or dienogest. The extended flexible regimen and placebo arms took 1 tablet daily without interruption for 4 months, with a 4-day tablet-free interval after 4 months or after ≥3 consecutive days of spotting and/or bleeding on days 25–120. After 24 weeks, placebo recipients were changed to a flexible extended regimen. Patients randomized to dienogest received 2 mg/day for 52 weeks in an unblinded reference arm. Compared with placebo, a flexible extended regimen significantly reduced severe pelvic pain assessed using a 100-mm VAS (mean difference in pain score −26.3 mm). However in the open-label parallel group treated with dienogest the pain score decreased even more (decrease of 50.0 mm) [31]. A flexible extended regimen also improved other endometriosis-associated pain and gynecologic findings and reduced endometriomas size. Pelvic pain improved after therapy despite no reduction in the number of bleeding/spotting days (Table 1) [31].

Table 1. Estrogen-progestin and endometriosis. Summary of studies comparing COCs with placebo, GnRH agonists, oral progestins, long-acting progestins and NSAIDs.

Hormonal Formulation	Study Reference	Patients Selection	Duration	Interventions	Main Outcomes
Cyclic COCs vs. placebo	Harada et al. [19]	100 symptomatic endometriosis (diagnosed by surgery or imaging)	4 months	EE 35 μg plus norethisterone 1 mg or placebo	In COCs users: -Three-fold greater reduction of dysmenorrhea VAS scores. -No clinically significant reduction in non-menstrual pain.
	Harada et al. [31]	312 symptomatic endometriosis (diagnosed by surgery or imaging)	52 weeks	Extended flexible regimen with EE 20 μg plus DRSP 3 mg versus placebo versus DNG 2 mg	-Flexible extended regimen significantly reduced severe pelvic pain compared with placebo (mean difference in pain score −26.3 mm using a 100-mm VAS). -In the dienogest group the pain score decreased even more (decrease of 50.0 mm).

Table 1. *Cont.*

Hormonal Formulation	Study Reference	Patients Selection	Duration	Interventions	Main Outcomes
Continuous vs. cyclic COCs	Caruso et al. [32]	63 versus 33 patients with endometriosis-associated pelvic pain	6 months	Continuous versus a 21-day cyclic regimen of EE 30 µg plus DNG 2 mg	Continuous regimen reported greater and faster reduction of endometriosis-associated pelvic pain and significant improvement of sexual activity and QoL than cyclical regimen.
COCs (continuous or cyclic) vs. GnRH agonists	Guzick et al. [33]	47 patients with endometriosis-associated pelvic pain.	48 weeks	Continuous EE 35 µg plus norethindrone 1 mg versus add-back norethindrone acetate 5mg and intramuscular injection of placebo or depot LA 11,25 mg every 12 weeks	Significant improvement in pain scores from baseline in both treatment groups and no significant difference in the extent of pain relief.
	Vercellini et al. [34]	57 patients with surgical diagnosis of endometriosis and pelvic pain	6 months	cyclic EE 20/30 µg and DSG 0.15 mg versus goserelin 3.6 mg in a 28-day subcutaneous depot formulation	-Significant reduction in deep dyspareunia in both groups, with goserelin being superior to COCs. -Significant improvement in dysmenorrhea and non-menstrual pain with no difference between groups.
	Zupi et al. [35]	133 patients with pelvic pain recurrence after surgery	12 months	group 1: LA alone, group 2: LA plus add-back therapy (transdermal E2 and oral norethindrone), group 3: cyclic EE 30 µg plus GSD 0.75 mg	-Groups 1 and 2 showed greater pain improvement compared to group 3. -Add-back therapy showed a reduced rate of adverse effects, good pain control, and better QoL than the other two treatments.
	Parazzini et al. [36]	47 versus 55 patients with laparoscopically confirmed endometriosis and pelvic pain	12 months	EE 30 µg plus gestroden 0.75 mg versus 4 months of tryptorelin 3.75 mg every 28 days followed by 8 months of COC	No significant differences between groups in pain relief.
	Di Francesco and Pizzigallo [37]	30 patients with chronic pelvic pain associated to endometriosis	6 months	Palmitoylethanolamide + trans-polydatin versus LA versus cyclic EE 30 µg plus DRSP 3 mg.	Dysmenorrhea, chronic pelvic pain, and dyspareunia intensity significantly decreased over time in all three groups, irrespective of the treatment applied.
	Granese et al. [38]	78 patients who underwent laparoscopic surgery for endometriosis combined with chronic pelvic pain	9 months	multiphasic pill with E2V 2 mg plus DNG versus LA 3.75 mg monthly	-Similar endometriosis relpase rate and VAS score. -Substantial improvement in QoL and health satisfaction with both treatments in all women with higher scores than preoperative values.
	Fedele et al. [39]	10 patients with bladder endometriosis.	6 months	continuous COC treatment versus GnRH agonist	Both regimens resulted in regression of the bladder lesions, with slightly better results with GnRH agonist than with COC.

Table 1. *Cont.*

Hormonal Formulation	Study Reference	Patients Selection	Duration	Interventions	Main Outcomes
COCs (continuous or cyclic) vs. oral progestins	Vercellini et al. [40]	90 patients with pain relapse after conservative surgery	6 months	Continuous monophasic EE 20 µg plus DSG 0.15 mg versus CPA 12.5 mg	-Similar improvement in non-menstrual pelvic pain, dysmenorrhea, dyspareunia, QoL, psychological profile and sexual satisfaction from both treatments. -Slightly higher satisfaction in CPA users. -Dysmenorrhea improved much more significantly than nonmenstrual pain with both treatments.
	Vercellini et al. [20]	90 patients with symptomatic rectovaginal endometriosis after surgery	12 months	Continuous EE 10 µg plus CPA 3 mg versus NETA 2.5 mg	-Dysmenorrhea, deep dyspareunia, nonmenstrual pelvic pain, and dyschezia scores were substantially reduced without major between-group differences -Slightly higher satisfaction in NETA users
	Razzi et al. [41]	40 patients with recurrent pelvic pain after conservative surgery	6 months.	EE 20 µg plus DSG 0.15 mg versus DSG 75 mcg	-Significant improvement of pelvic pain and dysmenorrhea in both groups. -More frequently breakthrough bleeding in POP group.
	Morotti et al. [42]	144 patients with symptomatic rectovaginal endometriosis and migraine without aura	6 months	Cyclic EE 20 µg plus DSG 0.15 mg versus continuous DSG 75 mcg	-Similar decrease in chronic pelvic pain and dyspareunia for both treatments. -POP is better tolerated than COC and it seems to ameliorate migraine attacks
Continuous COCs vs. long-acting progestins	Cheewadhanaraks et al. [43]	84 patients with symptomatic endometriosis after conservative surgery	24 weeks	EE 30 µg plus GSD 0.075 mg versus intramuscular DMPA 150 mg every 12 weeks	-No differences in treatment satisfaction and withdrawal rates between the two groups -Significantly higher VAS score per week for dysmenorrhea in COC group.
	Morelli et al. [38]	92 patients undergoing surgery for endometriosis	24 months	Multiphasic pill with E2V 2 mg plus DNG versus 52 mg LNG-IUS	-Statistically greater reduction in Ca125 levels and VAS scores in COC group. -Slightly lower recurrence rate in COC group. -Significantly higher patient satisfaction in LNG-IUS group.
Continuous COCs vs. NSAID	Grandi et al. [44]	34 patients with menstrual pain and endometriosis	24 weeks	Multiphasic pill with E2V 2 mg plus DNG versus ketoprofen 200 mg tablets	Significantly greater reduction in menstrual and intermenstrual pain and improvement of QoL during E2V/DNG treatment than NSAID therapy.

COCs: combined oral contraceptives; CPA: cyproterone acetate; DMPA: depot-medroxyprogesterone acetate; DSG: desogestrel; DNG:dienogest; DRSP: drospirenone; EE: ethinylestradiol; E2V: estradiol valerate; GSD:gestodene; LA: leuprolide acetate; LNG-IUS: levonorgestrel-releasing uterine system; NETA: norethisterone acetate; NSAID: nonsteroidal antiinflammatory drug; QoL: quality of life.

5.2. Continuous vs. Cyclic COCs

Only one observational comparative trial conducted by Caruso et al. analyzed the effects of a continuous versus a 21-day cyclic regimen of EE 30 µg plus dienogest (DNG) 2 mg on sexuality and QoL in patients with pelvic pain (63 versus 33 patients). VAS measurements at 3 and 6 months revealed a significant improvement in endometriosis-

related pain from baseline with the continuous regimen, while cyclic use resulted in a significant pain reduction at only 6 months. Despite the continuous regimen showing greater improvements than cyclical COC use, no statistically significant comparisons between groups were reported (Table 1) [32].

5.3. COCs (Continuous or Cyclic) vs. GnRH Agonists and Antagonists

Continuous COCs treatment comparing with GnRH agonist plus hormonal add-back therapy was investigated by Guzick et al. in a randomized double-blind study [33]. Forty-seven patients with endometriosis-related pelvic pain received a daily capsule containing COCs (EE 35 µg plus norethindrone 1 mg) or add-back norethindrone acetate 5 mg and an intramuscular injection of placebo or depot leuprolide 11.25 mg every 12 weeks. The verbal rating score, Biberoglu and Behrman scale, Beck Depression Inventory, and Index of Sexual Satisfaction were used to evaluate changes in pelvic pain over 48 weeks. Both treatment groups resulted in a significant improvement in pain from baseline and there was no significant difference in the extent of pain relief between the two arms. In both regimens improvements were evident from the first evaluation after 28 days [33]. Given the lower cost and generally low side effects of COCs, these findings support the efficacy of continuous administration of COCs as first-line therapy in the medical management of symptomatic endometriosis. Other studies have instead compared cyclic COCs with GnRH agonists treatment. Vercellini et al. in a open-label, randomized trial evaluated the efficacy of six-month treatment with goserelin versus a low-dose cyclic COCs in improving pelvic pain in fifty-seven patients with moderate or severe pelvic pain with surgical diagnosis of endometriosis. A significant reduction in deep dyspareunia was recorded at 6 months of therapy in both groups, with goserelin being superior to COCs. Patients taking COCs experienced a significant improvement in dysmenorrhea and non-menstrual pain had decreased with no difference between groups. At the end of the follow-up, symptoms reappeared with no differences in severity between treatments [34]. Zupi et al. randomized into three groups one hundred thirty-three women with pelvic pain recurrence after endometriosis surgery for 12 months: group 1 with leuprolide acetate (LA) alone, group 2 with LA plus add-back therapy (transdermal E2 and oral norethindrone), or group 3 with cyclic COC (EE 30 µg plus gestodene 0.75 mg). Groups 1 and 2 showed greater pain improvement compared to oral contraceptive therapy; in addition, patients treated with add-back therapy showed a reduced rate of adverse effects and better QoL than the other two treatments. Add-back therapy allows women with pain recurrence to be treated for a longer time, with decreased bone mineral density loss, good pain control, and better QoL compared with GnRH agonist alone or COCs [35]. Parazzini et al. compared 12 months of COC use (EE 30 µg plus gestroden 0.75 mg) with 4 months of GnRH agonist therapy followed by 8 months of COC and no significant differences between groups in pain relief were found [36]. The pilot study of Di Francesco and Pizzigallo evaluated the efficacy of treatment with micronized palmitoylethanolamide + trans-polydatin (a food supplement anti-inflammatory agent) in comparison to usual hormonal therapies [37]. Thirty outpatients of reproductive age with a history of chronic pelvic pain associated to endometriosis were randomly assigned to three groups of 10, who underwent a 6-month treatment with: palmitoylethanolamide + trans-polydatin, leuprorelin acetate or cyclic COCs (EE 30 µg plus drospirenone 3 mg). Dysmenorrhea, chronic pelvic pain, and dyspareunia intensity significantly decreased over time in all three groups, irrespective of the treatment applied. In spite of the study's limited sample size, the data demonstrate that palmitoylethanolamide + trans-polydatin is as effective as hormonal therapy in reducing painful symptomatology related to endometriosis in patients of reproductive age, without suppressing ovulation, allowing to conceive where possible and showing excellent tolerability [37]. The lack of adequate blinding and an unclear randomization scheme represent the limitations of these studies.

Due to higher cost, limited accessibility, hypoestrogenic side effects GnRH agonist are usually considered as second-line therapy. Long-term GnRH agonist treatments leads to loss of bone density together with hypoestrogenic status that comes with alteration of lipid

profile, hot flushes, urogenital atrophy, headaches and depression. For these reasons they should be used no longer than 6 months and an hormonal add-back therapy is strongly suggested (Table 1).

Promising preliminary results are available for oral elagolix, a new gonadotropin-releasing hormone antagonist, which is under investigation in multicenter Phase III trials [9,27]. Currently, two ongoing Phase III trials are evaluating the safety and efficacy of elagolix tablets in combination with combined oral contraceptive tablets to assess dysmenorrhea response in premenopausal women with endometriosis and associated moderate to severe pain (NCT03213457 and NCT04333576).

5.4. Continuous COCs vs. Oral Progestins

The compared effects of continuous COC versus oral progestin administration were assessed by the same Italian group in two different studies. In the first one, Vercellini et al. enrolled 90 patients with pain relapse after conservative surgical therapy to take either continuous monophasic COC containing EE 20 μg plus desogestrel (DSG) 0.15 mg or cyproterone acetate (CPA) 12.5 mg for 6 months [40]. Similar improvement in non-menstrual pelvic pain, dysmenorrhea, dyspareunia, QoL, psychological profile and sexual satisfaction was obtained from both treatments. Slightly higher satisfaction was reported in CPA users [40]. In the second trial, COCs containing CPA were compared with norethindrone acetate in treating patients with symptomatic rectovaginal endometriosis. Both groups reported equivalent pain relief with comparable results to those in the first study analyzed [20]. Furthermore, in both studies dysmenorrhea improved much more significantly than non-menstrual pain with both treatments. Razzi et al. in a 24 week RCT compared the effects of EE 20 μg plus DSG 0.15 mg versus DSG 75 mcg in 40 patients. A similar pain relief was reported in both groups, but women receiving POP complained more frequently breakthrough bleeding [41].

Piacenti et al., compared the efficacy of dienogest 2 mg vs continuous oral EE 20 μg plus levonorgestrel 0.1 mg on ovarian endometriomas, DIE, chronic pelvic pain (CPP), dyspareunia, QoL, compliance and side effects. A significantly higher reduction in ovarian endometriomas and DIE lesions, CPP, dyspareunia, and improvement of the QoL in women taking dienogest than in women taking continuous COC was found. Over 6 months a significant improvement was found, more frequently in patients taking dienogest. Patients compliance and side effects are similar in both groups (Table 1) [43].

5.5. Continuous COCs vs. Depot Progestins

Cheewadhanaraks et al. enrolled 84 patients with symptomatic endometriosis after conservative surgery and divided them into two groups: in group 1 (n = 42) women received intramuscular depot medroxyprogesterone acetate (DMPA) 150 mg every 12 weeks, while in group 2 (n = 42) a continuous regimen of COC (EE 30 μg plus gestodene [GSD] 0.075 mg) for 24 weeks was administrated [44]. No differences in treatment satisfaction rates between the two groups were recorded at weeks 12 and 24 of therapy, and withdrawal rates due to persistent pain or adverse effects were similar. Pain scores improved markedly in both groups, but a significantly higher VAS score per week for dysmenorrhea was found in women taking COCs (Table 1) [44].

5.6. COCs with Estrdiol Valerate

Treatment with a quadriphasic combination of E2 valerate (E2V) plus DNG for 24 weeks was compared with a non-steroidal anti-inflammatory drug (NSAID) used only for pain (ketoprofen 200 mg tablets) by Grandi et al. in women with menstrual pain and endometriosis using a patient preference clinical study design [45]. In E2V/DNG group VAS dysmenorrhea score markedly decreased by 61%, while intermenstrual pain and dyspareunia was reduced by 65% and 52%, respectively. NSAID therapy led to a lower reduction in menstrual and intermenstrual pain compared to treatment with E2V/DNG.

COC use ameliorated QoL both mentally and physically, and despite the onset of few adverse effects, none of these led to therapy discontinuation [45]. Granese et al. evaluated 9 months of E2V/DNG therapy versus 6 months of GnRH-a monthly (3.75mg LA) in seventy-eight patients with endometriosi-related chronic pelvic pain who underwent laparoscopic surgery [38]. The VAS score did not reveal any significant differences between the two groups. Endometriosis relapse rate was similar: 10.8% versus 13.7% in E2V/DNG and LA group, respectively. A patient questionnaire demonstrated substantial improvement in QoL and health satisfaction with both treatments in all women with higher scores than preoperative values [38]. The postoperative E2V/DNG treatment compared with 52 mg LNG-IUS were assessed by a retrospective Italian trial [46]. Disease recurrence rate and pain relapse at 11 and 22 months were the primary objectives of the study; treatment satisfaction at 22 months was a secondary endpoint. E2V/DNG treatment resulted in a statistically greater reduction in VAS pain scores at 11 and 22 months compared with LNG-IUS. Estro-progestins administration is more effective in lowering the relapse rate but not significantly; however a significantly higher patient satisfaction was recorded in LNG-IUS group at 22 months (97.7% vs 83.3%) (Table 1) [46].

5.7. Vaginal Ring and Transdermal Patch

The effectiveness of the vaginal ring releasing EE 15 μg plus etonogestrel (ETN) 120 μg per day (n = 123) compared to the transdermal patch releasing EE 20 μg plus norelgestromin 150 μg per day (n = 84) was assessed by Vercellini et al. in patients with moderate or severe recurrent pelvic pain related to endometriosis after conservative surgery, in a 48-week patient preference study [47]. Forty-six percent of subjects in the ring group and forty-two percent in the patch group moved from continuous to cyclic use because of irregular bleeding. Withdrawal rates were 36% and 61%, respectively. Both treatments improved scores for non-menstrual pelvic pain, dysmenorrhea, and dyspareunia compared to baseline scores, with greater ring efficacy in patients with deep endometriosis. In the intention-to-treat analysis, 88 of 123 ring users (72%) and 40 of 84 patch users (48%) were satisfied with the treatment received [47]. In a patient preference trial Leone Roberti Maggiore et al. compared the efficacy of cyclical vaginal ring releasing EE 15 μg /ETN 120 μg (n = 83) or DSG 0.075 mg (n = 60) in treating symptomatic women with ednometriosis infiltrating the rectum [48]. At 12-month follow up, patient satisfaction was higher in the POP group (n = 60) than in the group treated with the sequential combined contraceptive vaginal ring (n = 83). Despite both therapies significantly improving dyspareunia and non-menstrual pelvic pain, statistical superiority was obtained with DSG. Menstrual cycle suppression and complete resolution of dysmenorrhea were achieved with DGS, while cyclic vaginal ring treatment led a significant reduction in dysmenorrhea from baseline. Half of the women treated with the DSG-only contraceptive pill and 31.3% of those treated with vaginal ring were fulfilled with regard to gastrointestinal symptoms. Withdrawal rate at the end of the trial, nodule volume reduction, and rate of patients opting for surgery were similar between the two groups [48].

6. Estro-Progestins and Endometrioma

Regrowth of residual lesions or formation of de novo lesions are responsible for the recurrence rate of endometrioma between 30% and 50%. Thus, post-surgical hormonal regimens that reduce menstrual flow and suppress ovarian function may play a decisive role in preventing relapse of disease [49]. COCs have been recommended as first-line hormonal treatment in clinical practice guidelines for the treatment and prevention of endometrioma recurrence [16,50]. The prospective clinical study conducted by Taniguchi et al. evaluated the efficacy of 24/4 regimen of low-dose EE (20 μg) plus 3 mg drospirenone in treating ovarian endometrioma (larger than 3 cm in diameter diagnosed by ultrasound or magnetic resonance imaging). The maximum diameter and volume of the ovarian endometrioma significantly decreased after 3 and 6 cycles compared with pretreatment. VAS scores of dysmenorrhea pain were also reduced after 1, 3 and 6 cycles. A significant

correlation between the reduced size of the endometrioma and the decline of VAS scores was found [51]. Vercelli et al. evaluated the efficacy of treatment with EE 20 µg plus DSG 0.15 mg in 277 patients undergoing laparoscopic excision of ovarian endometriomas. The endometrioma recurrence rate was 6% in users group, while a percentage of 49% in non-users showed relapse ($p < 0.001$) at 36-month follow-up [52]. Continuous versus cyclical EE/DSG administration in 57 women after laparoscopic removal of endometriomas associated with pelvic pain was evaluated by Muzii et al. for 24 weeks [53]. The cyclical regimen group resulted in 4% of endometriomas recurrence, whereas no women in the continuous regimen showed relapse. Improvements from baseline in pain scores were reported in both regimens, and no significant differences between groups emerged. The degree of women satisfaction with treatment was similar between groups and most of them reported being satisfied or very satisfied. However, patients in the continuous EE/DSG group reported significantly more adverse effects, moderate to severe, and also a significantly higher treatment discontinuation rate [53]. A lower endometrioma relapse rate (2.9% rate) was obtained in women who used EE 35 µg plus NETA 1 mg for the entire 24-month follow-up period after surgery compared to those who have never used or discontinued it (35.8% rate). Post-surgical estro-progestins administration was found to be an independent variable correlated with lower endometrioma relapse (OR 0.054, 95% CI 0.007–0.429) [54]. After laparoscopic excision of endometrioma 217 women were enrolled by Seracchioli et al. to receive cyclical or continuous administration of EE 20 µg plus gestodene 0.075 mg or no therapy [55]. Over 24 months, the cyclic and continuous regimen groups reported a significantly lower endometrioma recurrence rate (14.7% and 8.2%, respectively) than non-users (29%), with no significant difference between cyclical versus continuous COC users. Furthermore, patients who were not taking COCs had a significantly shorter recurrence-free time than estro-progestins users. The mean endometrioma diameter at first follow-up visit was significantly lower in cyclic (2.17 ± 0.45 cm) and continuous groups (1.71 ± 0.19 cm) compared with non-users (2.73 ± 0.56 cm). The mean increase in diameter every 6 months of follow-up was significantly reduced in cyclic users (0.31 ± 0.18 cm) and continuous users (0.25 ± 0.09 cm) versus nonusers (0.48 ± 0.3 cm) (Table 2) [55]. Efficacy of COCs treatments in preventing endometrioma recurrence was also evaluated by meta-analyzes [56,57]. The first meta-analysis combined evidence from 1 RCT and 3 cohorts, indicating benefit of long-term (>1 year) use of either cyclic or continuous COCs compared to expectant management [56]. The second meta-analysis collected evidence from 3 RCTs and 1 cohort, reporting no difference in endometrioma recurrence, but significantly lower recurrence of dysmenorrhea in continuous COC users, compared with cyclic regimens given for at least 26 weeks after surgery [57]. Although these meta-analyzes confirmed the possible benefit of COCs in preventing endometrioma recurrence, evidence was based on small and not robust data. The most recent network meta-analysis confirmed and extended the previous two meta-analyses, comparing the efficacy of different hormonal regimens besides COCs [58]. The best evidence derived from the RCT network suggested that GnRHa plus LNG-IUS was the most effective regimen in lowering risk of endometrioma recurrence, followed by continuous COC and GnRHa. Long-term use of dienogest has been shown to be effective in preventing endometrioma recurrence, but the evidence was from cohort network [58].

Table 2. Estrogen-progestin and endometrioma. Summary of studies evaluating efficacy of COCs fot the treatment of endometriomas larger than 3 cm in diameter with or without recent surgical treatment. Regrowth of residual lesions or formation of de novo lesions are responsible for the recurrence rate of endometrioma between 30% and 50%. Thus, COCs have been recommended as first-line hormonal treatment in clinical practice guidelines for the treatment and prevention of endometrioma recurrence.

Inclusion Criteria	Study Reference	Number of Patients	Duration	Interventions	Main Outcomes
Ovarian endometrioma, without recent medical or surgical treatment	Taniguchi et al. [51]	49	6 months	Cyclic EE 20 µg plus DRSP 3 mg compared with pretreatment	-Maximum diameter and volume of ovarian endometriomas significantly decreased after 3 and 6 cycles. -VAS scores of dysmenorrhea were reduced after 1, 3 and 6 cycles.
	Harada et al. [19]	100	4 months	EE 35 µg plus norethisterone 1 mg or placebo	Endometriomas significantly reduced their volume only in the COCs group.
Laparoscopic excision of ovarian endometriomas	Vercelli et al. [52]	277	36 months	EE 20 µg plus DSG 0.15 mg versus non-users	Postoperative risk of endometrioma recurrence was 6% in users compared with 49% in the never users.
	Muzii et al. [53]	57	6 months	Continuous versus cyclic EE 20 µg plus DSG 0.15 mg	-Endometrioma recurrence rate was 4% in the cyclical regimen group, compared with 0% in the continuous group. -Improvements in pain scores in both groups with no significant differences. -More adverse effects and significantly higher treatment discontinuation rate in the continuous group.
	Takamura et al. [54]	87	24 months	Cyclic, 35 µg plus norethisterone 1 mg versus non-users	Endometrioma recurrence rate was 2.9% in users compared with 35.8% in the never used or discontinued.
	Seracchioli et al. [55]	217	24 months	Continuous versus cyclic EE 20 µg plus GSD 0.075 mg or no therapy.	-Lower endometrioma recurrence rate in continuous and cyclic regimen groups (14.7% and 8.2%) than non-users (29%). -Shorter recurrence-free time in non-users. -The mean increase in endometrioma diameter every 6 months was significantly reduced in COCs-users.

EE: ethinylestradiol; GSD: gestodene; DSG: desogestrel.

7. Estro-Progestins and Deep Infiltrating Endometriosis

COCs work by reducing cell proliferation and enhancing apoptosis in the eutopic endometrium. Moreover, hormonal treatment may be associated with significantly reduced nerve fiber density in deep infiltrating endometriosis (DIE) and this may be an important mechanism of action of hormonal therapy for pain symptoms control [59]. The results of Tarjanne et al. showed that the expression of estrogen-regulated nerve growth factor and its receptor was only in part suppressed during hormonal therapy, suggesting that local estrogen action is often maintained in the course of conventional hormonal treatment for DIE [59]. The safety, tolerability, and efficacy of COCs versus low-dose NETA in the management of persistent pain after failed conservative surgery for symptomatic rectovaginal endometriosis were investigated by a 2005 RCT. After one year, pain symptoms were significantly improved with no statistical differences between groups and women taking NETA reported higher patient satisfaction than COC users (73% versus 62%) [20]. A retrospective trial evaluated the efficacy of COCs in 106 patients with posterior DIE awaiting surgical treatment [60]. The diameter of endometriosic nodules at the beginning and at the end of the preoperative time was stable in COC users; while in women who did not take estro-progestins it was significantly increased. Moreover, the severity of chronic pelvic pain, dysmenorrhea, dyspareunia and dyschezia did not significantly change during the preoperative interval in the COC group, while dysmenorrhea and dyspareunia

significantly worsened in non-users [60]. A prospective non-randomized trial found that one-year COCs treatment resulted in a 19.6% reduction in endometriotic nodule volume in women with rectovaginal endometriosis [61]. The effectiveness of a continuous low-dose COC administration in treating pain and other symptoms related with colorectal endometriotic nodules diagnosed by rectal endoscopic ultrasonography was evaluated by a prospective observational study. A significant decrease of colorectal nodule volume evaluated by endoscopic ultrasonography was reported and patients had a significant reduction of bowel endometriosis-related symptoms [62]. Symptoms caused by bladder endometriosis can also be treated with COCs and Fedele et al. compared continuous COC treatment versus GnRH agonist in women with bladder endometriosis. After 6-month of therapy, both regimens resulted in regression of the bladder lesions, with slightly better results with GnRH agonist than with COC [39]. Morotti et al. compared continuous use of POP containing DSG 0.075 mg to cyclic administration of COC containing DSG for six cycles in women with symptomatic DIE and migraine. Similar decrease in chronic pelvic pain and dyspareunia was achieved for both treatments, as assessed by VAS. COCs also improved dysmenorrhea, unlike the POP group [42]. The role of estrogen-progestins in the treatment of DIE-associated pain has also been evaluated using different routes of administration [47,48]. A patient preference prospective trial suggested vaginal ring strength in women with endometriosis infiltrating the rectum, with significant recovery from pain and gastrointestinal symptoms [48]. There is sufficient evidence to recommend physicians to use COCs as first-line therapy to treat DIE-associated symptoms. Advantages of this therapy are their good tolerability even with long-term use and the availability of different formulations. Continuous treatment should be preferred in women suffering severe menstrual-associated symptoms (Table 1).

8. Discussion

CHCs block endogenous ovarian production of estrogen and establishes a progestin-dominant environment, capable of inhibiting the proliferation of endometriotic lesions down-regulating estrogen receptor response, nerve fiber density, and angiogenesis [63]. Hormonal treatments allow efficacious pain control in 80–90% of cases, but are not able to definitively eliminate endometriosis and symptoms recurrence is expected after all COCs are stopped [64]. In this context, the main objective is to obtain and maintain the woman's compliance, in order to avoid repeated surgery during her reproductive life. Depending on patient's preferences, the choice of COCs may be an oral preparation or based on another route of administration, such as vaginal or transdermal. Moreover, the choice of the type of estrogen (EE, E2V or micronised E2) combined with progestogins more focused on the endometrium is fundamental. In symptomatic patients it is not yet been fully clarified whether estrogen administration should be completely avoided or conceded at low doses; in effect low-dose estrogens administration would allow better bleeding control and greater adherence to therapy. Furthermore, formulations with the lowest dosage of EE or with natural estrogens should be the first choice, given the high thrombotic risk associated with the estrogenic component [29]. The dominant stimulus of synthetic progestins on endometriotic lesions proliferation is likely to be counterbalanced by the circulating plasma E2 levels induced by each formulation (POP or COC containing EE or natural estrogens) [65]. Specifically during a natural ovulatory cycle E2 circulating levels oscillate between 30 pg/mL and 140 pg/mL with high secretory peaks; during treatment with DNG 2 mg alone (labeled dose for the treatment of endometriosis but not the contraceptive dosage) levels remain balanced around 30–60 pg/mL [65]. In a quadrifasic regimen containing E2V/DNG, E2 levels are higher but stable throughout the menstrual cycle around 80 pg/mL; however, when DNG is combined with EE, lower E2 levels is reached, around 30–70 pg/mL, and daily peaks that stimulate andometriotic lesions may be recorded [66].

There is no strong evidence to establish the comprehensive superiority of COC therapy and its benefits over other approaches [29]. About one third of patients taking hormonal

preparations have been reported to not respond to therapy. Progesterone resistance in non-responders is mainly due to the imbalance of estrogen and progesterone receptor subtypes or adhesion molecules [67]. Close monitoring of response to therapy is required to detect progesterone resistance and possibly switch to other therapeutic options, as there are no predictive biomarkers. A step-by-step approach based on the use of COCs as the first line, progestogens (including POPs) as the second step, and GnRH agonists and antagonists as the third step was recommended [68]. Combined hormonal contraception present affordable and effective treatment options for women with endometriosis. Our review supports that these medications reduce menstrual and non-menstrual pain and improve quality of life. Continuous use may result in amenorrhea and further improve outcomes compared with cyclic use. Overall, the available literature is limited, but a consistency of effect is observed supporting these recommendations" [68]. Furthermore the exact factors that orchestrate the survival and subsequent implantation of the displaced endometrium remain unknown so the pathogenesis is still unclear. Hence, there is no uniform treatment line for all of the patients.

Currently, several treatments that address immunologic, angiogenic, and hormonal aspects of endometriosi pathogenesis are under investigation, but strong evidence is needed to conclude whether these therapies will be truly effective for treating endometriosis [69].

9. Conclusions

Endometriosis is a lifelong disease that can affect almost every organ in the body. The hormonal imbalance and the proinflammatory milieu alter neuronal signaling systems, which can alter pain processing. 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 and long-term therapies should balance clinical efficacy (pain control and prevention of recurrence after surgery) with an acceptable safety-profile. Combined hormonal contraceptives, available for multiple routes of administration, are commonly administered as first-line hormonal therapies. Several studies demonstrated that they succeed in improving pain symptoms in the majority of patients, are well tolerated, and are not expensive. An individualized approach is required for the initial pharmacologic plan, and this should be included in the perioperative treatment plan. The complex and multifactorial nature of endometriosis requires a multidisciplinary approach to treatment. A combination of medical, surgical, psychotherapeutic, and alternative treatments can improve quality of life for women who suffer from endometriosis.

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