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Laura BUGGIO, Edgardo SOMIGLIANA, Giussy BARBARA, Maria Pina FRATTARUOLO & Paolo VERCELLINI

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ORAL AND DEPOT PROGESTIN THERAPY FOR ENDOMETRIOSIS: TOWARDS A PERSONALIZED MEDICINE

Laura BUGGIO, M.D.[a,b] buggiolaura@gmail.com ORCID ID: 0000-0002-1199-1888

Edgardo SOMIGLIANA, M.D.[b,c] dadosomigliana@yahoo.it ORCID ID: 0000-0002-0223-0032

Giussy BARBARA, M.D. [a] giussy.barbara@gmail.com ORCID ID: 0000-0002-7760-1053

Maria Pina FRATTARUOLO, M.D. [a,b] mp.frattaruolo@gmail.com

Paolo VERCELLINI, M.D.[a,b] paolo.vercellini@unimi.it ORCID ID: 0000-0003-4195-0996

From the

[a] Unità Operativa Dipartimentale Ginecologia Chirurgica e Endometriosi, Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[b] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Italy

[c] Infertility Unit, Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy.

Correspondence: Edgardo Somigliana, M.D.

Infertility Unit, Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy, Via Fanti, 6 - 20122 Milan, Italy

Tel: +39.02.5503.4304; fax: +39.02.50320264; e-mail: dadosomigliana@yahoo.it

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ABSTRACT

Introduction: Endometriosis is an estrogen-dependent chronic inflammatory disorder that requires a life-long management plan. Long-term adherence to treatment is pivotal to ensure an effective clinical management. In this optic, one of the cornerstone of endometriosis medical treatment is represented by progestins.

Areas covered: This narrative review examines the clinical efficacy, safety and tolerability of oral and depot progestins used in the treatment of endometriosis. The material included in the current manuscript was obtained with a MEDLINE search through PubMed from inception until January 2017.

Expert opinion: Progestins are effective in controlling pain symptoms in the majority of women with endometriosis, and their effect seems not inferior to that achieved with other compounds used to treat the disease, such as gonadotropin-releasing hormone agonist. Available progestins include a broad range of both oral and depot compounds, and represent, in most cases, an inexpensive treatment option. In addition, progestins do not increase significantly thrombotic risk and could be adopted in those women with metabolic or cardiovascular contraindication to estrogen-progestins. The choice between the different available compounds should be tailored for every woman with preference to the most cost-effective treatment, depending on the most complained symptom and disease location.

KEYWORDS: desogestrel; dienogest; endometriosis; levonorgestrel-intrauterine device; medroxyprogesterone acetate; medical therapy; norethisterone acetate; progestin

1. INTRODUCTION

Endometriosis is a chronic inflammatory gynecological disorder associated with pelvic pain symptoms and infertility [1]. Endometriosis affects about 5% of women of reproductive age [2]. Women with endometriosis are at increased risk of abdominopelvic chronic pain, dysmenorrhea and deep dyspareunia compared to controls without the disease [3]. The origin of pain associated with endometriosis can be referred to different pathogenic mechanisms, such as increased production of pro-inflammatory cytokines and growth factors by activated macrophages and other cells associated with endometriotic implants, active bleeding from endometriotic lesions, and irritation or direct invasion of pelvic floor nerves by infiltrating endometriotic implants [4,5].

As suggested by the Practice Committee of the American Society for Reproductive Medicine (ASRM): "endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures" [6]. However, patients with endometriosis represent an extremely heterogeneous population regarding both symptoms severity and anatomic abnormalities [1]. In addition, not only the efficacy, but also the long-term tolerability and costs of the treatments should be taken into account. Long-term adherence to treatment is pivotal to ensure an effective clinical management. In this optic, a tailored patient management appears of primary importance, with the aim of identifying the specific issue and the appropriate treatment for every woman.

One of the cornerstone of endometriosis medical treatment is represented by progestins [1]. Progestins are synthetic compounds that mimic the effects of progesterone [7]. They can inhibit inflammatory pathways and responses, and provoke apoptosis in endometriotic cells [8]. In addition, progestins are able to reduce oxidative stress, through the reduction or the abolishment of uterine bleeding [9]. Moreover, this class of drug stimulate atrophy or regression of endometrial lesions, induce anovulation, inhibit angiogenesis, and decrease expression of matrix metalloproteinases, thus diminishing the invasiveness of endometriotic implants [7,10]. Finally,

they reduce the frequency and augment the amplitude of pulsatile gonadotropin-releasing hormone (GnRH) release; this leads to a reduced secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [7] with the establishment of a hypo-estrogenic milieu that could suppress endometriosis and prevent progression of the disease [10].

Numerous progestins compounds are used in the treatment of endometriosis; they can be administered via an oral, intramuscular/subcutaneous, intrauterine or subdermal route [1] (Table 1). In the endometriosis field, progestins are increasingly used as a monotherapy with great results [1,10]. Major advantages of these drugs are that they do not increase the thrombotic risk and can be safely used in those women with contraindication to estrogens [11] or in those who do not tolerate estrogens [12].

METHODOLOGY

In this narrative review, we aimed to provide a comprehensive overview of the role of both oral and depot progestins in the treatment of endometriosis, analyzing the pros and cons of every compound. We have included in our manuscript only those progestins specifically adopted for the treatment of endometriosis. For this review, the best quality evidence was selected with preference given to the most recent and definitive original articles and reviews. Information was identified by searches of MEDLINE and references from relevant articles, using combinations of MESH terms "endometriosis", "progestin", "progestin therapy", "medical therapy", "norethisterone acetate", "norethindrone acetate", "dienogest", "desogestrel", "cyproterone acetate", "medroxyprogesterone acetate", "depot medroxyprogesterone acetate", "levonorgestrel intrauterine device", and "etonogestrel". The search was limited to peer-reviewed, full-text articles in the English language. For most issues, papers published between June 1989 and February 2017 were considered.

2. ORAL PROGESTINS

2.1 NORETHISTERONE ACETATE

Norethisterone acetate (or norethindrone acetate, NETA) is a strong derivative of 19-nor-testosterone. Continuous use, at the lowest dose of 5 mg/d, is approved by the US Food and Drug Administration (FDA) for the treatment of endometriosis. However, numerous studies by independent groups demonstrated the efficacy of a reduced daily dose of 2.5 mg [13-16]. The lower dosage increases the tolerability, reducing weight gain and androgenic side effects, and limits the negative impact on serum cholesterol values [13]. In addition, NETA is partly metabolized to estrogens [17,18], with subsequent positive effects on bone metabolism. Another major advantage of NETA is its cost, in fact, in Italy, the monthly cost of treatment with 2.5 mg/d is less than 2 US $ [13].

Several studies demonstrated the beneficial effects of NETA in the management of symptomatic endometriosis. In 1998 Muneyyirci-Delale and Karakan [19] treated 52 women with surgically confirmed endometriosis with NETA at a daily dosage of 5 mg, which was increased by 2.5 mg up to 20 mg/d until amenorrhea was obtained. Overall, pain relief was achieved in 49/52 (94%) of patients, with a discontinuation rate of 15% (n = 8). The most common side effect was breakthrough bleeding, reported by 30 women (58%), that led to drop out in 4 (8%) patients.

The favorable impact of NETA on endometriosis symptoms was confirmed by Vercellini *et al.* [13] in a randomized trial comparing NETA, at a daily dosage of 2.5 mg, and an estrogen-progestin (EP) combination (ethinyl estradiol (EE) 0.01 mg + cyproterone acetate 3 mg). Both therapies were administered continuously for 12 months. Only patients with symptomatic rectovaginal endometriosis were enrolled (n = 90). Overall, 73% women in the NETA group were satisfied or very satisfied with treatment compared to 62% in the EP group. Both treatments were equally effective in the management of pain symptoms and on the reduction of lesion size at ultrasound. Both regimens caused minor unfavorable changes in the serum lipid profile. Weight

gain (27%; mean weight gain 3.6 +/- 2.3 kg) and decreased libido (9%) were the most frequent reported side effects in NETA treatment group.

In 2010, Ferrero *et al*. [14] performed a pilot study on the efficacy of NETA in the treatment of pain and gastrointestinal symptoms in 40 women with colorectal endometriosis. Patients received NETA 2.5 mg/d for 12 months, in case of persistent breakthrough bleeding patients were instructed to increase the dose to a 5 mg/d. The satisfaction rate was good (60%), more than half of the patients reported an improvement in gastrointestinal symptoms and an amelioration of chronic pelvic pain and deep dyspareunia. The study was completed by 32 patients (80%), the most frequent cause of interruption was weight gain (n = 2; 5%).

Kaser *et al*. [20] successfully tested NETA in a population of adolescents and young adults (n = 194) with histologically confirmed endometriosis. In this retrospective study, women were treated with higher dose of NETA (5-15 mg/d). 65% of the patients reported a reduction in pain scores. Confirming previous data, the most common side effect associated with NETA administration was weight gain (16%).

In 2012, continuous low-dose progestin therapy (NETA 2.5 mg/d) and surgical therapy for endometriosis-associated deep dyspareunia were compared in a patient-preference parallel cohort study with a 12-month follow-up [15,16]. Only women with severe deep dyspareunia were enrolled. A total of 154 patients were included in the study, 51 chose surgery and 103 progestin treatment. In the surgery group dyspareunia's improvement was marked and rapid, followed by partial recurrence of pain. Instead, in progestin group pain relief was more gradual but progressive throughout the whole study period. In addition, at the end of follow-up, patients treated with medical therapy reported a greater increase in the frequency of intercourse per month. Satisfaction rate was statistically significantly higher in the progestin group (59% versus 43%). At 1-year follow-up, NETA performed better than surgery in women without deep lesions, whereas in those with rectovaginal endometriosis, the two treatments showed comparable efficacy [15]. One of the major

drawbacks and potential source of selection bias of this study is the non-random allocation of treatments, as the choice between surgery and medical treatment was based on patient's preference.

Progestin therapies with NETA and dienogest (DNG) were directly compared by Vercellini *et al*. in 2016 [21]. The authors chose a before-after study design, in order to investigate the *effectiveness* (which of the two compounds performed better in real life) of the treatments. NETA has been shown to be as effective as DNG for pain relief, psychological status, sexual functioning and health-related quality of life (QoL). The proportion of satisfied plus very satisfied women after 6 months of treatment was almost identical between the two study groups (71% in NETA group versus 72% in DNG group). In this Italian study, DNG was better tolerated than NETA, but much higher cost limited its acceptance by the patients.

2.2 DIENOGEST

Dienogest (DNG) is a fourth-generation selective progestin that combines the pharmacological properties of 19-nortestosterone and of progesterone derivatives. When administered at the dosage indicated for the management of endometriosis (2 mg/d), DNG inhibits the production of gonadotropin with a decrease in the endogenous release of estradiol, with the establishment of a hypoestrogenic and hyperprogestinic environment that stimulates initial decidualization and subsequent atrophy of endometriotic lesions [22]. However, during DNG treatment (at a daily dose of 2 mg) the average estradiol (E_2) serum levels remain in the range of 20-50 pg/ml; this E_2 serum concentration should, at the same time, prevent bone mineral density (BMD) loss and avoid endometriotic lesions growth [22]. Moreover, DNG exerts strong antiandrogenic properties, whereas it has no glucocorticoid nor mineral corticoid effects [22,23].

However, regarding bone mineral density (BMD), the available data are inconsistent. In a recent study Lee *et al*. [24] have compared DNG (2 mg/d) with gonadotropin-releasing hormone agonist (GnRHa) with add-back (NETA 0.5 mg/d or estradiol 1 mg/d) therapy for the treatment of

endometriosis reporting a decline BMD at the lumbar spine in both treatment groups (-2.3% for DNG and -2.5% for GnRHa plus add-back). These data are in line with those of Momoeda *et al.* [25] that showed a significantly decrease (-1.6%) of lumbar spine BMD after 24 weeks of DNG treatment in patients with endometriosis. On the contrary, Strowitzki *et al*. [26] observed minimal changes in bone turnover markers and lumbar spine BMD after 6 months of DNG treatment.

DNG clinical efficacy has been investigated in studies against placebo [27], GnRH analogs [24,26,28-30], oral medroxyprogesterone acetate [31], and NETA [21,32] (Table 2). No randomized controlled trials (RCTs) assessing the effectiveness of DNG compared with combined oral contraceptives or with other progestins have been performed. Overall, a daily dose of 2 mg DNG has been significantly better than placebo in relieving pelvic pain and dysmenorrhea related to endometriosis and as effective as GnRH agonist therapy in relieving pain [33].

In 2014, Morotti *et al.* [32] evaluated patients' satisfaction after 6 months of treatment with DNG in 25 symptomatic women with rectovaginal endometriosis, who were non-responders to NETA. DNG performed better than NETA both in terms of pain relief and in terms of improvement of quality of life and quality of sexual life, evaluated, respectively, with the EHP-30 and FSFI questionnaires. No changes of volume of the rectovaginal plaques (endometriosis infiltrating the posterior vaginal and anterior rectal walls) were observed during treatment with DNG. These encouraging results were not confirmed in the comparative study between NETA and DNG that was discussed above [21].

The beneficial role of DNG in the improvement of QoL and sexual functions in women with symptomatic endometriosis has been confirmed by Caruso *et al.* [34], who enrolled 102 endometriotic patients, assigning them to DNG treatment (n = 54) or non-steroidal anti-inflammatory drugs (n = 48), the study period lasted 6 months. Patients were evaluated after 3- (first follow-up) and 6-months of treatment. Women in DNG group reported a significant amelioration compared to control group in pain symptoms and QoL at the first follow-up, and in

sexual life at the second follow-up. This latter element could be attributable to a progressive reduction of deep dyspareunia and pelvic pain.

Another field of application of DNG treatment is bladder endometriosis. A recent pilot study [35] on six patients treated for 12 months with DNG 2 mg/d showed an improvement of pain symptoms in all patients. In particular, urinary symptoms disappeared and at transvaginal ultrasound a significant decrease of bladder nodule size at 3- and 12-months evaluation was described. The potential beneficial effect of DNG on extragenital endometriosis has been evaluated in a small Japanese case series [36], in which four women with rectoisigmoidal endometriosis and one with bladder disease were enrolled. All patients received DNG at the standard daily dosage (2 mg/d) for over 6 months. For all cases, a relief in pain symptoms and a lesion size reduction at ultrasonography were confirmed at follow-up.

Finally, a recent prospective study [37] evaluated the effectiveness of DNG on 30 patients with deep infiltrating endometriosis. After one year of treatment there was a significant improvement in all pain symptoms, including deep dyspareunia, without a reduction in the volume of endometriotic lesions at transvaginal sonography.

The safety and efficacy of long-term use (52 weeks) of DNG at a daily dose of 2 mg have been investigated in a multicenter Japanese study on 135 patients with endometriosis [25]. The most common adverse effects observed during treatment were menorrhagia (71.9%), headache (18.5%), and constipation (10.4%). The severity of menorrhagia was mild in the majority of women (n = 82) and moderate in 15 cases. Breakthrough bleeding was the cause of two of the discontinuations and 11 washouts. During the study period, there was a progressive decrease of abnormal bleeding, indicating a tendency to amenorrhea with the extension of the treatment period. In a pooled analysis of four randomized, controlled, European trials [38] the most common adverse reactions were headache (9%), breast discomfort (5.4%) depressed mood (5.1%), and acne (5.1%). The bleeding pattern was well-tolerated, and only the 0.6% of the enrolled women reported bleeding events as the

main cause for premature discontinuation. In addition, no significant variations were registered in serum levels of lipids, glycated hemoglobin and estradiol. These results were in line with those observed by Schindler *et al*. [39], whose study analyzed the safety of high-dose (20 mg/day) treatment with DNG for 24 weeks. Overall, DNG is a well-tolerated drug with a rate of discontinuation related to adverse reactions <5% [22].

The principal limitation to the widespread use of DNG as first-line treatment for endometriosis is its cost, higher than other progestins and combined oral contraceptive (COC) available on the market. In fact, in Italy, the annual cost of treatment with 2 mg/d of DNG is about 770 US $. Moreover, further studies should compare the efficacy of this drug with other progestins.

2.3 DESOGESTREL

Desogestrel (DSG) is a third-generation 19-nortesterone derivative progestin. DSG is a prodrug, which after oral administration is absorbed and converted to its active metabolite, Etonogestrel (ETN). The effects of DSG progestin-only pill (POP) on lipid and carbohydrate metabolism and hemostasis are derived from studies of comparison with levonorgestrel POPs [40] and showed a slight decrease of HDL-cholesterol, a minimal impact on carbohydrate metabolism, and a reduction of pro-coagulative activity. DSG-POP represents a safe contraceptive method (monthly ovulation is inhibited in 97% of users), and can be used during breastfeeding [41].

Few studies investigated the role of DSG in the treatment of endometriosis [42-45]. In 2007 [42], continuous treatment with DSG-POP (75 μg) was compared to a COC (EE 20 μg + DSG150 μg) for the treatment of 40 women with laparoscopically confirmed mild endometriosis (stage I and II). After 6 months of treatments, a significant improvement of pelvic pain was observed in both study groups, without between-group differences. The principal side effect reported in DSG group was breakthrough bleeding (4/20; 20%). The combination of DSG-POP and letrozole (2.5 mg/d), an

aromatase inhibitor, for the treatment of stage IV endometriosis was tested in an open-label, prospective study [43]. A total of 12 women with persistent pelvic pain, not responding to previous surgical and medical therapy, were enrolled. Unfortunately, none of the patients completed the 6-months treatment protocol, due to the development of functional ovarian cysts, with a median length of treatment of 84 days (range 56-112). This secondary effect could be ascribable to aromatase inhibitors. In fact, these compounds, block the conversion of androgens to estrogens in ovarian granulosa cells, with a consequent reduction of the negative feedback at the pituitary–hypothalamus level, and therefore, increasing serum follicle-stimulating hormone levels that favor the growth of ovarian follicles [43]. During treatment, all the patients reported a significant improvement of dyspareunia and an amelioration of chronic pelvic pain. According to previous study the main adverse reaction was abnormal bleeding (75%), followed by weight gain (50%) and abdominal bloating (42%). In 2014, a patient preference trial [44] compared the contraceptive vaginal ring (EE 15 μg + etonogestrel 120 μg), administered cyclically, to the DSG-POP (75 μg/d) for the treatment of symptomatic women with rectovaginal endometriosis. The treatment period lasted 12 months; 60 women chose the DSG-only pill and 83 the vaginal ring. At the end of the study, the rate of satisfied women was higher in the group treated with DSG-POP (61.7% vs. 36.1%). The discontinuation rate and the reduction in volume of rectovaginal nodules were similar in the two study groups. Gastrointestinal symptoms, chronic pelvic pain and deep dyspareunia were improved more in the DSG-POP group. Finally, a second patient preference trial [45] evaluated patient satisfaction after 6 months of treatment with DSG-POP (75 μg/d) and cyclic COC (EE 20 μg + DSG 150 μg) in patients with symptomatic rectovag,inal endometriosis and migraine without aura. 62 women chose the DSG-only pill and 82 the COC, the withdrawal rate was higher in the COC group (24.4% versus 11.3%); the main cause of interruption in DSG-POP group was erratic bleeding (n = 5; 8%). Satisfaction rate was higher in POP group (61.2% versus 37.8%), a significant improvement in QoL, both in terms of mental and physical components, was demonstrated with DSG treatment. In addition, the severity and number of migraine attacks were significantly different

between baseline and 6-month treatment in POP group ($P < 0.001$) but not in COC group ($P = 0.078$). Regarding pain symptoms both treatments were equally effective.

2.4 CYPROTERONE ACETATE

Cyproterone acetate, a 17-hydroxyprogesterone derivative with antiandrogenic and antigonadotropic properties, represents one of the first progestins adopted for the treatment of endometriosis. In 1996, Moran *et al*. [46] performed a pilot study on seven women with laparoscopically confirmed endometriosis, with the aim of evaluating the effectiveness of a 6-month cyclical cyproterone acetate regimen (10 mg/d for 20 days, followed by 10 days without medication). Dysmenorrhea improved in all study subjects. At the end of the treatment, a second-look laparoscopy showed an amelioration of the endometriosis stage. Finally, a RCT [47] compared the efficacy and safety of low-dose cyproterone acetate (12.5 mg/d) versus a COC (EE 0.02 mg + DSG 0.15 mg). Both treatments were administered continuously for 6 months. Ninety patients with recurrent moderate or severe pelvic pain after conservative surgery for endometriosis were enrolled. Overall, at the end of treatment, 73% of the women in the cyproterone acetate group were satisfied or very satisfied compared with 67% in the COC group. Both treatments were equally effective in reducing pain symptoms and enhancing QoL and sexual satisfaction. The withdrawal rate was similar (nine and six patients); the main side effects causing suspension of the treatment in the cyproterone acetate group were bloating ($n = 1$), decreased libido ($n = 1$), depression ($n = 1$), and headache ($n = 1$). Interestingly, seven women in the cyproterone acetate group reported a substantial reduction in libido, probably due to the antiandrogenic properties of the compound. The mean weight gain was comparable between the two study groups (2.4 ± 0.5 kg in the progestin group versus 2.2 ± 0.4 kg in the COC group). Regarding blood pattern, amenorrhea was reached in two thirds of women under progestin therapy and in about half of those taking COC. No major variations in serum lipid profiles were detected in either study group.

3. DEPOT PROGESTINS

3.1 DEPOT MEDROXYPROGESTERONE ACETATE (DMPA)

Medroxyprogesterone acetate is a 17OH-progesterone derivative available as a depot formulation (DMPA), which can be administered intramuscularly or subcutaneously every three months. DMPA is a highly effective and inexpensive contraceptive method that has been adopted worldwide for several decades [48].

First evidence of the use of DMPA for the treatment of endometriosis are dated back 1996, when Vercellini *et al.* [49] performed a RCT comparing intramuscular DMPA (150 mg/3 months) to a combination of cyclic COC and low-dose oral danazol (50 mg/d) for the treatment of pelvic pain in women with endometriosis. The compounds were administered for one year; a total of 80 women were enrolled, 40 subjects were allocated in each study group. Overall, at the end of treatment, 72.5% of the women in the DMPA group were satisfied or very satisfied compared with 57.5% in the COC plus danazol group. A significant decrease was demonstrated in all symptoms scores in both study groups without significant between-group differences. A total of eleven women withdrew from the study (four in DMPA group and seven in COC plus danazol group). The main side effects in DMPA arm concern menstrual pattern, with eight women out of ten reporting breakthrough bleeding (15%) and spotting (65%). In addition, the median time to return of regular menstrual flow in women who received DMPA was seven months, with a maximum delay of 1 year. Finally, in both arms, a significant reduction in high-density lipoprotein cholesterol was observed.

Two large multicenter, evaluator-blinded, comparator-controlled trial [50,51] confront subcutaneous administration of DMPA 104 mg/0.65 ml (DMPA-SC) with leuprolide acetate, given every three months for six months, with 12 months of post-treatment follow-up. In both studies DMPA-SC was statistically equivalent to GnRHa in reducing pain symptoms after 12 months'

follow-up. Significant improvements in QoL, evaluated through EHP-30 and SF-36 scales, occurred in both treatment groups. Moreover, women in DMPA-SC arm referred a significant amelioration in their sexual relationship at month 6 [50]. Patients in the DMPA-SC group showed significantly less BMD loss than did leuprolide patients at month 6. In addition, BMD levels return to pretreatment levels at 12 months' follow-up in the DMPA-SC group but not in the leuprolide group. Regarding side effects, DMPA-SC was associated with fewer hypoestrogenic symptoms but more irregular bleeding, varying from light spotting to uterine hemorrhage. However, the discontinuation rate secondary to adverse events was low (2% in DMPA-SC group and 1.4% in leuprolide group) [50].

A RCT compared intramuscular DMPA (150 mg/3 months) with levonorgestrel-releasing intrauterine system (LNG-IUS) for the treatment of patients with moderate and severe endometriosis [52]. A total of thirty patients after conservative surgery for endometriosis underwent randomization; the treatment period lasted three years. A lumbar and hip DEXA scan was repeated yearly. Both treatments were effective in the management of pain symptoms through the study period. The only domains where no amelioration was observed were dyspareunia and urinary/bowel symptoms. No recurrences of lesions were detected at transvaginal ultrasound in both therapeutic groups. The drop-out rate was higher in DMPA group (53% versus 13%). The two main causes of discontinuation among the eight patients that interrupted DMPA were prolonged vaginal spotting (n = 3) and significant bone loss over lumbar spine (n = 2).

One of major sources of concerns regarding prolonged use of DMPA is the decrease of BMD and the increase risk of fracture, due to estrogen deficiency accompanying its use. Several studies have reported a reduction in BMD in DMPA users [53-62]. The greatest loss occurs during the first two years of treatment, and then BMD levels become stable [63-65]. In 2004, the FDA published a "black box warning" [66], and the Health Canada issued an advisory [67], recommending providers to adopt DMPA only if other methods were unsuitable or unacceptable and to limit its use to the shortest time possible, limiting its maximum use to 2 years. However, the

reversibility of the negative impact of DMPA on BMD toward or to baseline values within two years after discontinuation has been demonstrated in numerous studies [59,61,65,68]. Regarding the risk of fracture, two large-scale, population-based, case-control studies [69,70] showed a modest increase in the risk in DMPA users, particularly in long term users (ORs ≤ 1.5). These results were not confirmed in a large retrospective cohort study on more than 1.7 million women-years [71]. Further studies are needed to estimate the effect of DMPA use on the risk of fractures. Despite these premises, according to the American College of Obstetricians and Gynecologists (ACOG) [48] and WHO recommendations [72] the benefits of DMPA use surpasses the risks.

3.2 LEVONORGESTREL-RELEASING INTRAUTERINE SYSTEM (LNG-IUS)

The LNG-IUS releases levonorgestrel, a potent 19-nortesterone derivative, directly into the uterine cavity at a relatively constant rate of 20 μg/day over a 5-year period [73]. The LNG-IUS induces profound effects on the eutopic endometrium, which became atrophic and inactive, whereas ovulation is usually not inhibited [74]. In fact, anovulatory rates varies from 70-85% in the first months of use to 15-40% after that [75]. The plausible mechanisms at the basis of LNG-IUS use in endometriosis field comprehend the induction of endometrial glandular atrophy, an extensive decidual transformation of the stroma, the downregulation of endometrial cell proliferation, and the intensification in apoptotic activities [74]. Moreover, the ameliorative effects of LNG-IUS on endometriosis' symptoms are likely modulated through a decrease in the expression of glandular and stromal estrogen (α and β) and progesterone receptors in the ectopic endometrium [76, 77]. In addition, LNG-IUS increased Fas expression in both eutopic and ectopic endometrium of patients with endometriosis [76].

One of the first studies evaluating the effectiveness of LNG-IUS in the treatment of endometriosis was performed on 11 women with symptomatic rectovaginal endometriosis [78]. At 1-year follow-up the severity of all pain symptoms, including deep dyspareunia and dyschezia,

improved. Rectovaginal lesions size, evaluated through transrectal and transvaginal ultrasound, was significantly reduced after six months of therapy.

Moreover, the LNG-IUS has been evaluated in numerous RCTs for the treatment of symptomatic endometriosis (Table 3), with positive results. In particular, a Brazilian multicenter trial [80] compared the efficacy of the LNG-IUS and a depot GnRHa in 82 women with symptomatic endometriosis. At 6-months follow-up both treatments appeared to be similarly effective for endometriosis-related chronic pelvic pain, with a six-points decrease from baseline in VAS pain score in both study groups. At the end of the study, the 13% (n = 5) of patients in the LNG-IUS group and the 14% (n = 6) in the GnRHa group failed to reach a VAS pain score of less than three. In both treatment groups, the subgroup of patients that achieved the more rapid improvement in VAS score was the one of patients with stage III and IV of the disease.

The long-term efficacy of LNG-IUS in the management of endometriosis has been evaluated in a retrospective study [85], that showed the ability of the device in providing symptoms control throughout a 3-year study period. These results are in line with those obtained in a RCT [52] that compared LNG-IUS with DMPA in the long-term treatment (36 months) of patients with moderate and severe endometriosis.

As above mentioned, in the majority of patients, LNG-IUS is unable to suppress ovulation, raising concerns for the risk of endometrioma recurrence, in line with the theory of endometriomas originating from corpora lutea [86]. Moreover, women treated with the device are prone to develop functional ovarian cysts [87] that could be misdiagnosed with ovarian endometriomas. Few studies have evaluated the long-term effectiveness of the device for the prevention on endometrioma recurrence. In the RCT of Wong *et al.* [52] no recurrences were identified; however, the sample size was small (n =15) and the number of patients that continued the study throughout the whole follow-up period was even minor (n = 13). These outcomes are superimposable to those obtained by Tanmahasamut *et al.* [83], that did not identify any endometrioma recurrence after 12 months of

treatment with LNG-IUS. Two retrospective studies [88,89] compared the efficacy of postoperative use LNG-IUS with COC for preventing endometrioma recurrence. In both cases, postoperative LNG-IUS use seems comparable to that of COC in preventing endometrioma recurrence. On the contrary, another retrospective study [90] reported a cumulative postoperative endometrioma recurrence rate of 25% at 5-year follow-up. Accordingly, a recent RCT [84] showed a comparable endometrioma recurrence rate at 30-months' follow-up between women allocated in LNG-IUS group (10/40, 25%) and those in the expectant management group (15/ 40, 37.5%) (95% confidence interval: 0.27-1.33, $P = 0.2$). In both study groups, patients received an initial treatment, after laparoscopic cystectomy, with six cycles of GnRHa. The number of recurrent endometriotic cysts necessitating a second surgical intervention or hormone treatment was significantly higher in the control group (8/40, 20% versus 1/40, 2.5%). In line of recent evidence, we believe that the potential role of LNG-IUS in the prevention of endometrioma recurrence should be reconsidered, and an appropriate counseling with the patient on this risk is the needed prior to device insertion.

Therefore, the best candidates for this treatment modality seem to be women who have already completed their family project or wish to postpone pregnancy, whose main symptom is dysmenorrhea, who are in their forties, and who do not tolerate progestins used systemically [1]. Moreover, women should be informed that during the first months of treatment, significant menstrual bleeding abnormalities, including spotting and even menorrhagia, are expected. Whereas, after the first year of use, almost 20-30% of patients became amenorrheic [74].

3.3 ETONOGESTREL SUBDERMAL IMPLANT

The etonogestrel (ENG) subdermal contraceptive implant is a device containing 68 mg of ENG and is currently approved by the FDA for three years of use. Recent data suggest extended contraceptive efficacy to at least five years [91,92]. The implant should be inserted sub-dermally in the upper arm.

Few data are available on the use of this device for the treatment of endometriosis and the majority came from case reports and case series [93-95]. In 2005, Ponpuckdee *et al*. [96] evaluated the efficacy of ENG-subdermal implant in the treatment of fifty symptomatic women with surgically confirmed endometriosis, with an improvement of pain severity and a high satisfaction rate (80%). The follow-up lasted only 12 weeks, and 30% of the patients reported spotting and breakthrough bleeding. Walch *et al*. [97] conducted a RCT with the aim of comparing the therapeutic efficacies of ENG-subdermal implant (n = 21) and DMPA (n = 20) concerning pain relief in forty-one women with symptomatic endometriosis. During the 1-year follow-up, a substantial improvement in pain intensity was recorded in both study groups; after 6-months, the average reduction in pain was 68% in the ENG-subdermal implant group and 53% in the DMPA group. The overall satisfaction rate was almost identical in the two groups (57% in the ENG group versus 58% in the DMPA group). The percentage of withdrawal was higher in DMPA group (35%, n = 7) compared to ENG group (19%, n = 4). The principal cause of interruption in the latter group was unbearable bleeding irregularities (n = 2).

The effect of ENG-implant on BMD have been evaluated in a prospective comparative study in 2000 [98]. The effect of ENG-implant on BMD was compared to a non-hormone medicated IUS. Changes from baseline on the ENG-group were comparable from those in the IUS group. Contrarily, Bahamondes *et al.* [99] demonstrated a significantly decrease in BMD at the midshaft of the ulna after 18 months from the insertion of the device.

In March 2016, the FDA published a warning regarding the risk of migration of the implant within the arm from the insertion site, due to deep insertion of the implant [100]. In addition, there have also been post-marketing reports of implants migrated within the vessels of the arm and the pulmonary artery, which request an endovascular or surgical procedure for the removal. The FDA recommends the removal of the implant, prior identification of the site of migration if the device

cannot be palpated. The frequency of migration of radiopaque implant is 1.3/every millions of inserted devices [101].

4. CONCLUSIONS

Progestins therapies adopted for the treatment of endometriosis include a wide range of therapeutic options (Table 4), that appear effective in the management of pain symptoms associated with the disease but differ considerably regarding their cost and side-effects profile.

Advantages of depot preparations include avoidance of need of repeated administration, effective contraception, and absence of hepatic first-pass metabolic effect. In addition, absorption is not affected by episodes of diarrhea or vomiting and the continuous delivery maintains constant plasma drug levels and eliminates the peaks and troughs associated with the oral administration. The main disadvantage of depot compounds, contrarily to oral drugs, is the impossibility to promptly interrupt treatment in the event of adverse effects. This drawback seems particularly important in case of treatment with DMPA, where uterine breakthrough bleeding can be prolonged and difficult to correct. Moreover, with DMPA, a prolonged delay in the resumption of ovulation has been observed. Thus, this kind of treatment should be reserved for women with persistent or recurrent pain after hysterectomy for endometriosis [1].

Given the chronicity of endometriosis disease, the treatment of choice should ideally be taken until the establishment of menopause. In addition, endometriosis should not be seen as a unique disease, and a specific treatment for different endometriotic localizations should be considered. OCs may be first considered for women with endometriomas while progestins may be favored for those with deep endometriosis. This latter form of the disease deserves more careful management because of the possible clinical consequences. In fact, deep endometriosis could be defined as the truly severe endometriotic disease [1]. Noteworthy, these lesions commonly

infiltrates into richly innervated anatomic sites, and the presence of mast cells in deep nodules is more common compared to those in ovarian and superficial peritoneal lesions [1].

It appears of fundamental importance an appropriate counseling of the patient, in order to consider patient's preference and to provide a comprehensive overview of the available treatments and their relative effectiveness, side effects, and cost. In line with this view, the economic burden represents the main obstacle to the widespread of dienogest diffusion, in spite of the good outcomes in terms of pain management. The treatment should be tailored for every woman with preference to the most cost-effective compound, depending on the most complained symptom, disease location, and the need for contraception.

In other words, the clinical approach should be more patient-oriented than drug-oriented. There is not the best drug but, conversely, the best drug for this specific woman, a drug that minimizes the side effects deemed relevant for this particular woman and that consents to ensure long-term adherence. The cornerstone of endometriosis treatment is the long-term adherence of the patient to the treatment. In this optic, side-effects, costs and effectiveness should receive equal consideration. Low costs of medication and a favorable side-effects profile can play a crucial role for long-term adherence to treatment [1,11]. Moreover, shift from one agent to another during life should not be considered a failure. Definitely abandoning medical treatment is the real failure because it exposes women to recurrences and possible demanding and risky subsequent surgeries.

5. EXPERT OPINION

Endometriosis can be effectively controlled even if not definitely cured. Progestins are effective in controlling pain symptoms in approximately three out of four women with endometriosis, and their effect seems not inferior to that achieved with other compounds used to treat the disease, such as GnRHa [1]. Available progestins used in the treatment of endometriosis include a broad range of

both oral and depot compounds, and represent, in most cases, an inexpensive alternative treatment option. In addition, progestins do not increase significantly thrombotic risk and could be adopted in those women with metabolic or cardiovascular contraindication to estrogen-progestins [11].

However, many issues on medical management of endometriosis are still open and require a definitive answer, such as whether progestins are superior to estrogen-progestins, or one progestin is more effective or better tolerated than another, particularly in those patients with deep infiltrating lesions. As a matter of fact, we need more data from comparative studies among progestins in order to provide more valuable information to women. Unfortunately, this aspect has been up to now neglected (Figure 1). In addition, the efficacy (i.e., which one works better under ideal and highly controlled conditions, such as in an RCT) on the disease seems to be similar among drugs but the effectiveness (i.e., whether one drug works better than the other in real life, that is, under non-ideal circumstances) may radically differ. Of particular relevance, here is the need for real life studies. RCTs are obviously outstanding evidence, but they do not provide information on adherence. Future research should also focus on alternative routes for drug administration, such as the intravaginal one. In endometriosis field, the vagina represents a scarcely explored route for drug delivery, and the majority of available evidence came from studies on danazol and the estrogen-progestin contraceptive vaginal ring. However, advantages of the vaginal administration are several, such as the reduction of daily dosages, the continuity of drug release, the avoidance of the hepatic first-pass effect, and the possibility of extending the interval between doses, all factors that taken together could enhance patient's adherence to the drug regimen [104]. Moreover, is plausible to hypothesize that a local administration near the endometriotic nodules could result in higher concentrations of the drug in the surrounding area, with the potential result of a "target lesion" therapy.

The "definite" drug, i.e. the drug that could definitely eradicate endometriosis is not in our hands and will not be available in the next future. The main obstacle to research in this field is our

ignorance of the real causes of the disease. Progresses have been made in our understanding of the pathogenetic mechanisms but the causes remain obscure. In fact, new options that are foreseen for the management of endometriosis act on specific pathogenetic mechanisms and are thus not expected to overcome the need for long-term use that is the most important drawback of progestins [105]. Given their inevitably extremely higher costs consequent to the financial effort for their development and the generally favorable side-effects profile of progestins, the new agents are inherently intended to become second line treatments, i.e. agents to be used when progestins are ineffective or non-tolerated.

For future studies, we plea for a radical shift of the study design for the development of new agents for endometriosis. In particular, we argue against the commonly used superiority RCTs against placebo to demonstrate effectiveness and non-inferiority RCT against GnRH analogues to support clinical relevance. Even if these type of studies are required by some main authorities such as the Food and Drug Administration (FDA) to allow registration, they are of scant clinical interest [106]. Firstly, we should remember the existence of the placebo-effect, especially on trials, whose main objective is pain relief. Therefore, blinding is mandatory for any study addressing this issue; however, we have to underline that an ideal placebo for a treatment affecting menstruation is very arduous to realize. Moreover, allocating suffering women to a placebo arm is ethically questionable, and it has already been repeatedly demonstrated that any drug is better than placebo for pain relief [102,103]. Secondly, one may also question the use of GnRH agonists as comparator in non-inferiority trials. GnRH agonists are highly effective drugs but they cannot be administered for more than six months because of side-effects and endometriosis typically relapse once they are discontinued. A new compound that would be slightly less effective than GnRH agonists but that would consent long term safe use and even pregnancy seeking would be discarded by the FDA policy despite this advantageous profile.

ARTICLE HIGHLIGHTS

- Endometriosis is an estrogen-dependent chronic inflammatory disorder of fertile age that requires a chronic treatment. Long-term adherence to treatment is pivotal to ensure an effective clinical management.

- Progestins act through the inhibition of inflammatory pathways and responses, provoking apoptosis in endometriotic cells. Moreover, this class of drug stimulate atrophy or regression of endometrial lesions, induce anovulation, inhibit angiogenesis, and decrease expression of matrix metalloproteinases, thus diminishing the invasiveness of endometriotic implants.

- Available progestins adopted in the management of endometriosis include a wide range of both oral and depot compounds, and represent, in most cases, an inexpensive treatment option.

- As there are not enough robust data demonstrating the superiority of one progestin over the others, the first choice should be low-dose oral norethisterone acetate, given the extremely favorable cost-effectiveness profile.

- Future researches on progestins in the treatment of endometriosis should focus on comparison trials with others progestins or estrogen-progestins, and should be designed as superiority trials.

FIGURE LEGEND

Figure 1. Available comparative studies between progestins on endometriosis. Drugs highlighted in yellow are oral drugs. Depot agents are in blue. Black arrows indicate comparative studies. Red arrows indicate RCTs. The numbers in the circles refer to the specific publications. They are as follows: (1) Vercellini *et al*., 2016 [21]; (2) Morotti *et al*., 2014 [32]; (3) Walch *et al*., 2009 [97]; (4) Wong *et al*., 2010 [52]

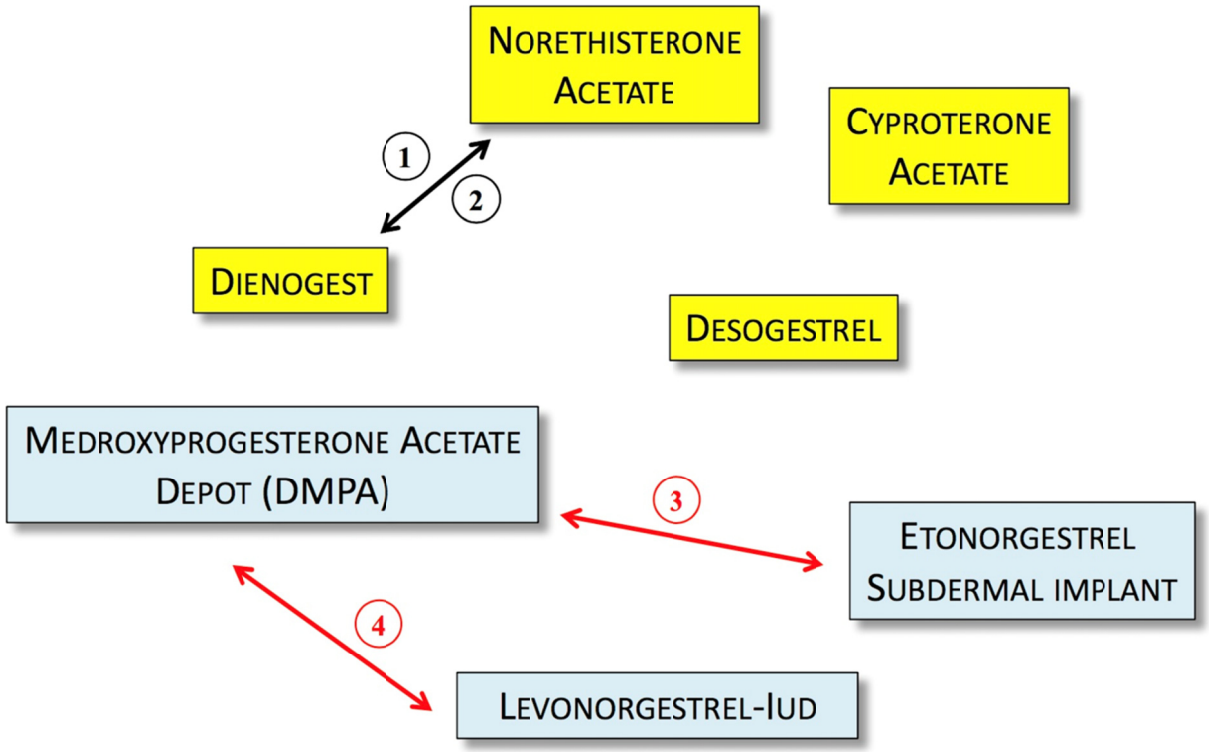

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Table 1. List of progestins utilized for medical treatment of endometriosis.

Drug	**Chemical structure**	**Route of administration**	**Cost** [a]
Cyproterone acetate (CPA)	17-OH progesterone derivative	Oral	24,00 € (25 pills of 50 mg)
Desogestrel (DSG)	19-nortesterone derivative	Oral	9,90-15,40 € (28 pills)
Dienogest (DNG)	19-nortesterone derivative	Oral	56,00 € (28 pills)
Etonogestrel (ENG)	19-nortesterone derivative	Subdermal implant	195,00 € (lifespan 3 years)
Levonorgestrel (LNG)	19-nortesterone derivative	Intrauterine device	242,00 € (lifespan 5 years)
Depot Medroxyprogesterone acetate (DMPA)	17-OH progesterone derivative	Intramuscular, subcutaneous	8,70 € (lifespan 3 months)
Norethisterone acetate (NETA)	19-nortesterone derivative	Oral	5,68 € (30 pills of 10 mg)

[a] Based on the Italian market

Table 2. Effect of dienogest (DNG), as assessed in comparative studies on the treatment of symptomatic endometriosis (literature data, 2002–2016).

Source	Study design	Number of patients enrolled	Study drug	Comparator	Treatment period	Follow-up period	Outcome
Cosson et al., 2002 [28]	RCT	142	DNG 2 mg/day per os (n = 74)	Triptorelin 3.75 mg depot i.m. injections/28 days (n = 68)	4 months	12 months (reproductive outcome only)	Similar postoperative pain relief during treatment; no pain evaluation at 12 months follow-up
Harada et al., 2009 [29]	RCT	271	DNG 2 mg/day per os (n = 137)	Buserelin 900 mg/day i.n. (n = 134)	6 months	No follow-up	Similar pain relief and improvement in QoL. More bleeding, but less hypo-estrogenic side effects and BMD loss with DNG.
Strowitzki et al., 2010 [26]	RCT	252	DNG 2 mg/day per os (n = 124)	Leuprolide 3.75 mg depot i.m. injections/28 days (n = 128)	6 months	No follow-up	Similar pain relief. Higher improvement in QoL with DNG. More bleeding but less hypo-estrogenic side effects and BMD loss with DNG.
Morotti et al., 2014 [32]	Open-label prospective study[a]	25	DNG 2 mg/day per os (n = 25)	NETA 2.5 mg/day per os (n = 25)	12 months (6 months of NETA + 6 months of DNG)	No follow-up	Improvement of pain symptoms, sexual function, QoL and satisfaction with DNG
Oh et al., 2015 [31]	Retrospective	218	DNG 2 mg/day per os (n = 98)	MPA 30-60 mg/day per os (n = 120)	6 months	No follow-up	Higher pain relief with DNG. More bleeding, alopecia, and headache with DNG. More weight gain, depression and breast tenderness with MPA.

Source	Study design	Number of patients enrolled	Study drug	Comparator	Treatment period	Follow-up period	Outcome
Takaesu *et al*., 2016 [30]	RCT	111	DNG 2 mg/day per os (*n* = 56)	Goserelin 1.8 mg depot s.c. injections/28 days (*n* = 55)	24 weeks	24 months	No difference in post-operative endometriosis recurrence rate. Similar pain relief, but fewer side effects with DNG.
Vercellini *et al*., 2016 [21]	Before-after study	90	DNG 2 mg/day per os (*n* = 90)	NETA 2.5 mg/day per os (*n* = 90)	6 months	No follow-up	Similar satisfaction with treatment, frequency of irregular bleeding and pain relief. Comparable improvements in QoL and sexual functioning. Better tolerability with dienogest. Higher discontinuation rate with DNG (owing to drug cost)
Lee *et al*. 2016 [24]	RCT	64	DNG 2 mg/day per os (*n* = 36)	Leuprorelin acetate 3.75 mg s.c. injections/28 days + NETA 0.5 mg/day or estradiol 1 mg/day per os (*n* = 28)	6 months	No follow-up	Similar pain relief. Comparable QoL improvements. Similar lumbar spine BMD loss in both groups (-2.5% for GnRHa plus add-back therapy and -2.3% with DNG)

[a] This study specifically selected patients with symptomatic rectovaginal endometriosis who had pain persistence and were unsatisfied after 6-months of treatment with NETA.

BMD, bone mineral density; DNG, dienogest; i.m., intramuscular; i.n., intranasal; MPA, medroxyprogesterone acetate; NETA, norethisterone acetate; QoL, quality of life; RCT, randomized controlled trial; s.c., subcutaneous

Table 3. Summary of randomized controlled trials on the use of LNG-IUS for the treatment of pain symptoms associated with endometriosis.

Source	Number of patients enrolled	Study drug	Comparator	Follow-up period	Outcome
Vercellini *et al*., 2003 [79]	40	LNG-IUS (*n* = 20)	Expectant management after laparoscopic treatment of endometriotic lesions (*n* =20)	12 months	Greater pain relief with LNG-IUS. Lower recurrence rate of dysmenorrhea in LNG-IUS group. Higher patient satisfaction rate with LNG-IUS.
Petta *et al*., 2005 [80]	82	LNG-IUS (*n* = 39)	Leuprolide 3.75 mg depot i.m. injections/28 days (*n* = 43)	6 months	Similar pain relief and psychological well-being. More bleeding with LNG-IUS.
Wong *et al*., 2010 [52]	30	LNG-IUS (*n* = 15)	DMPA 150 mg i.m. injections/3 months (*n* = 15)	36 months	Similar symptoms control and lesions recurrence rates. Irregular vaginal bleeding common in both group; frequency and severity of bleeding worse with DMPA. Improvement of BMD with LNG-IUS. Decline of BMD with DMPA. Better compliance in LNG-IUS group.
Ferreira *et al*., 2010 [81]	44	LNG-IUS (*n* = 22)	Leuprolide 3.75 mg depot i.m. injections/28 days (*n* = 21)	6 months	Similar pain relief. Significant reduction in VCAM, CRP, total cholesterol, triglycerides, LDL-C and HDL-C levels in LNG-IUS group.
Bayoglu Tekin *et al.*, 2012 [82]	40	LNG-IUS (*n* = 20)	Goserelin 3.6 mg depot s.c. injections/28 days (*n* = 20)	36 weeks (24 weeks of active treatment)	Similar pain relief at 1,3 and 6 months' follow-up; at 1 year follow-up patients treated with GnRHa had lower pain score compared with those treated with LNG-IUS. Higher patient satisfaction rate with GnRHa. More bleeding with LNG-IUS.
Tanmahasamut *et al*., 2012 [83]	55	LNG-IUS (*n* = 28)	Expectant management after laparoscopic treatment of endometriotic lesions (*n* =27)	12 months	Greater pain relief (dysmenorrhea and chronic pelvic pain) with LNG-IUS. Similar dyspareunia relief. Lower recurrence rate of dysmenorrhea in LNG-IUS group. Improvement in QoL in women treated with LNG-IUS.

Source	Number of patients enrolled	Study drug	Comparator	Follow-up period	Outcome
Chen YJ *et al*., 2017 [84]	80	GnRHa 3.75 mg depot i.m. injections/28 days for 6 months + LNG-IUS (*n* = 40)	GnRHa 3.75 mg depot i.m. injections/28 days for 6 months + expectant management (*n* = 40)	30 months	Similar endometrioma recurrence rate at 30 months' follow-up between the two groups. Longer duration to dysmenorrhea recurrence in LNG-IUS group. Greater pain relief with LNG-IUS. Higher analgesic use in control group. Greater reduction of CA125 levels with LNG-IUS. Higher irregular vaginal bleeding in LNG-IUS group.

DMPA, depot medroxyprogesterone acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; QoL, quality of life; BMD, bone mineral density; VCAM, vascular cell adhesion molecule; CRP, C-reactive protein; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

Table 4. Advantages and disadvantages of progestins utilized for medical treatment of endometriosis.

Drug	**Advantages**	**Disadvantages**
Cyproterone acetate (CPA)	- Improvement of pelvic pain symptoms - Regression of endometriotic lesions at second-look laparoscopy - No major variations in serum lipid profile - Low cost	- High percentage of women reporting a decrease in libido among the side effect
Depot Medroxyprogesterone acetate (DMPA)	- Safe contraceptive method - Low cost - No-inferior to GnRHa in the management of pain symptoms	- Prolonged, repeated and difficult to treat breakthrough bleeding - BMD loss - Prolonged delay in the resumption of ovulation
Desogestrel (DSG)	- Safe contraceptive method, even during breast-feeding - Effective in the treatment of endometriosis in patients with migraine	- Breakthrough bleeding - Limited data
Dienogest (DNG)	- Superior to placebo and no-inferior to GnRHa in the treatment of symptomatic endometriosis - Combines the pharmacological properties of 19-nortestosterone and derivatives of progesterone - Better tolerated than NETA	- High cost - Inconsistent data on BMD - No RCTs against COC or other progestins
Etonogestrel (ENG)	- Safe contraceptive method - Low-cost - Extended-use to 5 year - Comparable to DMPA in the treatment of symptomatic endometriosis	- Limited data - Risk of site migration - Inconsistent data on BMD
Levonorgestrel (LNG)	- Safe contraceptive method - Low cost (spread in a 5-year lifespan) - Fewer adverse effects than systemic progestins	- During the first months after insertion menstrual irregularities may occur - Does not inhibit ovulation, risk of endometrioma recurrence

Drug	Advantages	Disadvantages
	- No-inferior to GnRHa in the treatment of symptomatic endometriosis	
Norethisterone acetate (NETA)	- Low cost - Partly metabolized to estrogens, with positive effects on BMD - Improvement of pelvic pain symptoms - Effective in the treatment of deep dyspareunia, in particular in those women without deep lesions	- Principal side effects are breakthrough bleeding, weight gain and decreased libido - Minor unfavorable changes in lipid profile (in particular with dosages > 10 mg/d)