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Novel drug delivery methods for improving efficacy of endometriosis treatments

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Abstract

Introduction: Pharmacotherapy has a key role in the management of endometriosis. However, a significant proportion of patients gains only intermittent or limited benefits. In this regard, alternative and novel drug delivery methods are of paramount importance to improve efficacy and compliance of available treatments and develop alternative medical approaches.

Areas covered: This review aims to provide the reader with a complete overview of available evidence about alternative and novel drug delivery methods for endometriosis pharmacotherapy and highlight new research lines.

Expert opinion: Progestins and estroprogestins, which represent the first-line therapy, are already available in different formulations, being employed for contraception. Nevertheless, evidence on their adoption is still limited for some drug delivery methods, such as vaginal rings, patches, and subcutaneous implants. Further research is needed to define better their clinical utility in patients with endometriosis. Nanotechnologies have been investigated as novel drug delivery methods able to target the drug at the disease level. However, data are very limited and preliminary, and further research is needed to consider a possible clinical application in endometriosis.

Keywords: Endometriosis; drug delivery; adverse effects; nanotechnology; vaginal ring; intrauterine systems; depot preparation.
Article highlights

- Pharmacotherapy has a key role in treating endometriosis, but a significant proportion of patients gains only intermittent or limited benefits. Adopting alternative drug delivery methods could improve compliance, increase efficacy, and develop new therapeutic approaches.

- Progestins and estroprogestins therapy for endometriosis can take advantage of available formulations adopted for contraception, allowing personalizing the treatment, improving compliance, reducing adverse effects, and potentially increasing efficacy.

- In randomized controlled trials (RCTs) on endometriosis patients, levonorgestrel intrauterine systems (LNG-IUSs) were associated with improved pain and satisfaction compared to observation after surgery. LNG-IUSs compared to other therapies did not improve symptoms, but may improve satisfaction and compliance, although uncertainties about their efficacy on endometriomas have questioned their use.

- Multiple RCTs studied depot medroxyprogesterone acetate (DMPA) as a treatment for endometriosis. DMPA reduced pain similarly to GnRH analogs, but improved quality of life and reduced bone loss and hypoestrogenic symptoms. Irregular bleeding is the main adverse effect.

- Other progestin and estroprogestins delivery methods available for contraception, such as vaginal rings, patches, and subcutaneous implants, have been investigated to only a limited extent in patients with endometriosis. However, the vaginal ring has been investigated as a novel drug delivery method for danazol and aromatase inhibitors.

- Nanotechnologies are possible novel drug delivery methods preliminarily investigated in endometriosis animal models. They consist of bioconjugates delivering anti-inflammatory, antioxidant, anti-angiogenetic, and immunomodulating molecules at the disease level. However, data are very limited and preliminary at an early-stage proof-on-concept level. Further research is needed to evaluate a possible clinical application in endometriosis. Mouse models are not able to predict clinical efficacy.
1. Introduction

Endometriosis is a chronic hormone-dependent inflammatory disease affecting mainly premenopausal women, with a prevalence estimated between 5 and 10% [1–3]. The presence of ectopic endometrial tissue defines the disease, and clinical presentation is heterogeneous and consists mainly of pain symptoms, infertility, and anatomic disruption [4].

Surgery has a crucial role in treating most severe cases with significant anatomic disruption and organ damage, such as bowel occlusion [5–8] or ureteral hydronephrosis [9-11]. Conversely, the adoption of surgery is more debated for the treatment of infertility and pain due to the tendency of endometriosis to recur [12], and the uncertain resolution of symptoms and infertility [8,13–16]. Pain, infertility, and the anatomic extension of ectopic implants are not always correlated [17], and multiple factors are considered involved in the clinical presentation [18–20]. Therefore, it can be challenging to define the most appropriate treatment for each patient [21].

Medical therapy is paramount in managing symptoms and preventing disease progression or recurrence after surgery [21]. Progestins and estroprogestins represent the first-line pharmacotherapy for the treatment of endometriosis [21]. They inhibit the secretion of the gonadotropin-releasing hormone (GnRH) and gonadotropins, with subsequent suppression of the ovarian function. Moreover, the increased progesterone levels, determined by both options, and the hypoestrogenic state, induced by progestins in monotherapy, cause the decidualization of both eutopic and ectopic endometrium [22], with reduced activity and inflammation at the level of endometriotic implants [23–25].

Alternatively to progestins and estroprogestins, GnRH analogs are the second-line option in non-responsive cases [21]. They act blocking gonadotropins release and suppressing the ovarian function [26], which generates a hypoestrogenic state able to effectively control symptoms and induce the regression of endometriotic implants [27]. Nevertheless, significant adverse effects (AEs) [28] requires an add-back therapy and limit their utility [21].

Although the growing body of evidence on the etiopathogenesis of endometriosis is increasing the number of investigational drugs targeting the disease, such as aromatase inhibitors (AIs), selective progesterone receptor
modulators, immunomodulators, and histone deacetylase inhibitors [23,29–32], only some of these new drugs achieved the early clinical investigation. Therefore, endometriosis pharmacotherapy is still mainly based on standard hormone therapy [23], from which a significant proportion of patients gain only intermittent or limited benefit [21]. In almost 15% of patients, pain does not improve, and in 5%–59% of cases, pain is still present at the end of treatment. Moreover, AEs inherent to standard therapies induce the treatment discontinuation in almost 10% of patients [33]. On that basis, further investigation is mandatory to increase the available strategies and to personalize and improve the management of patients affected by endometriosis.

In this regard, innovation in pharmacotherapy is not limited to the development of new molecules but includes any change that can improve the efficacy of drugs, increase the compliance of patients, or reduce AEs. Among different options, the research of alternative drug delivery methods is a well-known strategy for developing new drugs and innovating established therapies [34]. Estrogens and progestin-based contraceptive hormones provide perfect examples of such innovation; from a drug delivery centered on the oral administration, many different delivery methods have been developed to improve compliance, efficacy, and tolerability [35]. These improvements have been extended from contraception to endometriosis treatment and represented a model that more recent research is applying to other medications [36–39]. Given the importance of alternative drug delivery methods in improving endometriosis pharmacotherapy, this review aims to provide the reader with an overview of available evidence about drug delivery methods that have been or are going to be investigated for the endometriosis treatments.

2. Methods

For this review, a literature search was performed from inception to May 2020 in the electronic database MEDLINE, EMBASE, The Cochrane Library, and Web of Science. The search strategy included the combinations of the Medical terms “endometriosis”, “drug delivery”, “vaginal ring”, “subcutaneous”, “intramuscular”, “depot”, “transdermal”, “nanoparticles”, and “nanofibers”. The literature search
was aimed to identify all preclinical and clinical studies published in the English language investigating the adoption of a novel drug delivery method for the treatment of endometriosis. No specific inclusion or exclusion criteria were adopted. Titles and abstracts of identified studies were screened independently by two authors (S.G., A.S.L.). The full text of potentially eligible studies was retrieved and individually assessed by two additional team members (J.C., F.B.). Any disagreement was resolved through discussion with a third author (S.F.). The reference lists of all identified studies were systematically revised to identify other eligible publications.

Given the present review focuses on different delivery methods for different available or investigational drugs, we did not adopt a systematic approach in the report of results. Instead, we reported more relevant studies selected based on the personal expert opinion of the authors to provide the reader with a complete and synthetic overview of novel drug delivery methods in endometriosis.

3. Drug delivery methods in endometriosis

Multiple drug delivery methods are available for the endometriosis treatment. Consolidated methods for the administration of estroprogestins and progestins for contraception are among those most investigated; moreover, the same delivery methods have been studied to deliver specific drugs for endometriosis. Nanotechnology represents instead a potential novelty. They could provide a new drug delivery method, although their application in endometriosis is still at a preclinical and proof-of-concept level. A summary of drug delivery methods for endometriosis and described below are reported in Table 1.

3.1 Vaginal rings

The vaginal administration route has been demonstrated as an effective drug delivery method for different medications, including hormones for contraception and replacement therapy [40]. Different types of vaginal rings are available based on the size, structure, polymer composition, and delivered hormones, but they all provide similar advantages than oral administration [41]. Vaginal rings continuously and steadily release hormones that are effectively absorbed by the vaginal mucosa. This administration route allows avoiding the first hepatic passage and provides a systemic exposure comparable to oral contraceptives.
with a lower total exposure of almost 50% [42]. The decreased exposure to steroids reduce AEs, and the impact on hemostatic function, maintaining ovulation inhibition [43,44]. Moreover, the adoption of vaginal rings in contraception has been associated with improved compliance, continuity of use, and acceptability [45,46]. Based on this experience, vaginal rings have been investigated for the treatment of endometriosis as an alternative route to the oral administration [47]. Noteworthy, the rationale to use vaginal rings as drug delivery method in endometriosis is mainly based on two reasons: 1) to reduce the systemic concentration and related AEs of drugs poorly tolerated when administered orally; 2) to take advantage of the local administration of the drug with the “uterine first-pass” effect, which could provide direct action on deep infiltrating endometriosis [47,48].

3.1.1 Estroprogestins

Regarding the potential advantage of a local administration of estroprogestins and progestins, Vercellini et al. [49] performed a patient preference trial comparing estroprogestins administered continuously for 12 months by a vaginal ring (ethinyl estradiol (EE) 15 μg + etonogestrel (ENG) 120 μg) versus transdermal patch (EE 20 μg + norelgestromin 150 μg) in women who underwent surgery for endometriosis. The withdrawal was high in both groups, but higher in the transdermal patch arm (36% versus 61%). The main withdrawal reason was AEs, followed by the desire to use a combined oral contraceptive (COC). Although suboptimal bleeding control and improved pain symptoms were reported similar in both groups, patients who used the vaginal ring experienced lower dysmenorrhea, lower deep dyspareunia, fewer AEs, and higher satisfaction, particularly in the presence of rectovaginal implants [49]. Regardless of these promising results, only a second trial investigated the vaginal route as a drug delivery method for estroprogestins in endometriosis. Combined contraceptive vaginal ring administered sequentially for 12 months was compared with desogestrel only pill (75 mcg/day) administered continuously for symptomatic rectovaginal endometriosis. In this patient preference trial, women who adopted desogestrel only pill reported higher satisfaction (61.7% vs. 36.1%) and greater improvement in gastrointestinal symptoms, chronic pelvic pain, and dyspareunia. However, no differences were
observed regarding the discontinuation rate and the reduction of rectovaginal nodules [50]. On that basis, although the vaginal route is effective and provides different advantages when estroprogestins are adopted for contraception [46], data about the endometriosis treatment are limited. Therefore, we cannot confirm that all advantages observed for contraception, such as compliance, are present when vaginal rings delivering estroprogestins are used for endometriosis. Each drug delivery method needs to be evaluated separately for every new clinical indication.

3.1.2 Danazol
The vaginal route has been investigated in endometriosis as an alternative delivery method for different drugs, with the aim to both take advantage of the local administration and the lower systemic levels. The majority of evidence is on danazol administration, a 17α-ethynyl-testosterone derivate able to suppress gonadotropin production, inhibit aromatase activity, and reduce inflammation, with subsequent atrophy of endometriotic implants [51]. The oral administration of danazol has been associated with AEs related to its mild androgenic activity, which does not allow a protracted administration [52].

Different studies investigated the vaginal administration of danazol to maintain efficacy and reduce AEs. The tested doses ranged between 95 and 200 mg/day for 6–12 months [53–57]. Pain symptoms were reported improved in all investigations, particularly in patients with deep infiltrating endometriosis. Noteworthy, all studies reported a reduction of rectovaginal nodules but no effect on the volume of endometriomas. Conversely to oral administration, serum levels of danazol were reported lower or even undetectable, with almost absent AEs related to the androgenic action. The concentration of danazol at the ovaries and uterus level was comparable to those after oral administration but only 1/20 of those in the serum [51]. This evidence shows how a different drug delivery method can dramatically change the efficacy and safety profile; the release of danazol by vaginal rings, in the proximity of deep endometriotic implants, generates high local concentrations reducing systemic levels and related AEs [54]. Notably, low systemic levels do not provide a contraceptive action. The persistent ovulation exposes the risk of female fetus virilization if
danazol is not withdrawn after conception; therefore, concomitant contraceptive methods are recommended [58].

3.1.3 Aromatase inhibitors
Third-generation AIs letrozole and anastrozole (ATZ) are reversible inhibitors that compete with androgens for aromatase binding sites [59]. They have been investigated in endometriosis based on the deeper suppression of estrogen production by blocking aromatase than those obtained through ovarian function inhibition. AIs can suppress estrogen production at the ovaries, peripheral tissues, and endometriotic implants [60]. In this regard, based on the local presence and activity of aromatase in endometriotic lesions [23], and the significant AEs after systemic administration [59], vaginal rings have been recently investigated to take advantage of the local administration and the lower systemic levels provided by this route [47].

Hefler et al. [61] conducted a single-arm open-label clinical trial in which 10 premenopausal women with rectovaginal endometriosis were treated for 6 months with daily ATZ 0.25 mg administered in a 2-g vaginal suppository. All patients received elemental calcium 2400 mg and vitamin D 800 IE daily. Compared to baseline values, chronic pelvic pain and dyspareunia did not improve during and after therapy; only dysmenorrhea, and quality of life assessed with the Short Form 36 (SF-36) health survey, showed an improvement. No changes in gonadotropin levels, estradiol levels, and bone mineral density (BMD) were reported. However, they established the dosage of ATZ from pharmacokinetics data of danazol suppositories and expected resorption capacity of vaginal walls.

Schultze-Mosgau et al. [62] were the first to conduct a randomized phase I trial to assess pharmacokinetics, pharmacodynamics, safety, and tolerability of ATZ and levonorgestrel (LNG) administered vaginally. Sixty healthy women aged 18–35 were randomized to three arms and wore the vaginal ring for two consecutive 28-day periods (A: 500 mcg/day ATZ and 20 mcg/day LNG; B: 1000 mcg/day ATZ and 30 mcg/day LNG; C: 1500 mcg/day ATZ and 40 mcg/day LNG). Investigators observed neither formation of ovarian cysts nor other significant AEs. Noteworthy, significant suppression of estradiol levels was observed only in groups B and C, and 40 mcg/day LNG were required to
achieve serum level comparable to oral administration. These results allowed defining the ATZ and LNG dosages for Phase 2 studies [63]. A randomized, parallel-group, double-blind phase IIb clinical trial has been recently concluded. The study evaluated the efficacy and safety of LNG 40 mcg with or without different doses of ATZ administered with a vaginal ring in endometriosis patients. They compared three months of therapy with placebo and leuprolide in symptomatic endometriosis (NCT02203331). The results will allow us to define whether the adoption of a vaginal ring may represent an innovation in using AIs to treat endometriosis [64].

3.2 Intrauterine systems
Intrauterine drug delivery systems (IUSs) were introduced in the early 1990s and rapidly became one of the most adopted contraception [65]. Among different available options, IUSs are those with the highest effectiveness due to protective effects independent from the subject motivation [66]. All available IUSs contain different dosages (total content: 13.5, 19.5, and 52 mg) of LNG (LNG-IUSs), which is a second-generation progestogen derived from 19-nortestosterone [67]. The intrauterine delivery method generates a locally high LNG concentration, with subsequent decidualization and atrophy of the endometrium, and concomitant low systemic levels, which reduce AEs and increase tolerability. Noteworthy, in the majority of patients, cycles remain ovulatory [68–70]. The high local LNG concentration was associated with additional non-contraceptive benefits. Different studies reported a significant reduction or resolution of heavy menstrual bleeding and dysmenorrhea (regardless of whether primary and secondary) [71]; other evidence showed a preventive and therapeutic role for endometrial hyperplasia [72]. Therefore, different studies investigated intrauterine administration as an alternative drug delivery method for LNG in endometriosis [73].

The rationale to use IUSs as a drug delivery method in patients with endometriosis is similar to that of vaginal rings. It is based on reducing systemic concentration and related AEs of LNG, combined with the advantage of the local administration. Moreover, LNG-IUSs do not require constant motivation and have a contraceptive function, with the potentiality of a long-term therapy
[68]. However, IUSs have the cons that require fitting by a health professional, although this characteristic is paramount for the reported high compliance. Since the first trials, LNG-IUSs in endometriosis were associated with improved pain symptoms, including dyschezia and deep dyspareunia, and reduced rectovaginal implants size, after 6 months of therapy [74]. These initial observations were confirmed by later randomized controlled trials (RCTs) (Table 2) [75–82]. LNG-IUSs were associated with greater improvement of pain symptoms and higher patient satisfaction versus expectant management after surgery [75,76]. Compared to other therapeutic options, such as GnRH analogs, depot medroxyprogesterone acetate, or ENG releasing contraceptive implant, LNG-IUSs resulted in similar pain symptoms improvement but overall higher, or at least similar, patient satisfaction and compliance, even after a long-term follow-up of 3 years [77–82]. All available trials support IUSs as a useful alternative drug delivery method for endometriosis, which appear well-tolerated and applicable for long-term therapy, being irregular bleeding the main AE that tends to reduce over time [68].

Despite these results, LNG-IUSs in endometriosis were questioned due to the uncertain prevention of endometrioma recurrence [73]. Most patients have persistent ovulatory cycles [68–70], and some authors raised concerns about the risk of endometrioma or misdiagnosis with functional ovarian cysts [73]. Retrospective studies comparing LNG-IUS with COC after surgery reported conflicting results. Two studies did not report differences between the two treatments in terms of endometrioma recurrence [83,84]; conversely, another study reported a cumulative incidence of endometrioma recurrence after 5 years of 25%.

Regarding RTCs, two studies did not report endometriomas, although the small sample size and the short follow-up do not allow achieving definitive conclusions [76,78]. Conversely, Chen at al. [81] reported a similar cumulative incidence of endometrioma recurrence after 30 months of LNG-IUS versus expectant management (25% vs. 37.5%, respectively; p=0.2) in women who underwent surgery and 6 months of GnRH analogs. However, only 2.5% of patients in the LNG-IUS group required a second surgery for endometrioma than 20% of patients after expectant management (p = 0.031). Based on these observations, IUSs can be considered a useful alternative drug delivery method...
for patients affected by endometriosis, mainly in patients with dysmenorrhea and looking for contraception [68]. Conversely, LNG-IUSs could be questioned and avoided in patients with a history of endometrioma, particularly if they did not complete their family plan [73].

3.2.1 Others non-LNG IUSs

Although all commercially available IUSs contain LNG [67], other drugs have been investigated adopting this delivery method in preclinical and preliminary clinical trials [36]. However, among those studied, only danazol is already a therapy for endometriosis. Like vaginal rings, danazol has been formulated into an IUS and tested in a mouse model of adenomyosis. Two months of treatment provided a significant reduction of adenomyosis nodules, similar to the oral administration, but with significantly lower serum levels [85]. Although danazol-loaded IUS was primarily developed for adenomyosis, the advantages provided by a local administration suggested investigating this delivery method even in endometriosis. In a pilot study, Cobellis et al. [86] investigated a danazol-loaded IUS containing 300–400 mg in 18 women with symptomatic endometriosis. After 6 months, dysmenorrhea, dyspareunia, and chronic pelvic pain were reported significantly decreased with proper compliance, suggesting that danazol-loaded IUS could be useful for symptomatic endometriosis.

3.3 Depot formulations

Long-acting delivery systems have the advantage of increasing patient compliance and avoiding the first hepatic-passage [87]. IUSs are one of the long-acting delivery methods adopted for endometriosis treatment. Other examples are GnRH analogs and progestogens when administered as long-acting injectable drugs or implants [36].

Progestins represent a cornerstone in endometriosis pharmacotherapy [21]. Different compounds are available, and all mimic natural progesterone action, with subsequent decidualization and atrophy of eutopic and ectopic endometrium. They inhibit inflammatory pathways, metalloproteases activity, and gonadotropins release, suppress ovarian function, and induce apoptosis in endometriotic cells [23]. Progestins are available in multiple formulations allowing personalizing the treatment. In addition to IUSs, subdermal,
subcutaneous, and intramuscular administration, through injection or implants, are well-known drug delivery methods adopted for contraception and investigated for endometriosis [73].

3.3.1 *Depot medroxyprogesterone acetate*

Medroxyprogesterone acetate is available as a long-acting depot formulation (DMPA) administered every 3 months by intramuscular (150mg/1.0mL) or subcutaneous injection (104mg/0.65mL). DMPA is a progesterone-only (17-OH progesterone derivate) injectable contraceptive, which has been extensively adopted worldwide [88]. Among the first RCTs on endometriosis, intramuscular DMPA every 3 months was compared with COC plus a low dose of danazol by Vercellini et al. in 1996 [89]; 40 women with endometriosis and chronic pelvic pain were randomized in each group and received the treatment for 1 year. Patients reported a significant reduction of pain symptoms in both treatments, which had comparable effects except for a better improvement of dysmenorrhea observed in the DMPA group. A higher but non-significant proportion of patients was satisfied by the DMPA compared to COC (72.5% vs. 57.5%; p=0.24). A second RCT comparing DMPA and COC reported similar results, but with equal satisfaction between groups, and lower dysmenorrhea in the group receiving DMPA [90].

Five other RCTs investigated DMPA for endometriosis; three RCTs compared subcutaneous DMPA with GnRH analogs (leuprolide acetate, elagolix) administered for 6 months [91–93]; one trial compared intramuscular DMPA with LNG-IUS for 36 months of treatment [78]; one RCT compared 1 year of DMPA with 1 year of ENG-releasing implant [94]. Subcutaneous DMPA and GnRH analog administered every 3 months for 6 months provided a similar reduction of pain symptoms and improved quality of life after 12 months of follow-up [91–93]. However, subcutaneous DMPA was associated with better sexual experience, significantly less BMD loss (only with leuprolide acetate) [93], and fewer hypoestrogenic symptoms [92]. Wong et al. [78] randomized 30 women to intramuscular DMPA every 3 months versus LNG-IUS for 36 months of treatment (Table 2); a similar reduction in pain symptoms with no recurrences was reported in both groups. However, a higher proportion of patients discontinued the therapy in the DMPA arm.
In all RCTs, the main AE of DMPA was the irregular bleeding, which was reported by most patients, mainly as spotting, and less frequently, as breakthrough bleeding. In all reports, irregular bleeding was significantly more frequent in the group who received the DMPA, which was additionally associated with a considerably longer time required to return at a regular menstrual flow. Only in the RCT by Walch et al. [94], no differences in efficacy, AEs, compliance, and satisfaction were observed between DMPA and ENG-releasing implant after 1 year of treatment.

A point of concern regarding the DMPA is the loss of BMD due to the induced hypoestrogenic state [95]. Although it was reported lower and able to return at basal levels than GnRH analogs [92], the long-term use of DMPA could be associated with increased risk of bone fracture [73]. However, even after long-term use, the reported BMD loss was limited to the first 2 years of treatment with subsequent stabilization. Different studies proved that the BMD return at normal levels within two years after suspension [95–97]. Finally, large-scale, population-based studies reported an only modest or absent increased risk of fracture in DMPA users [98–100]. On that basis, although further research is recommended, both the American College of Obstetricians and Gynecologists (ACOG) and the World Health Organization (WHO) consider benefits to outweigh risks [101,102]. They recommend DMPA as a strategy to increase patient adherence to progestin therapy in endometriosis, although not the first option [21].

3.3.2 Etonogestrel releasing implant
Single-rod subdermal ENG-containing implant (68 mg) provides contraception for 3 years, inhibiting ovulation [103]. Evidence on its role in treating endometriosis is limited, with only two RCTs [73]. Walch et al. [94] randomized 41 women with surgically confirmed endometriosis to receive DMPA or ENG-releasing implant for 1-year; both treatments reported a similar reduction of pain symptoms after 6 and 12 months of therapy. Regarding patient satisfaction, AEs, compliance, and drop-out, no statistically significant differences were observed between groups, with irregular bleeding as the main reported AE in both.
Similar efficacy is reported in a clinical trial without a control group [104]. Fifty women with symptomatic surgically confirmed endometriosis underwent the subcutaneous implant of the ENG-releasing system. A significant reduction in pain symptoms was observed, particularly for dysmenorrhea. Irregular bleeding was the main AE, with 42%, 28%, 26%, and 4% of patients who reported regular menstruation, amenorrhea, spotting, and breakthrough bleeding; however, 80% of patients were very satisfied or satisfied by the treatment. More recently, Carvalho et al. [82] reported the results of a RCT comparing ENG-releasing implant with LNG-IUS (52 mg) in the control of endometriosis-associated pelvic pain (Table 2). Both treatments reported similar improvement of pain symptoms and quality of life, with a comparable prevalence of AEs. Similar to DMPA, the use of the ENG-releasing system has been associated with BMD loss. However, the evidence is conflicting with studies reporting both stable [105] and reduced BMD [106]. Moreover, some concerns have been raised regarding implant migration, although it is estimated to have a frequency of 1.3/every million inserted devices [73].

3.3.3 Long-acting GnRH analogs
GnRH analogs are an established second-line therapy for endometriosis [21], and multiple administration routes are available [27], such as intranasal, intramuscular, subcutaneous, and oral [93]. Intranasal administration of GnRH analogs have been compared with both intramuscular [107] and subcutaneous [108–110] injection. Regardless of the efficacy of GnRH analogs compared to other drugs, when compared to each other, all GnRH delivery methods appeared equivalent in terms of effectiveness [27]. Therefore, GnRH analogs allow choosing the best delivery method based on the patient’s preference. With the development of long-acting depot formulation lasting up to 3 months, the treatment in patients with endometriosis can be performed with just two injections covering the 6 months, increasing patient compliance and adherence [36].

3.4 Nanotechnologies
Novel drug delivery methods are not aimed only to change the pharmacotherapy of existing drugs, but they are essential to overcome delivery
challenges for adopting new molecules and developing new therapeutic strategies [36]. Nanotechnologies have been investigated as novel drug delivery methods in endometriosis for new and already known compounds. They consist of bioconjugates able to deliver anti-inflammatory, antioxidant, anti-angiogenic, or immunomodulating molecules at endometriotic implants level. Nanotechnologies are mainly designed to enhance stability, delivery efficiency, and targeted release length for molecules with limited bioavailability [111]. Moreover, nanotechnologies can be combined with radiation physics for on-demand drug delivery. Nanoparticles can release drugs in response to a laser triggering photothermal effects, radiofrequency waves, and ultrasounds [112–115]. This new technology has been mostly reported for cancer [116], but theoretically, there is no difference from the drug delivery concept in endometriosis. However, the application of nanotechnologies in endometriosis is very preliminary at a preclinical or proof-on-concept level. Data are limited and based mainly on animal models. Therefore, further research is mandatory to confirm a possible clinical application. Caution and criticism are recommended in making conclusions from mouse models data to avoid misinterpretation or over-interpretation; mouse models are incapable of predicting nanotechnology’s clinical efficacy. [117].

3.4.1 Poly(lactic-co-glycolic) acid (PLGA) nanoparticles
Poly(lactic-co-glycolic) acid (PLGA) nanoparticles are a carrier polymer for nanoencapsulation considered safe by the FDA [118]. PLGA has been adopted to develop a dual drug-loaded nanoparticle with epigallocatechin gallate and doxycycline. Epigallocatechin gallate (the primary catechin of green tea) has antioxidant and antiangiogenic proprieties, and doxycycline inhibits metalloproteases function [111]. In a mouse model of endometriosis, the dual drug-loaded PLGA nanoparticle was associated with a reduction of oxidative stress markers, metalloproteases expression and activity, and angiogenic factors levels as compared to controls. The number of endometrial glands and the number and size of new microvessels were reduced at the histological examination [111].

PLGA nanoparticle has been further investigated as a delivery method for Copaiba Oleoresin (CPO) [119] and antibodies [120]. CPO is a natural product
obtained from trees of the genus Copaifera. It has antioxidant, anti-inflammatory, and antinoiceptive properties, which have potential therapeutic activity against endometriosis [121]. When tested in cell cultures, PLGA/CPO nanoparticles reduced cell viability in a time-dependent manner, after 48 hours of exposure, in both eutopic and ectopic endometrium of women affected by endometriosis. A minor and delayed reduction of cell availability was observed in the eutopic endometrium of women without endometriosis. Noteworthy, PLGA nanoparticle without CPO did not provide any effect [119].

The anti-CTLA-4 antibody is against CTLA-4 and represents one of the main suppressive immune checkpoints [122]. The block of CTLA-4 limits CD4+/CD25+/Tregs activation, regulating the Treg suppressor function that is involved in the maintenance of immunological self-tolerance [123]. The high concentration of Treg in the peritoneal fluid of women affected by endometriosis is one of the immunologic abnormalities considered involved in the endometriosis maintenance [124–126]. On that basis, the anti-CTLA-4 antibody has been investigated as a treatment for endometriosis. However, to enhance the stability, delivery efficiency, and prolong the targeted antibody release, anti-CTLA-4 antibody encapsulated in PLGA nanoparticles has been investigated as a drug delivery method to maximize the effect of anti-CTLA-4 at the level of endometriotic implants. Anti-CTLA-4/PLGA nanoparticles were reported constantly releasing anti-CTLA-4 antibody for 24 days with preserved bioactivity. This constant release provided, in a mouse model, a higher inhibition of ectopic endometrial cell proliferation and invasion as compared to anti-CTLA-4 alone. These results suggest that anti-CTLA-4 antibodies regulate the immunological self-tolerance involved in the endometriosis etiopathogenesis. The adoption of PLGA nanoparticles as a delivery method provided a sustained release of anti-CTLA-4 antibody in the micro-environment, leading to possible improved therapeutic outcomes [120].

Impaired function of peritoneal macrophages is an additional immunological dysregulation associated with endometriosis, which is involved in its pathogenesis. Endometriosis is characterized by a defect of pro-inflammatory M1 macrophages and an excess of anti-inflammatory and pro-fibrotic M2 macrophages [127,128]. PLGA nanoparticles have been investigated as carriers of anti-CCR5 antibodies to reduce the anti-inflammatory and pro-fibrotic activity
of macrophages in a mouse model of endometriosis. The bioconjugate anti-CCR5/PLGA provided a constant and controlled release of the anti-CCR5 up to 24 days. A significant reduction of macrophages, IL-10, and TGF-β levels was observed, with associated reduced proliferation and invasion ability of ectopic endometrial cells [129].

3.4.2 Aminopropyl mesoporous silica nanoparticles (AMNPs)
The role of macrophages in the pathogenesis of endometriosis has been associated with both an anti-inflammatory and pro-fibrotic activity and a defective clearance function. Peritoneal macrophages of endometriosis patients have been reported defective of membrane scavenger receptors SR-A1 and SR-B, which are involved in the peritoneal clearance of cellular debris [130]. Based on this impaired function, a derivative of Muramyl dipeptide (MDP; a fragment of peptidoglycan from Gram-positive and Gram-negative bacteria), the N-acetylglucosaminyl-N-acetylmuramyl-L-alanyl-D-isoglutamine (GMDP), has been proposed to stimulate both the innate and adaptive immune response to increase the clearance of endometriotic cells [130–132]. However, due to the low bioavailability (7%–13%), the immobilization of GMDP onto nanoparticles has been proposed to stabilize the drug and prolong the action. The use of aminopropyl modified and unmodified mesoporous silica nanoparticles (AMNPs) as nanocarriers of the GMDP was associated with an intensification of the immunomodulatory action on the peritoneal macrophages. The observed effect exceeded those of GMDP alone, with increased expression of scavenger receptors and macrophages activity [130].

3.4.3 Lipid nanoparticles
A recent study investigated lipid nanoparticles as possible drug delivery systems targeting endometriosis [133]. Lipid nanoparticles are artificial nanoparticles resembling low-density lipoproteins (LDLs) that can carry therapeutic molecules. Lipid nanoparticles are uptake by LDL receptors and can be used to effectively target drugs to tissues requiring high amounts of cholesterol, such as cancer and inflammatory tissues [134]. Based on the overexpression of LDL receptors by endometriotic implants [135], 14 patients who underwent surgery for severe endometriosis received lipid nanoparticles
with cholesterol [14C]-oleate intravenously the day before surgery. The study aimed to investigate whether lipid nanoparticles can target endometriotic tissues. The results showed the uptake of lipid nanoparticles by endometriotic implants, adjacent healthy peritoneum, and eutopic endometrium. In patients with ovarian and deep endometriotic lesions, the uptake was higher than in patients with intestinal endometriotic implants, supporting a possible application in deep endometriosis [133].

3.4.4 Nanoparticles-based photothermal ablation
Nanotechnologies have been investigated to deliver drugs for photothermal ablation with high specificity at the endometriotic implants. Hollow gold nanospheres (HAuNS) have been conjugated with the TNYL peptide, which has an affinity for a tyrosine kinase receptor overexpressed by endometriosis (EphB4 receptor). The conjugate efficiently accumulated at the level of endometriotic implants through permeable vessels and EphB4 receptor, and the photothermal ablation induced atrophy and degeneration of implants without AEs [136].

In a more recent study, Moses et al. [137] developed a nanoplatform based on the dye silicon naphthalocyanine (SiNc), which can be used for real-time near-infrared fluorescence and photothermal therapy. The authors conjugated the SiNc with a polymeric nanoparticle, which effectively delivered the SiNc at the endometriotic tissue level. Noteworthy, the nanoparticle was developed to be non-fluorescent before internalization, allowing it to potentially identifying endometriosis implants by real-time near-infrared fluorescence. This nanoplatform subsequently increased the temperature of the target tissue and provided photothermal ablation both in vivo and in vitro.

3.4.5 Nanofibers
Nanofibers can be used for scaffolds, wound healing, and drug delivery [138]. In Boroumand et al. [139], the authors investigated curcumin-loaded nanofibers as a novel drug delivery method for curcumin. Curcumin is a well-known phytochemical with anticancer, anti-inflammatory, and anti-oxidant properties, which has been reported potentially useful in treating endometriosis [31]. Oral administration is limited by the poor absorption, low water solubility, and rapid
metabolism of curcumin, limiting its bioavailability [140]. Therefore, the authors investigated curcumin loaded poly ε-Caprolactone (PCL) and polyethylene glycol (PEG) polymers nanofibers as an anti-endometriosis implantable scaffold able to release curcumin continuously at the endometriotic implants. In vitro, curcumin loaded PCL-PEG nanofibers released almost 25% of loaded curcumin in the first 30 minutes, and 50% in 30 days. In vivo, intraperitoneal implantation of curcumin-loaded nanofibers in a mouse model of endometriosis reduced endometriotic implants (both stroma and glands) and inflammatory cell infiltration as compared to controls [139]. However, these data are very preliminary and limited; further evidence is required to pursue further nanofibers. This study represents a proof-of-concept, and a significant amount of research is needed to conclude on a possible clinical application for endometriosis. Practical questions, such as how nanofibers can be administered, have to be answered.

4. Conclusion
Alternative drug delivery methods already available for the treatment of endometriosis derive from contraception. However, only LNG-IUSs and DMPA have been investigated with multiple RCTs to treat patients with endometriosis. These methods appear able to improve patient compliance and satisfaction compared to other consolidated therapeutic options, although DMPA was associated with irregular bleeding and BMD loss. Conversely, only a few RCTs investigated the adoption of vaginal rings delivering estroprogestins, ENG-releasing implant, or transdermal patch. Therefore, the evidence is still limited to achieve definitive conclusions regarding their utility in patients with endometriosis.

With possible direct action on deep endometriosis and lower systemic levels, the advantage of a local administration led the investigation of vaginal rings and IUSs as alternative drug delivery methods for danazol, with promising results. Instead, only vaginal rings have been investigated for AIs, requiring additional evidence to confirm a clinical utility.

Nanotechnologies are possible novel drug delivery methods that have been proven effective to deliver, in vitro and mouse models, molecules providing a specific therapeutic effect on endometriosis. However, data are minimal and
preliminary. Almost all methods are still in early experimental development, with only a few nanotechnologies already test on humans for other diseases. No one has been applied in clinical studies for the treatment of endometriosis, and mouse models are incapable of predicting nanotechnology’s clinical efficacy.

5. Expert opinion
Pharmacotherapy has a crucial role in the treatment of endometriosis [21]. However, available therapeutic options have different limitations: a significant proportion of patients gain only intermittent or limited benefit [21], in almost 10% of patients AEs cause the discontinuation of the treatment [33], and the consolidate options mainly target symptoms instead of the disease etiopathogenesis [29]. On that basis, it is undoubted that further research is needed to improve the pharmacological management of endometriosis. In this regard, the development and adoption of alternative drug delivery methods is a well-known strategy able to innovate established pharmacotherapies or develop new therapeutic strategies [34].

The advantage of alternative drug delivery methods in patients affected by endometriosis is that progestins and estroprogestins, which represent the first-line therapy, are already available in different formulations with extensive experience from contraception [35]. On that basis, the personalization of endometriosis pharmacotherapy should include the adoption of alternative delivery methods of hormones to find the best option to maximize the efficacy, reduce AEs, and improve compliance and quality of life. LNG-IUSs represent a perfect example of such an opportunity. Multiple RCTs support their effectiveness and improved patient satisfaction compared to other medications. Knowing the pros and cons of each drug delivery method can provide the patients with the best personalized therapeutic strategy.

Nevertheless, alternative drug delivery methods in patients with endometriosis should not be adopted based only on contraception experience. LNG-IUSs do not appear the best option in patients with endometriomas. Only studies on endometriosis defined the category of patients who may benefit more from this type of drug delivery method. Therefore, further research is needed to adopt alternative progestins and estroprogestins drug delivery methods other than
LNG-IUSs and DMPA. Each drug delivery method needs to be evaluated separately for every new clinical indication.
Nanotechnologies have been investigated to treat endometriosis as possible novel drug delivery methods for molecules targeting etiopathogenetic mechanisms [36]. Bioconjugate delivering anti-inflammatory, antioxidant, anti-angiogenetic, and immunomodulating molecules has been investigated and reported effective in mouse models; however, further research is required before possible clinical application. Almost all methods are still in early experimental development, with only a few nanotechnologies already test on humans for other diseases. No one has been applied in clinical studies for the treatment of endometriosis. The actual safety profile needs to be completely defined, as well as the administration route. A significant proportion of them may require the intraperitoneal administration, raising substantial concerns about an application limited at the end of surgical procedures. On that basis, further investigation is required both to prove the clinical efficacy and to confirm the possible clinical application. It is important to stress that caution is recommended in making conclusions from mouse models’ data to avoid misinterpretation or over-interpretation, because mouse models are incapable of predicting clinical efficacy.
In the future, the growing body of evidence on the etiopathogenesis of endometriosis will increase the number of drugs targeting the disease [23,29–32], and the experience with the development of alternative drug delivery methods would be of paramount importance to introduce in the clinical practice such molecules. The adoption of vaginal rings as a novel and alternative drug delivery method for AIs is an example, as well as the experience with danazol. On that basis, further investigation on alternative and novel drug delivery methods is mandatory to increase the available strategies and personalize and improve the management of patients affected by endometriosis, improve the efficacy of the drug, and increase patient compliance reducing AEs.
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**Reviewer disclosures**
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.
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* of interest
** of considerable interest


** Narrative review about current options for deep endometriosis therapy


* Complete review on currently employed and under investigation drug for treating endometriosis


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* Interesting manuscript about the rational of using levonorgestrel-releasing intrauterine system in endometriosis


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Table legend

Table 1. Alternative drug delivery methods for the treatment of endometriosis.
Table 2. Randomized controlled clinical trials that investigated the adoption of LNG-IUS for the treatment of endometriosis.
<table>
<thead>
<tr>
<th>Delivery method</th>
<th>Drug</th>
<th>Level of investigation</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal ring</td>
<td>Estroprogestins</td>
<td>Clinical</td>
<td>Conflicting results when compared with oral or transdermal routes. Limited investigation.</td>
</tr>
<tr>
<td></td>
<td>Danazol</td>
<td>Clinical</td>
<td>Effective with lower serum level and AEs, not contraceptive.</td>
</tr>
<tr>
<td></td>
<td>Aromatase inhibitors</td>
<td>Clinical</td>
<td>Ongoing investigation in patients with endometriosis.</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Estroprogestins</td>
<td>Clinical</td>
<td>Compared only with vaginal ring. Limited investigation.</td>
</tr>
<tr>
<td>Intrauterine system</td>
<td>Levonorgestrel</td>
<td>Clinical</td>
<td>Effective, higher or comparable satisfaction, contraceptive, not prevention of endometrioma</td>
</tr>
<tr>
<td></td>
<td>Danazol</td>
<td>Clinical</td>
<td>Effective with lower serum level and AEs. Limited investigation.</td>
</tr>
<tr>
<td>acting formulations</td>
<td>Injectable</td>
<td>Clinical</td>
<td>Effective, from higher to lower satisfaction based on comparison, irregular bleeding, concern on BMD loss.</td>
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<td></td>
<td>Medroxyprogesterone acetate</td>
<td>Clinical</td>
<td>Injectable Depot Medroxyprogesterone acetate Clinical Effective, comparable to DMPA in terms of satisfaction, efficacy, and AEs</td>
</tr>
<tr>
<td></td>
<td>Etonogestrel</td>
<td>Clinical</td>
<td>Implants Etonogestrel Clinical Effective, comparable to DMPA in terms of satisfaction, efficacy, and AEs</td>
</tr>
<tr>
<td></td>
<td>GnRH analogs</td>
<td>Clinical</td>
<td>Nanotechnologies (\text{GnRH analogs}) Clinical Multiple drug delivery option equally effective, 3 months depot formulation</td>
</tr>
<tr>
<td>Nanotechnologies</td>
<td>PLGA nanoparticles</td>
<td>Mouse model</td>
<td>Antioxidant and antiangiogenic + inhibition of metalloproteases. Reduction of endometriosic implants</td>
</tr>
<tr>
<td></td>
<td>Epigallocatechin gallate + doxycycline</td>
<td>Mouse model</td>
<td>Antioxidant, anti-inflammatory, and antinociceptive. Reduced cell viability.</td>
</tr>
<tr>
<td></td>
<td>Copaiba Oleoresin</td>
<td>In vitro</td>
<td>Copaiba Oleoresin In vitro Antioxidant, anti-inflammatory, and antinociceptive. Reduced cell viability.</td>
</tr>
<tr>
<td></td>
<td>Anti-CTLA-4 antibody</td>
<td>Mouse model</td>
<td>Anti-CTLA-4 antibody Mouse model Inhibition of CD4+/CD25+/Tregs. Sustained release of antibodies. Inhibition of proliferation and invasion of endometriosic cells.</td>
</tr>
<tr>
<td></td>
<td>anti-CCR5 antibodies</td>
<td>Mouse</td>
<td>anti-CCR5 antibodies Mouse Reduce anti-inflammatory and pro-fibrotic activity of</td>
</tr>
<tr>
<td>AMNPs</td>
<td>GMDP</td>
<td>In vitro</td>
<td>Increased stability and action of GMDP. Enhanced expression of scavenger receptors and macrophages activity.</td>
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<tr>
<td>Lipid nanoparticles</td>
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<td>Clinical</td>
<td>Lipid nanoparticles are up taken by the endometriotic implants, adjacent healthy peritoneum, and eutopic endometrium.</td>
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<tr>
<td>TNYL peptide</td>
<td>HAuNS</td>
<td>Mouse model</td>
<td>Accumulation in and photothermal ablation of endometriosic implants without AEs</td>
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<tr>
<td>nanoparticle s</td>
<td>silicon naphthalocyanine</td>
<td>Rhesus macaques</td>
<td>Accumulation in, visualization of, and photothermal ablation of endometriosic implants without AEs</td>
</tr>
<tr>
<td>nanofibers</td>
<td>curcumin</td>
<td>Mouse model</td>
<td>Continuous release of curcumin up to 30 days. Reduction of endometriosic implants and inflammatory infiltrate.</td>
</tr>
</tbody>
</table>

PLGA, Poly(lactic-co-glycolic) acid; AMNPs, Aminopropyl mesoporous silica nanoparticles; GMDP, N-acetylglucosaminyl-N-acetylmuramyl-L-alanyl-D-isoglutamine; HAuNS, hollow gold nanospheres; AEs, adverse effects; BMD, bone mineral density.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Design</th>
<th>Patient number</th>
<th>Treatments</th>
<th>FU (m)</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vercellini et al.</td>
<td>2003</td>
<td>double arm, OL, RND</td>
<td>20 vs 20</td>
<td>• LNG-IUS 52mg AS</td>
<td>12</td>
<td>Moderate or severe dysmenorrhea recurrence in 10% vs 45% of patients (p=0.03). NNT = 3. 75% vs 50% were satisfied.</td>
</tr>
<tr>
<td>Petta et al.</td>
<td>2005</td>
<td>double arm, OL, RND</td>
<td>39 vs 43</td>
<td>• LNG-IUS 52mg</td>
<td>6</td>
<td>6-point decrease in VAS pain score in both groups (p=0.656). 5 vs 6 patients failed to achieve &lt; 3 VAS pain score. 30% vs 2% reported irregular bleeding. No difference in AEs.</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>2010</td>
<td>double arm, OL</td>
<td>15 vs 15</td>
<td>• LNG-IUS 52mg</td>
<td>36</td>
<td>Similar significant reduction of pain symptoms with no recurrences in both groups. Irregular bleeding more severe in DMPA. 87% vs 47% completed the study (p&lt; 0.025).</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Design</td>
<td>Arm 1</td>
<td>Arm 2</td>
<td>Follow-up</td>
<td>Results</td>
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<tr>
<td>Ferreira et al.</td>
<td>2010</td>
<td>RND</td>
<td>double arm, OL, RND</td>
<td>22 vs 22</td>
<td>6</td>
<td>Similar (p=0.21) significant reduction of pain symptoms with no recurrences in both groups (p&lt;0.001). Significant reduction in inflammatory markers and lipid profile in LNG-IUS group.</td>
</tr>
<tr>
<td>Bayoglu Tekin et al.</td>
<td>2011</td>
<td>RND</td>
<td>double arm, OL, RND</td>
<td>20 vs 20</td>
<td>12</td>
<td>Similar significant reduction of pain symptoms in both groups at 1, 3, and 6 months; after 1-year lower pain only in Goserelin group, with higher satisfaction and less irregular bleeding.</td>
</tr>
<tr>
<td>Tanmasamat et al.</td>
<td>2012</td>
<td>DB</td>
<td>double arm, DB, RND</td>
<td>28 vs 26</td>
<td>6</td>
<td>Higher reduction of dysmenorrhea and CPP (p=0.006; p=0.038). 7.4% vs 39.1% reported recurrent moderate/severe pain (p=0.014). NNT = 3.7. Only in LNG-IUS: reduction of dyspareunia and improvement of QoL.</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>2017</td>
<td>RND</td>
<td>double arm,</td>
<td>40 vs 40</td>
<td>30</td>
<td>Similar endometrioma (&gt; 3 cm) recurrence (25% vs 37.5%; p=0.228), but less second surgery (2.5% vs 20%; p=0.031). Higher reduction of dysmenorrhea and CPP (p&lt;0.001;</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>DB, RND</td>
<td>Treatment</td>
<td>p-value</td>
<td>Results</td>
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<tr>
<td>Carvalho et al.</td>
<td>2018</td>
<td>double arm, OL, RND</td>
<td>Leuprolide 3.75mg/4w IM (6 m) + Observation AS</td>
<td>p=0.014</td>
<td>Later recurrence of dysmenorrhea and lower use of analgesics (17.5% vs 45%; p=0.008). Higher rate of irregular bleeding. NNT = 5.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>DB, RND</th>
<th>Treatment</th>
<th>p-value</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvalho et al.</td>
<td>2018</td>
<td>double arm, OL, RND</td>
<td>LNG-IUS 52mg ENG-releasing contraceptive implant</td>
<td></td>
<td>Similar significant reduction of pain symptoms in both groups (dysmenorrhea and CPP). Similar significant QoL improvement. Similar irregular bleeding pattern.</td>
</tr>
</tbody>
</table>

LNG-IUS, levonorgestrel intrauterine system; ENG, etonogestrel; OL, open label; DB, double blind; RND, randomization; NNT, number need to treat; IM, intra muscular; AS, after surgery; FU, follow-up; w, week; m, months; QoL, Quality of life; CPP, chronic pelvic pain; vs, versus.