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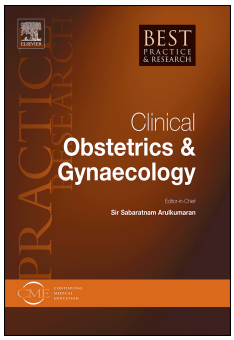

Medical treatment of endometriosis related pain

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MEDICAL TREATMENT OF ENDOMETRIOSIS RELATED PAIN

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ABSTRACT

Available medical treatments for symptomatic endometriosis act by inhibiting ovulation, reducing serum oestradiol levels, and suppressing uterine blood flows. To this aim, several drugs can be used, with a similar magnitude of effect, in term of pain relief, independently of the mechanism of action. Conversely, safety, tolerability, and cost differ. Medications for endometriosis can be categorised into low-cost drugs, including OCs and most progestogens, and high cost drugs, including dienogest and GnRH agonists. As the individual response to different drugs is variable, a stepwise approach is suggested, starting with OCs or low-cost progestogens, and stepping up to high-cost drugs only in case of inefficacy or intolerance. Oral contraceptives may be used in women with dysmenorrhoea as their main complaint, and when only superficial peritoneal implants or ovarian endometriomas < 5 cm are present, while progestogens should be preferred in women with severe deep dyspareunia and when infiltrating lesions are identified.

KEYWORDS: endometriosis, dysmenorrhoea, dyspareunia, pelvic pain, oral contraceptives, progestogens, dienogest, GnRH agonists, GnRH antagonists

1. INTRODUCTION: "GIMME SOME TRUTH"*

*Lennon J. In: Imagine. U.K., Apple Records, 1971

Numerous useful literature reviews on medical treatment for endometriosis have been published during recent years. Several of them are systematic and some include meta-analyses [1-4]. In most reviews, not only available drugs are evaluated, but also novel compounds under investigation [5-8]. Therefore, here we have tried to address the issue from another perspective, that is, defining the conceptual framework underpinning hormonal therapy for endometriosis; suggesting theoretical and practical instruments for selecting, interpreting, and implementing data on the medications most frequently used to treat endometriosis; and describing the general healthcare scenario in which physicians have to act together with their patients. In addition, the position of scientific institutions and authoritative experts in the field on specific controversial issues has been addressed.

Concerning the first point, the common final mechanism of action of hormonal drugs, and the reasonable expectations regarding their use should be highlighted once more. With few exceptions, different drugs, through diverse endocrine pathways, achieve a similar end-result, i.e., interference with pituitary gonadal stimulation, anovulation, induction of a steady hormonal milieu, and reduction or suppression of menstrual flow. If the ectopic endometrium derives from the mucosa lining the uterine cavity, the response to gonadal hormones' variations may not be substantially different from that of the original epithelium, despite purported peculiar endocrine metabolism within extra-uterine implants (progesterone resistance; increased local oestrogen synthesis). Indeed, compounds have been developed to suppress the growth and the activity of the ectopic mucosa, precisely based on the principle that the ectopic endometrium responds to variations in circulating ovarian steroids similarly to the intrauterine one [9].

Nevertheless, the hypo- or atrophic glandular state induced by hormonal drugs is temporary by definition, as no definitive cytoreductive action can be expected by simply altering ovarian steroid levels. If adequately stimulated, the atrophic endometrium of a postmenopausal woman may resume its proliferative potential even after years of profound hypo-oestrogenism. Therefore, until hormonal compounds will be used in women with endometriosis, disease *control* is a sensible goal, whereas disease *cure* is not. Given their mechanism of action, current medications for endometriosis works *during* treatment, whereas there seems to exist no rationale to hypothesize an enduring effect *after* treatment discontinuation.

However, some authoritative experts in the field of endometriosis have a different opinion and maintain "*there is evidence to suggest that in many women who do not respond to therapy, symptoms return after cessation of treatment, even after short follow-up periods*" and "*there remains an unmet clinical need among women with endometriosis for a specific disease-modifying therapy to provide long-term symptom relief that persists after the treatment period*" [4]. Women afflicted by endometriosis-related pain are eagerly waiting the advent of such intelligent drugs able to discriminate between the eutopic and the ectopic endometrium and to destroy selectively the latter one. In fact, only this type of drug would allow treatment for a limited period of time, achieving a long-lasting cure of pelvic endometriosis, but at the same time without causing uterine sterility due to disappearance of the intrauterine endometrium. How this differential effect could be obtained remains an unanswered question. In this regard, information from ongoing or completed trials on novel drugs for endometriosis is currently discouraging [9-11].

Comparing endometriosis with another frequent chronic disorder outside the gynaecological field may help clarify the issue further. Authoritative gastroenterologists do not maintain that proton pump inhibitors (PPIs) are inadequate for the treatment of severe erosive gastroesophageal reflux disease (GERD) because not all patients respond satisfactorily to medical treatment, or some of them

report side effects, or almost all of them experience quick and severe symptom recurrence at drug discontinuation [12,13]. In fact, generally no medical therapy is effective on all patients with a chronic condition; effective drugs with no side effects just do not exist; and medications for chronic disorders are, by definition, symptomatic. Moreover, also in this case rapid symptom recurrence at drug discontinuation is expected and constitutes no surprise. Indeed, the development of PPIs has been beneficial for about two thirds of patients suffering from GERD whose symptoms were not sufficiently relieved by previously available therapies. The only reasonable alternative to PPIs is here a complex surgical procedure such as Nissen antireflux fundoplication, diaphragmatic hiatoplasty and fundopexy, with the well-known associated short- and long-term complications [14]. In fact, authoritative experts in the field recognize that PPIs, without surgery, must be taken for decades, precisely because they are not definitively curative. Therefore, "inefficacy", is here defined as lack of symptom relief *during* treatment and not *after* treatment [12,13].

Until agreement will be achieved on these two concepts, i.e., a similar response of ectopic and eutopic endometrium to hormonal compounds and the temporary pharmacological effect of currently available drugs, physicians and investigators will possibly nurture unfounded expectations. More importantly, when using medications for a few-month periods, patients might not receive a treatment that adequately limit the physical and psychological consequences of endometriosis.

Accepting the above principles means accepting that medical treatment for endometriosis may be needed for years. This also means that when medications are compared in randomised, controlled trials (RCTs), they should not be assessed only in terms of efficacy on pain. According to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), a multi-factorial evaluation is needed to determine whether a difference between the effect of an experimental drug and that of an available alternative option for the treatment of chronic pain is clinically meaningful [15]. In fact, in order to define a clinically meaningful between-group differences, several factors in addition to

pain improvement should be considered, including safety, tolerability, improvements in physical and emotional functioning, and cost. Thus, whether a difference in pain reduction is worth a change in the medications used for a given condition is not only a matter of effect size, but rather of a balanced assessment of the overall risk-benefit ratio. Consequently, to quantify the magnitude of change that is considered clinically meaningful to chronic pain patients, the authors recommend to use not only central tendency statistics (e.g., means ± SD or SEM), but rather anchor-based methods, such as patient ratings of patient satisfaction. According to the authors, "*Although not without shortcomings, the use of global measures of improvement or overall treatment satisfaction in chronic pain trials allows patients to provide their integrated evaluation of a treatment, including but not limited to relief of pain, and such measures therefore have unique value as anchors in establishing clinical importance*" [15].

In this regard, ideally our clinical goal is complete elimination of pain [16], provided this primary aim does not compromise safety, quality of life, and economic stability of women and their families. Otherwise, a reasonable compromise between all of these factors could be preferable, especially when prolonged periods of treatment are foreseen. For this reason, in the present review particular emphasis has been put on the overall "therapeutic balance" of various medications, as well as on patient satisfaction, an important global patient reported outcome, rather than on pain score variation as an isolated measure of the effect size of treatments.

2. PROS AND CONS OF COMBINED ORAL CONTRACEPTIVES

In a large, multicentre, placebo-controlled RCT conducted in women with symptomatic endometriosis, a low-dose OC substantially improved not only dysmenorrhoea, but also other pain symptoms, including non-menstrual pain and deep dyspareunia [17]. The findings of this Japanese study confirm the vast amount of published data concerning the appreciable degree of satisfaction with treatment that can be achieved with OCs in patients with the disease [3; Table 1]. However, Casper suggested that

progestogens should be preferred to OCs as a first-line treatment, based on the consideration that oestrogen and progesterone receptors would be, respectively, over- and under-expressed in ectopic endometrial implants [29]. Thus, administering OCs would be counterproductive, resulting in oestrogen dominance in the presence of progesterone resistance, with the potential risk of lesion progression. Interestingly, Casper notes that the amount of ethinyl-oestradiol (EE) contained even in so-called low-dose OCs (20 to 30 μg EE) is supraphysiologic, as 5 μg of EE are equivalent to about 1 mg of micronized oestradiol or 0.625 mg of conjugated equine oestrogens [29].

According to Casper [29], this hypothesis is supported by clinical data suggesting that previous use of OCs is associated with an increased risk of endometriosis in general [30] and of deep lesions in particular [31]. On the other hand, it has also been demonstrated that dysmenorrhea as a reason to initiate OCs is significantly more common in women with a subsequent diagnosis of endometriosis than in women without the disease [31]. In other words, undiagnosed endometriosis likely was already present before OC use, and OCs were initiated precisely to relieve endometriosis-related pain. Confounding might thus explain the previously reported mild association between endometriosis and past OC use [32]. The currently available epidemiological data do not support a pathogenic role of OCs in the development of endometriosis [30], and more robust evidence seems to be needed before depriving many patients of a safe, well tolerated, and affordable modality to relieve endometriosis-associated complaints.

Nevertheless, oestrogens do have a stimulatory effect on the metabolic activity of the endometrial mucosa, be it within or outside the uterine cavity. Therefore, when OCs are chosen as a modality to manage endometriosis, combinations with the lowest possible oestrogen dose should be chosen, such as those with only 15-20 μg of EE or 1.5 mg of 17 β-oestradiol (E2). Moreover, a very low oestrogen dose generally translates in a very limited amount of withdrawal bleeding secondary to minimal endometrial growth [33]. Indeed, menstrual flow is more abundant in women with

endometriosis than in those without the disease [34]. This may favour transtubal retrograde blood flow with increased likelihood of displacement of endometrial fragments in the pelvis and increased oxidative stress derived from saturation of the phagocytic capacity of pelvic macrophages toward refluxed erythrocytes [35]. Reducing monthly uterine blood flow by using very-low-dose OCs may translate in a substantial reduction also of retrograde flow and of the consequent pelvic oxidative stress that underpin the development of endometriosis, the inflammatory status, fibrosis generation, and pain insurgence [36]. Data from RCTs indicate that an OC containing 1.5 mg of 17 β-oestradiol and 2.5 mg of nomegestrol acetate (NOMAC) in a 24/4 formulation is associated with a prevalence of absent scheduled bleeding as high as 30% [37].

Finally, in addition to limiting endometriotic implant metabolism and minimizing monthly withdrawal bleeding, using OCs with a very low oestrogen content has the additional advantage of reducing the thrombotic risk. In fact, it has been repeatedly observed that the risk of both venous and arterial thrombosis is associated not only with the type of progestin included in OCs, but also with the oestrogen dose [38-41]. The use of decision aids may greatly help patients understand the actual increase in risk of thrombosis, as well as that of breast cancer, associated with prolonged OC use [42]. Detailed instructions for physicians on how to use the patient decision aid are freely available [43].

Two questions may here spontaneously arise: if reducing the amount of uterine bleeding is deemed important, why not systematically using OCs continuously instead of cyclically? Moreover, if a stimulatory effect of even a very low oestrogen dose cannot be ruled out, why not using progestogens as a first-line treatment anyway?

Regarding cyclic versus continuous OC use, the writing Committee of the guideline NG73 "Endometriosis: diagnosis and management", issued by the National Institute for Health and Care Excellence (NICE), stated "*The evidence showed that cyclic use of the combined oral contraceptive pill is effective, but the Committee were also aware that continuous and tricycling (where three packets are*

taken in a row, followed by a pill free interval) use of the pill are used in clinical practice, and although evidence was not available on these regimens in the literature, the Committee have found in their experience that these were also effective with limited adverse events" [44, page 236].

The advantage of continuous OC use is, as expected, a reduction of dysmenorrhoea compared with cyclic OC use. However, when pooling published data, no statistically significant differences were observed between the two treatment schedules in other pain symptoms, including deep dyspareunia, as well as in postoperative ovarian endometrioma recurrence rate [45].

On the other hand, using OC continuously increases the likelihood of erratic bleeding that, if not promptly dealt with via tailored cycling [17], may cause prolonged pain [3]. Moreover, in the absence of clear and substantial benefits of continuous over cyclic OC use, priority should be given to individual patient preference. Some women may prefer the absence of monthly uterine blood flows, whereas others may feel reassured by them, considering amenorrhoea a non-physiological condition despite in-depth information. Thus, cyclic OC use may increase therapeutic compliance in the latter patients.

More in general, women with endometriosis are psychologically vulnerable and may suffer from disease labelling [46-48]. The psychological implications of any medical intervention should be carefully weighed, especially in adolescent and young patients. In these latter cases, not only using a drug that is associated with fertility and not considered a "therapeutic" for a specific illness, but also using it in the same manner as healthy friends, schoolmates, or colleagues do, may be reassuring, thus reducing the psychological consequences of feeling diseased. However, research is needed in this regard. If OCs do not need to be always used continuously from the very beginning, a shift from cyclic to continuous OC use may be suggested specifically in those women who experience pain at withdrawal bleeding. It has been demonstrated that four out of five patients with persistent

dysmenorrhoea despite cyclic OC use, are satisfied two years after a shift to continuous use of the same low-dose OC [49].

Regarding the possible use of progestogens as first-line medical therapy in all women with endometriosis, in addition to the above psychological aspects, it should also be taken into account that treatments may be needed for years. Therefore, safety aspects are of utmost importance here. The progestogens most frequently studied in women with endometriosis are nor-ethisterone acetate (NETA), and dienogest (DNG) [29]. Indeed, both progestogens are associated with potential safety drawbacks, as the former may modify serum cholesterol lipoprotein distribution [21,50], whereas the latter may decrease bone mineral content [51-53]. Whether these variations in surrogate markers might translate into increased incidence of cardio-vascular events or pathologic fractures is currently unknown, also considering that this information would be available in the distant future, given the young age of women who have used or are using these progestogens. Most low-dose OCs do not alter serum lipid profile and do not decrease bone mineral content, and may be safely used for many years.

Moreover, as demonstrated by Harada *et al*. [17], the number of days of spotting are less and management of bleeding episodes is easier in women using an OC with tailored cycling (a 4-day tablet-free interval after three consecutive days of bleeding and/or spotting), than in those using dienogest. This may impact on health-related quality of life (HRQL) and patient satisfaction. More in general, OCs are the medication associated with the lowest risk of discontinuation due to adverse events, compared with progestogens alone (oral or intramuscular) and GnRH agonists with or without add-back therapy [44, page 203].

In addition, OCs are contraceptive by definition, whereas progestogens (and GnRH agonists and antagonists) are not. Consequently, despite the recognised anti-gonadotropin activity of progestogens and the anovulatory state generally associated with currently indicated daily doses, women should be formally advised to use barrier contraception, with potential consequences on long-term treatment

adherence. Indeed, part of endometriosis patients would have used OCs for contraceptive purposes anyway, independently of their disease. Therefore, the opportunity cost of prescribing OCs in these circumstances is nil, as using OCs as a first-line treatment for endometriosis in these women would not displace health-care resources compared with a high-cost progestogen such as dienogest.

Finally, Casper correctly maintains that the use of OCs for endometriosis is "off-label". Nonetheless, in several international guidelines issued by authoritative societies and professional organisations, OCs are included among the first-line medications to be used in symptomatic women [44,54-57]. In particular, recommendation #37 of the recent guideline NG73 "Endometriosis: diagnosis and management" issued by the NICE states "*Offer hormonal treatment (for example, the combined oral contraceptive pill or a progestogen) to women with suspected, confirmed or recurrent endometriosis*" [44]. At the same time, the Committee notes that "*At the time of publication (September 2017), none of these medicines had UK marketing authorisations for this indication. The General Medical Council (GMC), in its Prescribing guidance: prescribing unlicensed medicines, states that although doctors should usually prescribe licensed medicines for their licensed indications, they may prescribe unlicensed medicines when it is necessary to do so to meet the specific needs of the patient. […] It also states that when prescribing an unlicensed medicine is supported by authoritative clinical guidance (such as a NICE guideline), it may be sufficient to describe in general terms why the medicine is not licensed for the proposed use or patient population"* [44, page 238].

3. PROS AND CONS OF PROGESTOGENS

Several progestogens have been evaluated for the treatment of endometriosis using different modalities of administration, including the oral, intramuscular, subcutaneous, and intrauterine route [see, as reviews, 3 and 58]. Some characteristics of the mostly studied progestogens are shown in Table 2. Low-cost progestogens include medroxyprogesterone acetate (MAP), nor-ethisterone acetate (NETA),

levonorgestrel (LNG), and nomegestrol acetate (NOMAC). Dienogest (DNG) is the only high-cost progestogen currently licensed for the treatment of endometriosis.

Medroxyprogesterone (MAP) acetate has been used by the oral, intramuscular, and subcutaneous route. Despite findings from RCTs demonstrated a similar effect on pain of subcutaneous depot MAP (DMPA) and an intramuscular GnRH agonist [66,67], this progestogen has not gained vast popularity for endometriosis treatment. Erratic bleeding may be burdensome to manage and the anovulatory state may extend well behind the predicted three-month DMPA injection duration [68]. This may be problematic in case of insurgence of untoward effects or pregnancy desire. The cost of intramuscular 150 mg DMPA is very low. Findings on the use of MPA by the oral route are scanty. Due to the lack of direct comparisons with other progestogens, it is unclear whether the currently limited use of MPA for endometriosis is due to suboptimal efficacy or tolerability or other reasons.

Oral NETA, at the dose of 2.5 to 5 mg per day, has been repeatedly assessed in observational studies and a RCT [21, 69-76]. In particular, NETA was demonstrated effective in patients with deep dyspareunia and rectovaginal lesions [73,74]. The reduction in pain at intercourse was gradual but progressive during time [73]. The residual androgenic activity of NETA causes part of the untoward effects experienced by women using this drug, such as weight gain, acne, and seborrhoea. On the other hand, being partly metabolised to oestradiol [50,77], NETA does not cause hypo-oestrogenic effects and may be used for prolonged period without detrimental consequences on bone mineral content.

Levonorgestrel has been used via an intrauterine device releasing very-low progestin doses during a 5-year period (LNG-IUD). Thus, despite the high cost of the device, the resulting yearly cost progressively decreases with duration of use. The effect of the LNG-IUD has been assessed in five RCTs. When evaluated as a postoperative measure, LNG-IUD use was associated with a significantly lower dysmenorrhoea recurrence rate and higher HRQL compared with expectant management. No or limited effect was observed on deep dyspareunia [20,78]. Moreover, the effect of the LNG-IUD on

pelvic pain symptoms and HRQL was similar to that of a GnRH agonist [79], though patient satisfaction was lower [80].

Advantages of the LNG-IUD include avoidance of daily drug intake and contraception. However, ovulation is not inhibited, except for the first few months after insertion. This constitutes an important disadvantage, because it has been demonstrated that ovarian endometriomas originates from haemorrhagic corpora lutea [81], and that the post-operative endometrioma recurrence rate is about 10% per year for the first quinquennium of follow-up if ovulation is not suppressed [82,83]. The effect of the LNG-IUD in the prevention of postoperative endometrioma recurrence has been investigated in a RCT comparing two groups of 40 participants each allocated to receive the device or not after laparoscopic excision of endometriotic cysts [84]. The endometrioma recurrence rate did not differ significantly at 30 month-follow-up, being 25% in the LNG-IUD group and 37% in the control group. The authors concluded that long-term maintenance therapy using a LNG-IUD is not effective for preventing endometrioma recurrence. Therefore, the best candidate for the use of the LNG-IUD seems to be a parous woman with no further pregnancy desire and with dysmenorrhoea as her main or only pain symptom. The LNG-IUD may not have the same effect of other progestogens used systemically on deep dyspareunia.

Nomegestrol acetate is a progestogen used for the treatment of irregular uterine bleeding and dysmenorrhoea that has been tested in an animal model of endometriosis with favourable preliminary results [85]. Nomegestrol acetate has pharmacological and hormonal properties similar to dienogest [Table 2] and, when combined with oestradiol in an OC used cyclically (NOMAC, 2.5 mg; oestradiol, 1 mg], was frequently associated with absence of withdrawal bleeding [37]. This progestogen is inexpensive and well tolerated, but further studies are needed in women with symptomatic endometriosis.

Oral dienogest, at the daily dose of 2 mg, is the progestogen supported by the largest evidence originated from RCTs and cohort studies [86]. Dienogest was better than placebo and not inferior to a GnRH agonist in relieving endometriosis-associated pain [52,87-89]. Compared with NETA in a before and after study, it was similarly effective on pain, but better tolerated [75]. Despite this, its effectiveness was inferior to that of NETA because, due to the high drug cost, about one third of women declined its use.

Indeed, cost seems to be the only major drawback of this effective and well-tolerated progestogen, and the price appears difficult to justify, also considering that DNG is an old molecule synthesized in 1979 and investigated in the 80' by Jenapharm as a potential component of an OC. In Italy, the yearly cost of treatment with dienogest for endometriosis, 2 mg/day per os, is €730. In the same country, some monophasic OCs combining 30 μg of EE and 2 mg of dienogest per pill are marketed with the classic 21/7 schedule at the cost of €14-15 per pack. This means that the identical amount of dienogest (2 mg) is sold at a prize of about €0.7 when combined with EE and used for contraception, and of €2 when marketed as monotherapy for the treatment of endometriosis. This policy ultimately affects specifically women suffering from endometriosis.

Overall, progestogens are safe, can be used when OCs are not tolerated or contraindicated [27], and should be preferred in women with deep lesions, including colorectal nodules, or those with deep dyspareunia as their main complaint [3,74,90,91]. Abundant evidence originated from controlled studies consistently demonstrates that about two thirds of patients are satisfied with the use of progestogens for symptomatic endometriosis [Table 3]. Side effects associated with these drugs are frequent but seldom cause therapy abandonment. The main issue remains erratic bleeding that usually causes temporary pelvic pain relapse. In case of persistent bleeding, discontinuing treatment for some days was found effective in restoring amenorrhoea [20-22,75]. Comparative

effectiveness research is still needed in order to identify those molecules and/or those doses associated with the smallest risk of spotting and breakthrough bleeding.

4. CHOOSING GnRH AGONISTS AND ANTAGONISTS WISELY

Several studies were conducted in the past decades on the effect of GnRH agonists for the treatment of endometriosis. The profound hypo-oestrogenic state achieved during the use of these drugs explains their efficacy in terms of pelvic pain relief and, at the same time, their limited tolerability and safety. The combination of GnRH agonists with add-back therapy (generally a bone-sparing progestogen such as NETA or an oestrogen-progestogen hormone replacement therapy) limits vasomotor side effects and prevent bone resorption, but further increases costs.

In a RCT, the combination of leuprolide in a 12-week depot formulation plus NETA 5 mg/day as add-back therapy was not superior to an OC containing NETA 1 mg and EE 35 μg in reducing pain symptoms and improving psychological status and sexual function [96]. The cost of the 48-week treatment was $8,006 with leuprolide depot 11.25 mg plus NETA and $454 with the OC. According to the authors, to achieve a reduction in pain that was not significantly different from OC therapy, a 48-week treatment with leuprolide would cause an extra-cost of $7,552 per patient.

The results of two large phase 3 trials on the effect of elagolix, a non-peptide GnRH antagonist, for the treatment of endometriosis were recently published [97]. The GnRH antagonist at the oral daily dose of 150 or 400 mg was tested against a placebo. At 3-month evaluation the percentages of women who had a clinical response with respect to dysmenorrhoea were 43-46% and 72-76% in, respectively, the lower- and the higher-dose elagolix group, compared with 20-23% in the placebo group. This is expected, given that the frequency of dysmenorrhoea is inversely related to the frequency of amenorrhoea achieved by any hormonal drug. In fact, at the end of the 6-month study period, the percentage of participants experiencing amenorrhoea in the higher elagolix dose group in the two trials

varied from 47 to 66%. The differences with respect to non-menstrual pelvic pain were smaller, as the percentages of women who had a clinical response were 50% and 55-58% in, respectively, the lower- and the higher-dose elagolix group, compared with 37% in the placebo group.

The tolerability and safety profile of elagolix reflected the induced hypo-oestrogenic state. Hot flushes were the most frequent side effect, reported by 42-48% of women in the higher elagolix dose group. The mean percent bone mineral density (BMD) reduction at the lumbar spine observed at 6-month follow-up in women in the higher elagolix dose group varied from -2.49 to -2.61. A reduction of more than 5% in BMD at the lumbar spine was identified in 16-21% of women in that group. Elagolix did not completely suppress ovulation at either of the doses. Women were instructed to use two forms of non-hormonal contraception (e.g., condom plus spermicide) but, despite this, eight women using elagolix conceived. In one of the two trials, the unplanned pregnancy rate in women using elagolix was over 1% (6/497).

Elagolix has been assessed versus an active comparator in a single, phase 2 multicentre RCT [68]. A daily elagolix dose of 150 mg was not inferior to a depot three-monthly subcutaneous MPA formulation in terms of BMD variation and pain symptom reduction. It is interesting to note that the effect of cheap DMPA was similar to that of the novel experimental drug. Three out of 168 participants (1.8%) allocated to elagolix got pregnant compared with none in the DMPA group.

Elagolix induces a dose-dependent suppression of ovarian oestradiol production. Indeed, the induction of a hypo-oestrogenic milieu is a mainstay of hormonal treatment of endometriosis. The possibility of modulating the degree of induced hypo-oestrogenism has on one hand the advantage of limiting subjective and metabolic side effect, but on the other hand exposes to the risk of unplanned conception as ovulation is inconsistently inhibited. The teratogenic potential of GnRH antagonists is currently undefined, and it is unclear if women will have to perform serial urine tests during treatment in order to discriminate between drug- and pregnancy-induced amenorrhoea. The need for barrier

contraception may limit compliance and potentially increase the discontinuation rate. In addition, a clear dose-response effect on pain has been observed. This means that the degree of pain relief and the incidence and severity of untoward effects are positively correlated. In case higher elagolix doses have to be used to control severe pain symptoms, whether add-back therapies should be added to allow prolonged drug needs to be ascertained. Moreover, whether oral daily use is preferable to monthly or three-monthly intramuscular or subcutaneous depot injections is a subjective matter, and different patients may prefer either one or the other modality. GnRH antagonists avoid the flare-up phase, typical of GnRH agonists. However, injecting depot GnRH agonists during the mid-luteal phase prevents this potential drawback. Alternatively, using an oral progestogen for the first 7-10 days after the first GnRH agonist injection may avoid the initial gonadotropin surge.

Therefore, unless GnRH antagonists will be marketed at lower price than GnRH agonists, the advantages of the former compounds over the latter ones may reveal smaller than expected. Finally, further trials should be conducted in order to define the incremental benefit of GnRH agonists and antagonists, in terms of pain relief and patient satisfaction, over low-dose OCs or low-cost oral progestogens. The opportunity cost associated with the use of these molecules should also be evaluated. GnRH agonist may be used for a few months before starting progestogens [98,99], or intermittently during progestogen treatment in case of phases of pain relapse or prolonged bleeding and, combined with add-back therapy, in patients not responding to progestogens and unwilling to undergo surgery or in those at very high surgical risk.

5. SELECTIVE PROGESTERONE RECEPTOR MODULATORS FOR ENDOMETRIOSIS: A SAFE OPTION?

Selective progesterone receptor modulators (SPRMs) interact with progesterone receptors and should inhibit endometrial cell proliferation, and suppress uterine bleeding and synthesis of

prostaglandin [100]. In most reviews on medical treatment of endometriosis these drugs are included among the promising future compounds under investigation [6,8,101]. However, the evidence in support of SPRM for endometriosis appear limited. Kettel *et al*. [102] treated nine patients with mifepristone, 50 mg/day per os for six months and reported pain symptom relief in all of them without hypo-oestrogenic side effects. In one patient liver enzymes increased during treatment. The same drug at a lower dose (5 mg/day) improved pain in six out of the seven women studied, but caused irregular bleeding in four of them [103].

The effect of asoprisnil was assessed in a double-blind, placebo-controlled, RCT conducted on 130 participants [104]. The three doses studied (5, 10, 25 mg/day for 12 weeks) all reduced pain symptoms scores significantly and induced amenorrhoea in a dose dependent manner, with no effect on serum oestradiol levels [104]. However, the full report of this industry-sponsored trial does not seem to have been published in a peer-reviewed journal. Chwalisz *et al*. maintained that asoprisnil may provide a novel, tissue-selective approach to control endometriosis-related pain [101]. However, according to Tosti *et al*. [100] and Bedaiwy *et al*. [6], the trials on asoprisnil were stopped because of development of endometrial hyperplasia in some women. In our view, this is precisely the reason to be careful when hypothesizing the use of SPRM in women with endometriosis.

Most data regarding the long-debated endometrial effects of SPRM originates from the use of these drugs in women with uterine fibroids. According to some pathologists, the so called PAEC (progesterone receptor modulators associated endometrial changes) should not be considered as true cytological or structural atypia [105]. Despite this, the intermittent treatment modality indicated for ulipristal acetate (three months on/two months off) appears dictated specifically to prevent the endometrial effects of this class of drugs. In fact, SPRMs show anti-progestogenic activity that might lead to endometrial hyperplasia after prolonged, uninterrupted use. Thus, "*intermittent courses allow menstrual shedding of the endometrium and allow a complete menstrual cycle to take place between*

each treatment course, with physiological progesterone influence on the endometrium" [106; page 46]. In light of available histological evidence, Stewart highlights that "*long-term safety data are lacking to show that progesterone modulators do not increase the risk of endometrial abnormalities*" [107].

Hyperplasia of eutopic endometrium usually can be easily identified at transvaginal ultrasonography and, in this case, an aspiration biopsy can be readily obtained. The problem here is that hyperplastic modifications of endometrium at ectopic sites could go undetected. In addition, hyperplasia of intrauterine endometrium may not translate inevitably into increased mortality from endometrial adenocarcinoma, whereas the consequences may reveal dramatic in case atypical changes of ectopically implanted endometrium increase the incidence of “ovarian” endometrioid carcinomas. Indeed, it is currently accepted that most endometrioid and clear-cell ovarian adenocarcinomas originate from pelvic endometriosis [108]. Using a class of drug that may potentially induce endometrial hyperplasia precisely in women who are already at increased risk of developing endometrioid ovarian cancer [109] may raise safety concerns.

Although on theoretical grounds SPRMs may constitute another medical option for women with endometriosis, more data are needed concerning the long-term effect on the endometrium and overall drug safety before they can be suggested for prolonged use.

6. POSTOPERATIVE MEDICAL TREATMENT: ETHICS BEYOND EFFECTIVENESS

It has been repeatedly demonstrated that lesion and symptom recurrence after surgery is substantially higher in women who undergo postoperative expectant management compared with those who use postoperative medical treatment [83,110]. The recurrence rate in the former group of women is around 10% a year for the first five years of follow-up [82]. Data for longer periods of follow-up are limited. Endometrioma recurrence is detrimental for future fertility, and cyst excision is associated with reduced ovarian reserve [111,112]. The likelihood of conception after second-line surgery for recurrent ovarian

endometriomas is halved in comparison with that after first-line procedures for primary lesions [113]. Although this finding should be interpreted with caution because of obvious selection bias and possible confounding, measures aimed at reducing the risk of development of recurrent cysts after endometrioma excision seem of utmost importance in order to preserve the already compromised reproductive potential.

It has been observed that ovarian endometriomas developed from haemorrhagic corpora lutea [81]. Moreover, suppressing ovulation by using OCs dramatically reduced the postoperative endometrioma recurrence rate [114]. This finding has been consistently and repeatedly confirmed by independent groups using different study designs [45,115,116]. The effect size appears unusually large, as the reduction in risk is over 80%. In a systematic literature review and meta-analysis, a recurrent endometrioma was identified in 8% of "always" OC users and in 34% women who underwent expectant management (pooled odds ratio 0.12; 95% C.I., 0.05 to 0.29). The effect of OC is strictly related to duration of use, as the risk increases soon after drug discontinuation. In fact, when "always" users were compared with "ever" users, and "ever" with "never" users, the pooled odds ratio was, respectively, 0.21 (95% confidence interval 0.11-0.40) and 0.39 (95% confidence interval 0.23-0.66), thus supporting the validity of the overall result [115]. The modality of OC use (i.e., cyclic vs continuous) does not seem to influence the outcome [45,115].

In the recent guideline NG73, the NICE Committee maintained "*in view of the high rate of recurrence of endometriosis, affecting long-term quality of life for many women, improvement in long-term control of the condition was felt by the Committee to be clinically very important. The Committee were aware of the high rate of reoperation for endometriosis with associated risks of surgery and, as there was strong evidence to support this, considered that avoidance of repeat surgery by the use of long -term medical therapy would be beneficial. […] Based on the evidence, the beneficial effect of all hormonal therapies was similar (probably because all work through similar mechanisms) and so the*

Committee considered the adverse effects of the various treatments in making their recommendation, as there are known side effects with hormonal treatments that some women may wish to avoid. In general, the Committee considered that the combined oral contraceptive pill or long-acting reversible progestogen contraceptives were the most acceptable treatments" [44, page 303]. Accordingly, recommendation #46 of NICE guideline NG73 states "*After laparoscopic excision or ablation of endometriosis, consider hormonal treatment (with, for example, the combined oral contraceptive pill), to prolong the benefits of surgery and manage symptoms*" [44].

Given the abundant evidence on the beneficial effects of OCs and progestogens after surgery for endometriosis, and considering the unequivocal recommendations issued by authoritative organizations, not informing patients and not adequately explaining the advantages of prolonged postoperative hormonal treatment, and not suggesting it in women not seeking pregnancy immediately, may nowadays raise ethical perplexities. Clinical behaviours that deprive women of demonstrated, large benefits and that expose them to the risk of repeated surgical procedures and further reduction of the reproductive potential should be discouraged. The final decision is left to the patient.

7. A LESION-BASED, THREE-TIERED RISK STRATIFICATION SYSTEM

Variability in the response to medical treatments is observed among patients with symptomatic endometriosis. This may be due to several factors, including the different number of nerve fibres close to or within endometriotic lesions, various degrees of peripheral as well as central sensitisation (type and degree of excitatory neural response to stimuli and endogenous pain-modulatory processes), symptom characteristics (e.g., dysmenorrhoea vs deep dyspareunia), and psycho-social factors [3,46-48,117-119]. However, when trying to assess the phenotypic characteristics that are most predictive of individual variation in medical therapy outcomes, we suggest to give adequate weight to the type of lesion present [3]. We have proposed a differentiated approach based on what is known about the

492 natural course of different forms, as well as on the associated risk of clinical, anatomical, and surgical
493 complications.

494 a. Low-risk lesions

495 According to the three-tiered risk stratification system [3], superficial peritoneal implants are
496 considered "low-risk" lesions. In fact, based on the findings of several RCTs, superficial peritoneal
497 lesions evaluated at follow-up laparoscopy progressed in only one third of women allocated to placebo
498 or no treatment, and remained stable or regressed in the remaining two thirds [120,121]. Thus, the
499 natural history of early peritoneal lesions appears highly variable. Although these limited lesions can be
500 removed easily at laparoscopy and with a very low risk of surgical complication, they also usually
501 respond well to OCs [3], which create a predominantly progestogenic milieu and may reduce or abolish
502 retrograde menstruation [36]. The former action exerts an anti-inflammatory effect by inhibiting
503 endometrial cell metabolism and favouring apoptosis [122,123]. In addition, early peritoneal implants
504 alone are mostly found in young women [124] who, as previously considered, may be better candidates
505 for treatment with OCs rather than with progestogen monotherapies.

506 b. Medium-risk lesions

507 Ovarian endometriomas may be categorised as "medium-risk" lesions for several reasons,
508 including the demonstrated fertility implications. Their excision is generally not particularly difficult
509 and the risk of immediate surgical complications is low. However, a local gonadal damage may result,
510 with potential worsening instead of improvement of the likelihood of conception. The therapeutic goal
511 in women not seeking pregnancy is achieving anovulation, as it has been demonstrated that ovulation is
512 the main pathogenic mechanism for the development or progression of endometriomas [81]. Thus, low-
513 dose OCs, used cyclically or continuously, may be indicated in symptomatic women with typical
514 unilocular endometriomas not wanting children, either as an alternative to first-line surgery or to avoid
515 second-line procedures for cyst recurrence. There is no consensus on the maximum cyst diameter

above which surgery is deemed mandatory. Unfortunately, most guidelines on endometriosis are inconsistent or somewhat vague, as a cut-off of 3 cm, 4 cm, or no cut-off have all been indicated [55, 56,125,126].

According to the recent ACOG Practice Bullettin #174 on Evaluation and Management of Adnexal Masses [126], "*Although endometriomas of 5 cm or more have been associated with lower ovarian follicle density, several studies have found similar fertility outcomes among women with or without endometriomas who underwent assisted reproduction. Thus, asymptomatic endometriomas do not require intervention for infertility*". Moreover, according to the First International Consensus Report on Adnexal Masses [127], unilocular endometriomas should be categorized among the "almost certainly benign" lesions. Endometriomas that have a "classic appearance" can benefit from conservative management, often with serial follow-up sonography. The members of the panel stated "*endometriomas have a low association with malignancy, typically less than 0.8%. Therefore, […] it is prudent to follow these [cysts] over time to assess for morphologic changes, in particular, looking for lesions that show rapid growth or develop solid vascular elements. There is an increased risk of malignant transformation in larger endometriomas (>9 cm) and older women (>45 years). Overall, there is no definitive data to indicate that early surgical treatment of endometriotic implants is associated with a reduced risk of malignancy*".

The above authoritative positions appear aligned with the proposal of Muzii *et al*. to initially withhold surgery and verify whether OCs relieve pain in women with endometriomas smaller than 5 cm, and to schedule "*serial ultrasound scans, preferably after 3 to 6months if the cyst is diagnosed for the first time, and then yearly if there is no fast growth or change in sonographic features in the short-term period*" [45].

c. <u>High-risk lesions</u>

Deep fibrotic nodules and plaques infiltrating the rectosigmoid, vagina, parametria, and bladder constitute the really severe disease in terms of frequency and degree of pain symptoms, technical difficulties at excision, and risk of intra- and post-operative complications. In case of lesion progression, ureteral stenosis may also ensue. Progestogens, instead of OCs, should generally be considered the first-line medical treatment for these “high-risk” lesions. In fact, given the severity of the condition, it seems wise to avoid even a limited oestrogenic stimulus despite the potential drawbacks in terms of serum lipid pattern or bone mineral density variation. Progesterone receptors have been identified in all the above lesion types [128] and the findings of several studies consistently confirmed that about two-thirds of patients with deep endometriosis respond favourably to progestogen treatment [3,90,91]. In addition, OCs usually control well pain at menstruation, but less so pain at intercourse [129]. Progestogens have been demonstrated effective in improving deep dyspareunia associated with deep lesions of the posterior compartment [71,73,74,130,131]. Moreover, the intravaginal use of progestogens should be investigated in patients with the “deep lesion-deep dyspareunia” anatomic-clinical phenotype [132-134].

8. A SYMPTOM BASED, STEPPED-CARE APPROACH

According to the guidelines on endometriosis management issued by major international scientific societies, different medications have substantially similar effects in terms of pain relief, but have different safety and tolerability profiles and sometimes very different costs. Consequently, safe, well-tolerated, and inexpensive OCs and progestogens are suggested as first-line treatments in symptomatic patients [44,54-57]. Based on a systematic critical appraisal of the evidence, the NICE Committee confirmed two fundamental principles: 1) "*all treatments led to a clinically significant reduction in pain on the VAS when compared to placebo. The magnitude of this treatment effect was similar for all treatments, suggesting that there was little difference between them in their capacity to reduce pain. No*

563 *other significant differences were found between the hormonal treatments*" [44, page 198]; and 2) "*it is*
564 *known that there are a cluster of extremely cheap hormonal treatments (including the combined oral*
565 *contraceptive pill) and a cluster of extremely high-cost treatments including dienogest and GnRHas*"
566 [44, page 230].

567 Any long-term therapeutic strategy for women with endometriosis-associated pain should be
568 based on these two concepts. However, about one third of patients will not respond to OCs or
569 progestogens owing to the subjective variability to drugs' effect. Regrettably, the reliable identification
570 before starting treatment of which women will respond successfully to which drugs, appears currently
571 problematic. In this condition, it seems reasonable, practical, and cost-effective to use the safest, better
572 tolerated, and inexpensive medications first, stepping up to less safe or less tolerated or more costly
573 drugs only in case the former ones are ineffective, not tolerated or contraindicated [3, 91]. This
574 stepped-care approach is indicated in women who are not seeking pregnancy, who prefer medical
575 rather than surgical treatment, and who do not have absolute surgical indications, such as sub-occlusive
576 bowel stenosis, obstructive uropathy, endometriomas over 5 cm in diameter, and adnexal masses of
577 doubtful ultrasonographic characteristics.

578 According to this model, low-dose OCs should be used cyclically in women with peritoneal and
579 ovarian endometriosis, stepping up to continuous use with tailored cycling only in those women with
580 persistent dysmenorrhoea despite cyclic OC use. In case of inefficacy on pain during OC use, patients
581 should step up to a low-cost progestogen such as NETA. Independently of pain relief, women should
582 step up to progestogens also in case of intolerance to OC (e.g., migraine). Starting directly with a low-
583 cost progestogen should be considered in patients with deep lesions or with deep dyspareunia as their
584 main complaint, as well as in those with contraindications to OCs. Stepping up from a low-cost to a
585 high-cost progestogen (i.e., DNG) should be advised only in case of intolerance to NETA, as it has
586 been demonstrated the DNG, being devoid of androgenic activity, is better tolerated than NETA [75].

Shifting from NETA to DNG for inefficacy on pain is not supported by sufficient evidence. In case of inefficacy of or intolerance to progestogens, patients may step up to GnRH agonists or antagonists, provided they are thoroughly informed on the aims, pros and cons of this option. Informed patients should be invited to consider also the surgical alternative. This is particularly true the more a woman advances through the stepwise algorithm, as careful evaluation of potential benefits, potential harms, and costs of medical and surgical options may tip the balance in favour of the latter choice, especially when the procedure is presumably at low risk.

According to Taylor, "*the goal of endometriosis therapy should always be absence of pain; if this end point is not achieved with oral contraceptives, the patient should be offered more definitive therapy. Many patients fail to adequately respond to oral contraceptives while others develop progestin resistance with disease progression despite using a progestin based therapy* […] *The realization that all therapies have different efficacy and the availability of new endometriosis drugs will allow more rapid progression to definitive therapy*" [16]. In this regard, the adoption of the above stepwise approach allows the identification of that third of patients that would benefit from the use of drugs associated with suboptimal safety or tolerability profiles or high costs. In fact, demonstration of the efficacy of dienogest and GnRH agonists and antagonists in exploratory RCTs should not translate in systematic prescription of these drugs to all women with symptomatic endometriosis in routine practice. This is particularly important considering that novel medications are generally more costly than existing ones and that obtaining reasonably priced treatments for our patients is difficult. Until robust data will demonstrate that new and costly drugs are curative and not just symptomatic, and therefore can modify the natural history of endometriosis, the stepped-care approach may prevent the needless prescription of those medications to at least two thirds of patients who do not need them.

9. TAYLORING MEDICAL THERAPY TO PROVIDE MINIMALLY DISRUPTIVE ENDOMETRIOSIS MANAGEMENT

Women with severely symptomatic endometriosis, in addition to pain, usually experience major worsening in health-related quality of life, psychological status, sexual functioning and marital relationship, social life, and school or work productivity [46-48,135-138]. This is the "burden of illness". The International Minimally Disruptive Medicine Workgroup considers that patients with chronic disorders also experience the so-called "burden of treatment" [139] that, in the case of endometriosis, includes taking medications, managing side effects, attending gynaecological visits, performing imaging investigations and repeated blood tests, undergoing surgical procedures, self-monitoring, lifestyle changes, administrative task to access and coordinate care, full or partial payment of treatments, and other hidden costs.

The combined effect of the burden of illness and the burden of treatment may result disruptive for the life of women with endometriosis and their families. Awareness of the additive impact of these two factors on individual capacity to cope with the disease seems limited in the endometriosis scientific community. Indeed, taking into account the burden of treatment when selecting the type of medications to be used, may improve outcomes [139]. Planning long periods of medical therapy with OCs or progestogens has the potential to decrease greatly not only the burden of illness, but also the burden of treatment. Allowing women with endometriosis to live a life as normal as possible appears an important comprehensive goal. Substantially limiting lesion and symptom relapse for years, may greatly reduce the frequency of visits, tests, and procedures, as well as the economic impact of care. This may also aid in improving the degree of anxiety and depression of women, preventing in part the consequences of disease labelling [140]. This is precisely what can be obtained in about two thirds of patients with low-dose OCs and low-cost progestogens [3,9]. According to the International Minimally Disruptive Medicine Workgroup, "*the value of care for patients should reflect the health outcomes*

achieved and the degree of burden that patients and their caregivers must bear to achieve those outcomes" [139].

A minimally disruptive approach also seems aligned with the position of the Practice Committee of the American Society for Reproductive Medicine that indicates "*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*" [56]. The same position is held in the NICE guideline NG73, when it states "*the Committee agreed with the evidence and further highlighted that the benefit from hormonal treatments was due to their efficacy in stopping or reducing periods. There was a desire from the Committee to reduce the number of repeated operations for women with endometriosis, further supporting maintenance of pain relief using hormonal treatments wherever possible*". [44, page 236]

However, LeFevre warns that "*every dollar spent on health care is someone's income stream. In any move to do less, there will be efforts from those who lose income to push back*" [141].

10. PROSPECTUS: MEASURING CLINICAL EFFECTIVENESS, COST-EFFECTIVENESS, AND OPPORTUNITY COST

Also in the endometriosis field, the technology tsunami is paving the way for costly interventions with still uncertain benefits and potential harms. Blood tests could greatly expand the boundaries of endometriosis diagnosis, blurring the limits between diseased and non-diseased populations. Genetic testing could be offered directly to consumers, transforming a potentially useful tool for assessing risk (and not for definite diagnosis) into an uncontrolled mean for home-made and misled screening of asymptomatic women. Robotic surgery is gradually replacing traditional laparoscopy despite the repeatedly demonstrated disadvantages in terms of costs and overall operating room time. In the same vein, new and presumably costly drugs are on the horizon. It is currently unclear to what extent, beyond

widespread enthusiasm, their entry into the market will modify the natural history of endometriosis and health-related quality of life of patients.

There is a dearth of comparative effectiveness research also in the field of medical treatment for endometriosis. Pragmatic trials conducted by independent investigators, and including a low-dose OC or a low-cost progestogen as a comparator, are needed to assess the actual *incremental* benefit of new drugs over currently used ones. Only the determination of that incremental benefit (if any) will allow us to understand if using novel medications is worth the extra cost. According to Dworkin *et al*., "*The cost of a treatment is another important source of patient non-adherence with treatment, of course, and is also important in considerations of cost-effectiveness*" [15].

Patients may not benefit directly from explanatory trials, conducted for registration purposes, that include a placebo as a comparator, because defining the size of the effect over a placebo does not answer a meaningful question that matters to them. The same is partly true when GnRH agonists are used as comparators, because most patients do not use these drugs as their standard treatment. In this regard, we challenge the popular tenet suggesting that surgical devices are often introduced into practice without adequate comparative experimentation, whereas new drugs are subject to rigorous testing before entering the market. In the endometriosis field this may not be always true, as formally faultless methodology and clinical meaningfulness are not necessarily synonymous.

The thresholds for cost-effectiveness that should be accepted when considering the opportunity cost of using dienogest and GnRH agonists and antagonists extensively in women with severe pain symptoms, are currently scarcely or not yet defined. The combination of high thresholds combined with high frequency of the condition implies that costly medications for symptomatic endometriosis would have a substantial impact on health care system budgets and, therefore, a large opportunity cost. Evaluation of opportunity cost should be included in analyses of economic evaluation of cost of implementation of every novel medical intervention for patients with endometriosis, be it for screening,

682 diagnosis, medical therapy, or surgical treatment. When novel drugs show a demonstrated large
683 incremental benefit, in terms of pain relief and health-related quality of life, compared to OCs and
684 progestogens, the use of additional resources and the associated opportunity cost may be justified.
685 However, from a justice perspective, the magnitude of the effect, as well as the evidence on which the
686 magnitude has been determined, should be carefully scrutinized [142,143]. If later studies conducted by
687 independent groups will demonstrate lower than expected cost-effectiveness for novel drugs for
688 endometriosis, then the a-priory accepted threshold might be exceeded with waste of money [144] and
689 implications regarding the ethical principle of equitable distribution of finite health-care resources, as
690 other patients (in and outside the endometriosis field) are potentially deprived of beneficial medical
691 interventions (or care at large), although their needs might be similarly or even more pressing [145,
692 146].

693 We may not be expert of health-care economic analysis. Still, we have the moral duty of
694 reasoning on individual patient conditions in order to try to achieve the best possible outcome for that
695 woman, at the same time avoiding the needless displacement of excessive resources, thus respecting the
696 entire population of similar patients. It is a fact that low-dose OCs and low-cost progestogens allow
697 adequate control of endometriosis symptoms and lesions in about two thirds of patients, including those
698 with deep infiltrating forms. One third of women will need second-line medical therapies or surgery,
699 and future genetic and pharmacological research should focus specifically on this population subgroup
700 at worse prognosis with the objective of improving outcomes that matter to these patients.

701

SUMMARY

Available medical treatments for symptomatic endometriosis act by modifying the hormonal milieu with the goal of inducing atrophy of the ectopic endometrium. This is generally achieved by inhibiting ovulation, reducing serum oestradiol levels, and suppressing uterine blood flows. To this aim, several drugs can be used, with a similar magnitude of effect, in term of pain relief, independently of the mechanism of action. Conversely, safety, tolerability, and cost differ. This has important practical implications, given that prolonged periods of treatment should be planned in symptomatic women not seeking pregnancy. In fact, all hormonal medications used for endometriosis are symptomatic and not curative. Moreover, hypothesising a selective cytoreductive effect on eutopic, but not eutopic endometrium appears currently unfounded. Medications for endometriosis can be categorised into low-cost drugs, including OCs and most progestogens, and high cost drugs, including dienogest and GnRH agonists. As the individual response to different drugs is variable, a stepwise approach is suggested, starting with OCs or low-cost progestogens, and stepping up to high-cost drugs only in case of inefficacy or intolerance. According to the available evidence, about two thirds of symptomatic patients can be managed successfully with the former group of compounds, whereas the remaining third needs high-cost compounds or surgery. Oral contraceptives may be used in women with dysmenorrhoea as their main complaint, and when only superficial peritoneal implants or ovarian endometriomas < 5 cm are present, while progestogens should be preferred in women with severe deep dyspareunia and when deep infiltrating lesions are identified.

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Practice Points:

- Available hormonal compounds for endometriosis are symptomatic and not curative
- As symptom recurrence is the rule at drug discontinuation, long periods of treatments should be planned in women not seeking pregnancy
- Medications for endometriosis have different safety and tolerability profiles and costs, but do not differ in terms of magnitude of the effect on pain
- Low-dose oral contraceptives and low-cost progestogens should be considered first-line medications
- High-cost compounds should be used only in women not responding or not tolerating first-line medications

Research Agenda:

- Non-teratogenic compounds that relieve pain without suppressing ovulation would allow treating also women seeking conception
- Only drugs with a selective cytoreductive effect on ectopic but not eutopic endometrium would consent the modification of the natural history of endometriosis without compromising fertility
- Epidemiological data are needed to define the potential long-term effects of prolonged use of different medications for endometriosis
- Pragmatic trials including low-dose oral contraceptives or low-cost progestogens as active comparators are needed to define the incremental benefit of novel experimental drugs
- Comparative effectiveness research on medications for endometriosis should include aspects of healthcare economic analysis such as quantification of opportunity costs

763 REFERENCES

764 [1] Vercellini P, Crosignani PG, Somigliana E, Berlanda N, Barbara G, Fedele L. Medical treatment for
765 rectovaginal endometriosis: what is the evidence? Hum Reprod. 2009;24:2504-14.

766 [2] Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. Cochrane Database Syst
767 Rev. 2014 Mar 10;(3):CD009590.

768 [3] Vercellini P, Buggio L, Berlanda N, Barbara G, Somigliana E, Bosari S. Estrogen-progestins and
769 progestins for the management of endometriosis. Fertil Steril. 2016;106:1552-1571.e2.

770 [4] Becker CM, Gattrell WT, Gude K, Singh SS. Reevaluating response and failure of medical
771 treatment of endometriosis: a systematic review. Fertil Steril. 2017;108:125-136.

772 [5] Leone Roberti Maggiore U, Ferrero S. An overview of early drug development for endometriosis.
773 Expert Opin Investig Drugs. 2016;25:227-47.

774 [6] Bedaiwy MA, Alfaraj S, Yong P, Casper R. New developments in the medical treatment of
775 endometriosis. Fertil Steril. 2017;107:555-65.

776 [7] Goenka L, George M, Sen M. A peek into the drug development scenario of endometriosis - A
777 systematic review. Biomed Pharmacother. 2017;90:575-585.

778 [8] Rafique S, Decherney AH. Medical Management of Endometriosis. Clin Obstet Gynecol.
779 2017;60:485-496.

780 [9] Vercellini P, Crosignani P, Somigliana E, Viganò P, Frattaruolo MP, Fedele L. ”Waiting for
781 Godot”: a commonsense approach to the medical treatment of endometriosis. Hum Reprod. 2011;26:3-
782 13.

***[10] Guo SW, Evers JL. Lack of transparency of clinical trials on endometriosis. Obstet Gynecol. 2013;121:1281-90.**

[11] Guo SW. An overview of the current status of clinical trials on endometriosis: issues and concerns. Fertil Steril. 2014;101:183-190.e4.

[12] Maret-Ouda J, Wahlin K, El-Serag HB, Lagergren J. Association Between Laparoscopic Antireflux Surgery and Recurrence of Gastroesophageal Reflux. JAMA. 2017;318:939-946.

[13] Spechler SJ. The Durability of Antireflux Surgery. JAMA. 2017;318:913-915.

[14] Garg SK, Gurusamy KS. Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev. 2015 Nov 5;(11):CD003243.

***[15] Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009;146:238-44.**

[16] Taylor HS. Clinical diagnosis of endometriosis and optimal medical therapy. Fertil Steril. 2017 Sep 30. doi: 10.1016/j.fertnstert.2017.09.005. In press.

***[17] Harada T, Kosaka S, Elliesen J, Yasuda M, Ito M, Momoeda M. Ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen for the management of endometriosis-associated pelvic pain: a randomized controlled trial. Fertil Steril. 2017 Sep 11. doi: 10.1016/j.fertnstert.2017.07.1165. In press.**

[18] Vercellini P, De Giorgi O, Oldani S, Cortesi I, Panazza S, Crosignani PG. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for

804 long-term treatment of pelvic pain associated with endometriosis. Am J Obstet Gynecol. 1996;175:396-
805 401.

806 [19] Vercellini P, de Giorgi O, Mosconi P, Stellato G, Vicentini S, Crosignani PG. Cyproterone acetate
807 versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after
808 conservative surgery for symptomatic endometriosis. Fertil Steril 2002;77:52–61.

809 [20] Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of
810 an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a
811 cyclic pill regimen. Fertil Steril. 2003;80:560-3.

812 [21] Vercellini P, Pietropaolo G, De Giorgi O, Pasin R, Chiodini A, Crosignani PG. Treatment of
813 symptomatic rectovaginal endometriosis with an estrogen-progestogen combination versus low-dose
814 norethindrone acetate. Fertil Steril 2005;84:1375-87

815 [22] Vercellini P, Barbara G, Somigliana E, Bianchi S, Abbiati A, Fedele L. Comparison of
816 contraceptive ring and patch for the treatment of symptomatic endometriosis. Fertil Steril
817 2010;93:2150–61.

818 [23] Cheewadhanaraks S, Choksuchat C, Dhanaworavibul K, Liabsuetrakul T. Postoperative depot
819 medroxyprogesterone acetate versus continuous oral contraceptive pills in the treatment of
820 endometriosis-associated pain: a randomized comparative trial. Gynecol Obstet Invest 2012;74:151–6.

821 [24] Ferrari S, Persico P, DI Puppo F, Vigano P, Tandoi I, Garavaglia E, et al. Continuous low-dose
822 oral contraceptive in the treatment of colorectal endometriosis evaluated by rectal endoscopic
823 ultrasonography. Acta Obstet Gynecol Scand. 2012;91:699-703.

824 [25] Morelli M, Sacchinelli A, Venturella R, Mocciaro R, Zullo F. Postoperative administration of
825 dienogest plus estradiol valerate versus levonorgestrel releasing intrauterine device for prevention of
826 pain relapse and disease recurrence in endometriosis patients. J Obstet Gynaecol Res 2013;39:985–90.

827 [26] Leone Roberti Maggiore U, Remorgida V, Scala C, Tafi E, Venturini PL, Ferrero S. Desogestrel-
828 only contraceptive pill versus sequential contraceptive vaginal ring in the treatment of rectovaginal
829 endometriosis infiltrating the rectum: a prospective open-label comparative study. Acta Obstet Gynecol
830 Scand 2014;93:239–47.

831 [27] Morotti M, Remorgida V, Venturini PL, Ferrero S. Progestogen-only contraceptive pill compared
832 with combined oral contraceptive in the treatment of pain symptoms caused by endometriosis in
833 patients with migraine without aura. Eur J Obstet Gynecol Reprod Biol 2014;179:63–8.

834 [28] Revised American Fertility Society classification of endometriosis: 1985. American Fertility
835 Society. Fertil Steril 1985;43:351–2.

836 [29] Casper RF. Progestin-only pills may be a better first-line treatment for endometriosis than
837 combined estrogen-progestin contraceptive pills. Fertil Steril. 2017;107:533-536.

838 [30] Vercellini P, Eskenazi B, Consonni D, Somigliana E, Parazzini F, Abbiati A, et al. Oral
839 contraceptives and risk of endometriosis: a systematic review and meta-analysis. Hum Reprod Update
840 2011;17:159–70.

841 [31] Chapron C, Souza C, Borghese B, Lafay-Pillet MC, Santulli P, Bijaoui G, et al. Oral
842 contraceptives and endometriosis: the past use of oral contraceptives for treating severe primary
843 dysmenorrhea is associated with endometriosis, especially deep infiltrating endometriosis. Hum Reprod
844 2011;26:2028–35.

845 [32] Somigliana E, Vercellini P, Vigano P, Abbiati A, Benaglia L, Fedele L. Endometriosis and
846 estroprogestins: the chicken or the egg causality dilemma. Fertil Steril. 2011;95:431-3.

847 [33] Matteson KA, Rahn DD, Wheeler TL 2nd, Casiano E, Siddiqui NY, Harvie HS, et al. Nonsurgical
848 management of heavy menstrual bleeding: a systematic review. Obstet Gynecol 2013;121:632-43.

849 [34] Vercellini P, De Giorgi O, Aimi G, Panazza S, Uglietti A, Crosignani PG. Menstrual
850 characteristics in women with and without endometriosis. Obstet Gynecol. 1997;90:264-8.

851 [35] Donnez J, Binda MM, Donnez O, Dolmans MM. Oxidative stress in the pelvic cavity and its role
852 in the pathogenesis of endometriosis. Fertil Steril 2016;106:1011–7.

853 [36] Donnez J, Taylor RN, Taylor HS. Partial suppression of estradiol: a new strategy in endometriosis
854 management? Fertil Steril. 2017;107:568-70.

855 [37] Mansour D, Westhoff C, Kher U, Korver T. Pooled analysis of two randomized, open-label studies
856 comparing the effects of nomegestrol acetate/17β-estradiol and drospirenone/ethinyl estradiol on
857 bleeding patterns in healthy women. Contraception. 2017;95:390-7.

858 [38] Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous
859 thromboembolism from use of oral contraceptives containing different progestogens and oestrogen
860 doses: Danish cohort study, 2001–9. BMJ 2011;343:d6423

861 [39] de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T,
862 et al. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev 2014:CD010813

863 [40] Roach RE, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral
864 contraceptives: the risk of myocardial infarction and ischemic stroke. Cochrane Database Syst Rev
865 2015:CD011054.

866 [41] Weill A, Dalichampt M, Raguideau F, Ricordeau P, Blotière PO, Rudant J, et al. Low dose
867 oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial
868 infarction in five million French women: cohort study. BMJ 2016;353:i2002.

869 [42] National Institute for Health and Care Excellence. Patient decision aid. Hormone treatment for
870 endometriosis symptoms – what are my options? September 2017.
871 https://www.nice.org.uk/guidance/ng73/resources/patient-decision-aid-hormone-treatment-for-
872 endometriosis-symptoms-what-are-my-options-pdf-4595573197 [Accessed 7 November 2017].

873 [43] National Institute for Health and Care Excellence. Putting NICE guidance into practice. Hormone
874 therapy for endometriosis symptoms: patient decision aid user guide for healthcare professionals.
875 September 2017. https://www.nice.org.uk/guidance/ng73/resources/patient-decision-aid-user-guide-
876 hormone-therapy-for-endometriosis-symptoms-patient-decision-aid-user-guide-for-healthcare-
877 professionals-pdf-4595573198 [Accessed 7 November 2017].

878 ***[44] National Institute for Health and Care Excellence. Endometriosis: diagnosis and**
879 **management. NICE guideline NG73. September 2017.**
880 **https://www.nice.org.uk/guidance/ng73/evidence/full-guideline-pdf-4550371315 [Accessed 3**
881 **November 2017].**

882 [45] Muzii L, di Tucci C, Achilli C, di Donato V, Musella A, Palaia I, et al. Continuous versus cyclic
883 oral contraceptives after laparoscopic excision of ovarian endometriomas: a systematic review and
884 meta-analysis. Am J Obstet Gynecol 2016;214:203–11.

885 [46] Facchin F, Barbara G, Saita E, Erzegovesi S, Martoni RM, Vercellini P. Personality in women
886 with endometriosis: temperament and character dimensions and pelvic pain. Hum Reprod.
887 2016;31:1515-21.

888 [47] Facchin F, Barbara G, Dridi D, Alberico D, Buggio L, Somigliana E, Saita E, Vercellini P. Mental
889 health in women with endometriosis: searching for predictors of psychological distress. Hum Reprod.
890 2017;32:1855-1861.

891 [48] Facchin F, Saita E, Barbara G, Dridi D, Vercellini P. "Free butterflies will come out of these deep
892 wounds": A grounded theory of how endometriosis affects women's psychological health. J Health
893 Psychol. 2017. doi: 10.1177/1359105316688952. In press.

894 [49] Vercellini P, Frontino G, De Giorgi O, Aimi G, Zaina B, Crosignani PG. Comparison of a
895 levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery
896 for symptomatic endometriosis: a pilot study. Fertil Steril. 2003;80:305-9.

897 [50] Chwalisz K, Surrey E, Stanczyk FZ. The hormonal profile of norethindrone acetate: rationale for
898 add-back therapy with gonadotropin-releasing hormone agonists in women with endometriosis. Reprod
899 Sci 2012;19:563–71.

900 [51] Momoeda M, Harada T, Terakawa N, Aso T, Fukunaga M, Hagino H, et al. Long-term use of
901 dienogest for the treatment of endometriosis. J Obstet Gynaecol Res. 2009;35:1069-76.

902 [52] Strowitzki T, Marr J, Gerlinger C, Faustmann T, Seitz C. Dienogest is as effective as leuprolide
903 acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-
904 label trial. Hum Reprod 2010;25:633–41.

905 [53] Lee DY, Lee JY, Seo JW, et al. Gonadotropin-releasing hormone agonist with add-back treatment
906 is as effective and tolerable as dienogest in preventing pain recurrence after laparoscopic surgery for
907 endometriosis. Arch Gynecol Obstet. 2016;294:1257–63.

908 [54] American College of Obstetricians and Gynecologists. Management of endometriosis. ACOG
909 practice bulletin no. 114. Obstet Gynecol 2010;116:223-36.

910 [55] Leyland N, Casper R, Laberge P, Singh SS, Society of Obstetricians and Gynaecologists of
911 Canada. Endometriosis: diagnosis and management. J Obstet Gynecol Can 2010;32:S1–32.

912 [56] Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain
913 associated with endometriosis: a committee opinion. Fertil Steril 2014;101:927–35.

914 [57] Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, de Bie B, et al. ESHRE
915 guideline: management of women with endometriosis. Hum Reprod 2014;29:400–12.

916 [58] Buggio L, Somigliana E, Barbara G, Frattaruolo MP, Vercellini P. Oral and depot progestin
917 therapy for endometriosis: towards a personalized medicine. Expert Opin Pharmacother. 2017;18:1569-
918 1581.

919 [59] Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, et al.
920 Classification and pharmacology of progestins. Maturitas 2003;46 (Suppl. 1):S7–16.

921 [60] Sitruk-Ware R. Pharmacological profile of progestins. Maturitas 2004;47: 277–83.

922 [61] Sitruk-Ware. New progestagens for contraceptive use. Human Reproduction Update 2006, Vol.12,
923 No.2 pp. 169–178.

924 [62] Lello S. Nomegestrol Acetate. Pharmacology, Safety Profile and Therapeutic Efficacy. Drugs
925 2010;70:541-59.

926 [63] Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr. Progestogens Used in Postmenopausal
927 Hormone Therapy: Differences in Their Pharmacological Properties, Intracellular Actions, and Clinical
928 Effects. Endocrine Reviews 2013;34:171–208.

929 [64] Hapgood JP, Africander D, Louw R, Ray RM, Rohwer JM. Potency of progestogens used in
930 hormonal therapy: Toward understanding differential actions. Journal of Steroid Biochemistry &
931 Molecular Biology 2014;142:39–47.

932 [65] Schindler AE. Pharmacology of Progestogens. In: Carp H. (eds) Progestogens in Obstetrics and
933 Gynecology 2015. Springer, Cham

934 [66] Schlaff WD, Carson SA, Luciano A, Ross D, Bergqvist A. Subcutaneous injection of depot
935 medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-
936 associated pain. Fertil Steril 2006;85:314–25.

937 [67] Crosignani PG, Luciano A, Ray A, Bergqvist A. Subcutaneous depot medroxyprogesterone acetate
938 versus leuprolide acetate in the treatment of endometriosis-associated pain. Hum Reprod 2006;21:248–
939 56.

940 [68] Carr B, Dmowski WP, O'Brien C, Jiang P, Burke J, Jimenez R, et al. Elagolix, an oral GnRH
941 antagonist, versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis:
942 effects on bone mineral density. Reprod Sci 2014;21:1341–51.

943 [69] Muneyyirci-Delale O, Karacan M. Effect of norethindrone acetate in the treatment of symptomatic
944 endometriosis. Int J Fertil Womens Med. 1998;43:24–27.

945 [70] Ferrero S, Camerini G, Seracchioli R, Ragni N, Venturini PL, Remorgida V. Letrozole combined
946 with norethisterone acetate compared with Norethisterone acetate alone in the treatment of pain
947 symptoms caused by endometriosis. Hum Reprod 2009;24:3033–41.

948 [71] Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Remorgida V. Norethisterone acetate in
949 the treatment of colorectal endometriosis: a pilot study. Hum Reprod. 2010;25:94-100.

950 [72] Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Seracchioli R, et al. Letrozole and
951 norethisterone acetate in colorectal endometriosis. Eur J Obstet Gynecol Reprod Biol. 2010;150:199-
952 202.

953 [73] Vercellini P, Somigliana E, Consonni D, Frattaruolo MP, De Giorgi O, Fedele L. Surgical versus
954 medical treatment for endometriosis-associated severe deep dyspareunia: I. Effect on pain during
955 intercourse and patient satisfaction. Hum Reprod. 2012;27:3450-9.

956 [74] Vercellini P, Frattaruolo MP, Somigliana E, Jones GL, Consonni D, Alberico D, et al. Surgical
957 versus low-dose progestin treatment for endometriosis-associated severe deep dyspareunia II: effect on
958 sexual functioning, psychological status and health-related quality of life. Hum Reprod 2013;28:1221–
959 30.

960 [75] Vercellini P, Bracco B, Mosconi P, Roberto A, Alberico D, Dhouha D, et al. Norethindrone
961 acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil
962 Steril 2016;105:734-43.e3.

963 [76] Morotti M, Venturini PL, Biscaldi E, Racca A, Calanni L, Vellone VG, et al. Efficacy and
964 acceptability of long-term norethindrone acetate for the treatment of rectovaginal endometriosis. Eur J
965 Obstet Gynecol Reprod Biol 2017;213:4-10.

966 [77] Chu MC, Zhang X, Gentzschein E, Stanczyk FZ, Lobo RA. Formation of ethinyl estradiol in
967 women during treatment with norethindrone acetate. J Clin Endocrinol Metab 2007;92:2205–7.

968 [78] Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Indhavivadhana S,
969 Leerasiri P. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis related
970 pain: a randomized controlled trial. Obstet Gynecol 2012;119:519–26.

971 [79] Petta CA, Ferriani RA, Abrao MS, Hassan D, Rosa E, Silva JC, et al. Randomized clinical trial of
972 a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic
973 pelvic pain in women with endometriosis. Hum Reprod 2005;20:1993–8.

974 [80] Bayoglu Tekin Y, Dilbaz B, Altinbas SK, Dilbaz S. Postoperative medical treatment of chronic
975 pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus
976 gonadotropin releasing hormone analogue. Fertil Steril 2011;95:492–6.

977 [81] Vercellini P, Somigliana E, Vigano P, Abbiati A, Barbara G, Fedele L. ‘‘Blood on the tracks’’
978 from corpora lutea to endometriomas. BJOG 2009;116:366–71.

979 ***[82] Guo SW. Recurrence of endometriosis and its control. Hum Reprod Update 2009;15:441–**
980 **61.**

981 ***[83] Koga K, Takamura M, Fujii T, Osuga Y. Prevention of the recurrence of symptom and**
982 **lesions after conservative surgery for endometriosis. Fertil Steril 2015;104:793–801.**

983 [84] Chen YJ, Hsu TF, Huang BS, Tsai HW, Chang YH, Wang PH. Postoperative maintenance
984 levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled
985 study. Am J Obstet Gynecol 2017;216;582.e1-582.e9.

986 [85] Zhang J, Zhu Y, Zhou X, Hao S, Xie S, Zhou J, et al. Evaluation of biodegradable microspheres
987 containing nomegestrol acetate in a rat model of endometriosis. Eur J Pharm Sci. 2014;65:15-20.

988 [86] Andres Mde P, Lopes LA, Baracat EC, Podgaec S. Dienogest in the treatment of endometriosis:
989 systematic review. Arch Gynecol Obstet. 2015;292:523-9.

990 [87] Cosson M, Querleu D, Donnez J, Madelenat P, Koninckx P, Audebert A, et al. Dienogest is as
991 effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a
992 prospective, multicenter, randomized study. Fertil Steril. 2002;77:684–692.

993 [88] Harada T, Momoeda M, Taketani Y, Aso T, Fukunaga M, Hagino H, et al. Dienogest is as
994 effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis: a
995 randomized, double-blind, multicenter, controlled trial. Fertil Steril. 2009;91:675–681.

996 [89] Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-
997 associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet
998 Gynecol Reprod Biol. 2010;151:193–198.

999 [90] Ferrero S, Alessandri F, Racca A. Leone Roberti Maggiore U. Treatment of pain associated with
1000 deep endometriosis: alternatives and evidence. Fertil Steril 2015;104:771–92.

1001 [91] Vercellini P, Buggio L, Somigliana E. Role of medical therapy in the management of deep
1002 rectovaginal endometriosis. Fertil Steril 2017; in press.

1003 [92] Vercellini P, Aimi G, Panazza S, De Giorgi O, Pesole A, Crosignani PG. A levonorgestrel-
1004 releasing intrauterine system for the treatment of dysmenorrhea associated with endometriosis: a pilot
1005 study. Fertil Steril. 1999;72:505-8.

1006 [93] Lockhat FB, Emembolu JO, Konje JC. The evaluation of the effectiveness of an intrauterine-
1007 administered progestogen (levonorgestrel) in the symptomatic treatment of endometriosis and in the
1008 staging of the disease. Hum Reprod. 2004;19:179-84.

1009 [94] Walch K, Unfried G, Huber J, Kurz C, van Trotsenburg M, Pernicka, et al. Implanon versus
1010 medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis—a
1011 pilot study. Contraception 2009;79:29–34.

1012 [95] Morotti M, Sozzi F, Remorgida V, Venturini PL, Ferrero S. Dienogest in women with persistent
1013 endometriosis-related pelvic pain during norethisterone acetate treatment. Eur J Obstet Gynecol Reprod
1014 Biol. 2014;183:188-92.

1015 [96] Guzick DS, Huang LS, Broadman BA, Nealon M, Hornstein MD. Randomized trial of leuprolide
1016 versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. Fertil
1017 Steril 2011;95:1568–73.

1018 [97] Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of
1019 Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. N Engl J Med. 2017;377:28-
1020 40.

1021 [98] Kitawaki J, Ishihara H, Kiyomizu M, Honjo H. Maintenance therapy involving a tapering dose of
1022 danazol or mid/low doses of oral contraceptive after gonadotropin-releasing hormone agonist treatment
1023 for endometriosis-associated pelvic pain. Fertil Steril. 2008;89:1831-5.

1024 [99] Kitawaki J, Ishihara H, Kiyomizu M, Honjo H.Kitawaki J, Kusuki I, et al. Maintenance therapy
1025 with dienogest following gonadotropin-releasing hormone agonist treatment for endometriosis-
1026 associated pelvic pain. Eur J Obstet Gynecol Reprod Biol. 2011;157:212-6.

1027 [100] Tosti C, Biscione A, Morgante G, Bifulco G, Luisi S, Petraglia F. Hormonal therapy for
1028 endometriosis: from molecular research to bedside. Eur J Obstet Gynecol Reprod Biol 2017;209:61-6.

1029 [101] Chwalisz K, Perez MC, Demanno D, Winkel C, Schubert G, Elger W. Selective progesterone
1030 receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endocr
1031 Rev. 2005;26:423-38.

1032 [102] Kettel LM, Murphy AA, Morales AJ, Ulmann A, Baulieu EE, Yen SS. Treatment of
1033 endometriosis with the antiprogesterone mifepristone (RU486). Fertil Steril 1996;65:23–8.

1034 [103] Kettel LM, Murphy AA, Morales AJ, Yen SS. Preliminary report on the treatment of
1035 endometriosis with low-dose mifepristone (RU 486). Am J Obstet Gynecol 1998;178:1151–6.

1036 [104] Chwalisz K, Mattia-Goldberg C, Elger W, Edmonds A. Treatment of endometriosis with the
1037 novel selective progesterone receptor modulator (SPRM) asoprisnil. Fertil Steril 2004;82:S83–4.

1038 [105] Whitaker LH, Murray AA, Matthews R, Shaw G, Williams AR, Saunders PT, et al. Selective
1039 progesterone receptor modulator (SPRM) ulipristal acetate (UPA) and its effects on the human
1040 endometrium. Hum Reprod. 2017 1;32:531-43.

1041 [106] Australian Government. Department of Health. Therapeutic Goods Administrations. Australian
1042 Public Assessment Report for ulipristal acetate. https://www.tga.gov.au/sites/default/files/auspar-
1043 ulipristal-acetate-161019.pdf [Accessed 5 November 2017].

1044 [107] Stewart EA. Clinical practice. Uterine fibroids. N Engl J Med. 2015;372:1646-55.

1045 [108] Kurman RJ, Shih IeM. The dualistic model of ovarian carcinogenesis: revisited, revised, and
1046 expanded. Am J Pathol 2016;186:733–47.

1047 [109] Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al. Association between
1048 endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control
1049 studies. Lancet Oncol 2012;13:385–94.

1050 ***[110] Seracchioli R, Mabrouk M, Manuzzi L, Vicenzi C, Frasca C, Elmakky A, et al. Post-**
1051 **operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-**
1052 **recurrence after conservative surgery for endometriosis. Hum Reprod 2009;24:2729–35.**

1053 [111] Somigliana E, Ragni G, Benedetti F, Borroni R, Vegetti W, Crosignani PG. Does laparoscopic
1054 excision of endometriotic ovarian cysts significantly affect ovarian reserve? Insights from IVF cycles.
1055 Hum Reprod. 2003;18:2450-3.

1056 [112] Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian
1057 reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2012;97:3146-54.

1058 [113] Vercellini P, Somigliana E, Viganò P, De Matteis S, Barbara G, Fedele L. The effect of second-
1059 line surgery on reproductive performance of women with recurrent endometriosis: a systematic review.
1060 Acta Obstet Gynecol Scand. 2009;88:1074-82.

1061 [114] Vercellini P, Somigliana E, Daguati R, Vigano P, Meroni F, Crosignani PG. Postoperative oral
1062 contraceptive exposure and risk of endometrioma recurrence. Am J Obstet Gynecol 2008;198:504.e1–
1063 5.

1064 [115] Vercellini P, de Matteis S, Somigliana E, Buggio L, Frattaruolo MP, Fedele L. Long-term
1065 adjuvant therapy for the prevention of postoperative endometrioma recurrence: a systematic review and
1066 meta-analysis. Acta Obstet Gynecol Scand 2013;92:8–16.

1067 [116] Zorbas KA, Economopoulos KP, Vlahos NF. Continuous versus cyclic oral contraceptives for
1068 the treatment of endometriosis: a systematic review. Arch Gynecol Obstet. 2015;292:37-43.

1069 [117] Anaf V, Simon P, El Nakadi I, Fayt I, Simonart T, Buxant F, et al. Hyperalgesia, nerve
1070 infiltration and nerve growth factor expression in deep adenomyotic nodules, peritoneal and ovarian
1071 endometriosis. Hum Reprod 2002;17:1895–900.

1072 [118] McKinnon B, Bersinger NA, Wotzkow C, Mueller MD. Endometriosis-associated nerve fibers,
1073 peritoneal fluid cytokine concentrations, and pain in endometriotic lesions from different locations.
1074 Fertil Steril 2012;97:373–80.

[119] Morotti M, Vincent K, Becker CM. Mechanisms of pain in endometriosis. Eur J Obstet Gynecol Reprod Biol. 2017;209:8-13.

[120] Evers JL. Is adolescent endometriosis a progressive disease that needs to be diagnosed and treated? Hum Reprod 2013;28:2023.

[121] Vercellini P, Giudice LC, Evers JL, Abrao MS. Reducing low-value care in endometriosis between limited evidence and unresolved issues: a proposal. Hum Reprod 2015;30:1996–2004.

[122] Meresman GF, Augé L, Barañao RI, Lombardi E, Tesone M, Sueldo C. Oral contraceptives suppress cell proliferation and enhance apoptosis of eutopic endometrial tissue from patients with endometriosis. Fertil Steril. 2002;77:1141-7.

[123] Minami T, Kosugi K, Suganuma I, Yamanaka K, Kusuki I, Oyama T, et al. Antiproliferative and apoptotic effects of norethisterone on endometriotic stromal cells in vitro. Eur J Obstet Gynecol Reprod Biol. 2013;166:76-80.

[124] Vercellini P, Fedele L, Arcaini L, Bianchi S, Rognoni MT, Candiani GB. Laparoscopy in the diagnosis of chronic pelvic pain in adolescent women. J Reprod Med. 1989;34:827-30.

[125] Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 2005;20:2698–2704.

***[126] American College of Obstetricians and Gynecologists' Committee on Practice Bulletin-Gynecology. Practice bulletin No. 174: evaluation and management of adnexal masses. Obstet Gynecol 2016;128:e210-26.**

***[127] Glanc P, Benacerraf B, Bourne T, Brown D, Coleman BG, Crum C, et al. First international consensus report on adnexal masses: management recommendations. J Ultrasound Med 2017;36:849–63.**

[128] Noël JC, Chapron C, Bucella D, Buxant F, Peny MO, Fayt I, et al. Estrogen and progesterone receptors in smooth muscle component of deep infiltrating endometriosis. Fertil Steril 2010;93:1774-7.

[129] Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2008;90:1583-8.

[130] Yela DA, Kajikawa P, Donati L, Cursino K, Giraldo H, Laguna Benetti-Pinto C. Deep infiltrating endometriosis treatment with dienogest: a pilot study. Journal of Endometriosis and Pelvic Pain Disorders 2015; 7: 33-7.

[131] Leonardo-Pinto JP, Benetti-Pinto CL, Cursino K, Yele DA. Dienogest and deep infiltrating endometriosis: The remission of symptoms is not related to endometriosis nodule remission. Eur J Obstet Gynecol Reprod Biol 2017; 211:108-11.

[132] Schultze-Mosgau MH, Waellnitz K, Nave R, Klein S, Kraetzschmar J, Rautenberg T, Schmitz H, Rohde B. Pharmacokinetics, pharmacodynamics, safety and tolerability of an intravaginal ring releasing anastrozole and levonorgestrel in healthy premenopausal women: a Phase 1 randomized controlled trial. Hum Reprod. 2016 Aug;31(8):1713-22.

[133] Reinecke I, Schultze-Mosgau MH, Nave R, Schmitz H, Ploeger BA. Model-Based Dose Selection for Intravaginal Ring Formulations Releasing Anastrozole and Levonorgestrel Intended for the Treatment of Endometriosis Symptoms. J Clin Pharmacol. 2017 May;57(5):640-651.

[134] Buggio L, Lazzari C, Monti E, Barbara G, Berlanda N, Vercellini P. "Per vaginam" topical use of hormonal drugs in women with symptomatic deep endometriosis: a narrative literature review. Arch Gynecol Obstet. 2017 Jun 29. doi: 10.1007/s00404-017-4448-z. In press.

[135] Culley L, Law C, Hudson N, Denny E, Mitchell H, Baumgarten M, Raine-Fenning N. The social and psychological impact of endometriosis on women's lives: a critical narrative review. Hum Reprod Update 2013;19: 625–639.

[136] Barbara G, Facchin F, Buggio L, Somigliana E, Berlanda N, Kustermann A, Vercellini P. What Is Known and Unknown About the Association Between Endometriosis and Sexual Functioning: A Systematic Review of the Literature. Reprod Sci. 2017. doi: 10.1177/1933719117707054. In press.

[137] Barbara G, Facchin F, Meschia M, Berlanda N, Frattaruolo MP, VercellinI P. When love hurts. A systematic review on the effects of surgical and pharmacological treatments for endometriosis on female sexual functioning. Acta Obstet Gynecol Scand. 2017;96:668-687.

[138] Buggio L, Barbara G, Facchin F, Frattaruolo MP, Aimi G, Berlanda N. Self-management and psychological-sexological interventions in patients with endometriosis: strategies, outcomes, and integration into clinical care. Int J Womens Health. 2017 2;9:281-293.

***[139] Spencer-Bonilla G, Quiñones AR, Montori VM; International Minimally Disruptive Medicine Workgroup. Assessing the Burden of Treatment. J Gen Intern Med. 2017 Jul 11. doi: 10.1007/s11606-017-4117-8. In press.**

[140] Vercellini P, Facchin F, Buggio L, Barbara G, Berlanda N, Frattaruolo MP, et al. Management of Endometriosis: Toward Value-Based, Cost-Effective, Affordable Care. J Obstet Gynaecol Can. 2017 Oct 5. doi: 10.1016/j.jogc.2017.07.011. In press.

1136 [141] LeFevre ML. Swimming upstream: doing less in health care is hard: comment on "No
1137 Papanicolaou tests in women younger than 21 years or after hysterectomy for benign disease" and
1138 "Cervical cancer screening intervals, 2006 to 2009". JAMA Intern Med. 2013;173:856-8.

1139 [142] Thokala P, Devlin N, Marsh K, Baltussen R, Boysen M, Kalo Z, et al. Multiple Criteria Decision
1140 Analysis for Health Care Decision Making--An Introduction: Report 1 of the ISPOR MCDA Emerging
1141 Good Practices Task Force. Value Health. 2016;19:1-13.

1142 [143] Marsh K, IJzerman M, Thokala P, Baltussen R, Boysen M, Kaló Z, et al. Multiple Criteria
1143 Decision Analysis for Health Care Decision Making--Emerging Good Practices: Report 2 of the ISPOR
1144 MCDA Emerging Good Practices Task Force. Value Health. 2016;19:125-37.

1145 [144] Vallejo-Torres L, García-Lorenzo B, Castilla I, Valcárcel-Nazco C, García-Pérez L, Linertová R,
1146 et al. On the Estimation of the Cost-Effectiveness Threshold: Why, What, How? Value Health.
1147 2016;19:558-66.

1148 [145] Beauchamp TL, Childress JF. Principles of Biomedical Ethics, 7 ed., Oxford University Press,
1149 New York, 2013.

1150 [146] Sandman L, Liliemark J. From evidence-based to hope-based medicine? Ethical aspects on
1151 conditional market authorization of and early access to new cancer drugs. Semin Cancer Biol.
1152 2017;45:58-63.

Table 1. Studies evaluating satisfaction with estrogen-progestogens for the treatment of symptomatic endometriosis (literature data, 1996–2017).

Source	Study design	Number of patients enrolled	Endometriosis location or stage[a]	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate[b]
Vercellini et al., 1996 [18]	RCT	80	Stage I *n* = 14; Stage II *n* = 30; Stage III *n* = 21; Stage IV *n* = 15	DMPA 150 mg i.m. injections/3 months (*n* = 40)	Cyclic low-dose monophasic OC (EE 0.02 +DSG 0.15 mg)/day + danazol 50 mg/day for 21 days of each 28-day cycle (*n* = 40)	12 months	ITT	Higher satisfaction with treatment in DMPA group (73% vs 58% in the OC group)
Vercellini *et al.*, 2002 [19]	RCT	90	Stage I *n* = 20; Stage II *n* = 19; Stage III *n* = 30; Stage IV *n* = 21	Continuous low-dose monophasic OC (EE 0.02 + DSG 0.15 mg)/day (*n* = 45)	Cyproterone acetate 12.5 mg/day per os (*n* = 45)	6 months	ITT	Slightly higher satisfaction with treatment in the cyproterone acetate group (73% vs 67% in the OC group)
Vercellini *et al.*, 2003 [20]	Prospective self-controlled	50[c]	Women with histologically proven endometriosis (stage not specified)	Continuous low-dose monophasic OC (EE 0.02 + DSG 0.15 mg)/day per os	NA	2 years	ITT	80% of women were satisfied or very satisfied with continuous OC use
Vercellini *et al.*, 2005 [21]	RCT	90	Rectovaginal endometriosis	Continuous low-dose monophasic OC (EE 0.01 + cyproterone acetate 3	NETA 2.5 mg/day per os (*n* = 45)	12 months	ITT	Higher satisfaction with treatment in NETA group (73% vs 62% in the OC group)

Source	Study design	Number of patients enrolled	Endometriosis location or stage[a]	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate[b]
				mg)/day (*n* =45)				
Vercellini *et al.*, 2010 [22]	PPT	207	Stage I *n* = 56; Stage II *n* = 45; Stage III *n* = 52; Stage IV *n* = 54 Rectovaginal endometriosis *n* = 59	Vaginal ring (EE 15 μg + etonogestrel 120 μg) (*n* =123; rectovaginal endometriosis sub-group *n* = 38)	Transdermal patch (EE 20 μg + norelgestromin 150 μg) (*n* = 84; rectovaginal endometriosis sub-group *n* = 21)	12 months	ITT	Higher satisfaction with treatments in vaginal ring group (71% vs 48% in the transdermal patch group). In the sub-group of patients with rectovaginal endometriosis higher satisfaction rate in vaginal ring group (79% vs 57%)
Cheewadhanaraks *et al.*, 2012 [23]	RCT	84	Stage I *n* = 23; Stage II *n* = 15; Stage III *n* = 13; Stage IV *n* = 33	DMPA 150 mg i.m. injections/3 months (*n* = 42)	Continuous mid-dose monophasic OC (EE 0.03 mg + gestodene 0.075 mg)/day (*n* = 42)	24 weeks	ITT	Similar satisfaction rates (93% in DMPA group vs 88% in OC group)
Ferrari *et al.*, 2012 [24]	Prospective non-comparative	26	Colorectal endometriosis (medium-low rectum nodules *n* = 4; proximal rectum, *n* = 14; recto-sigmoid junction/sigmoid, *n* = 8)	Continuous low-dose monophasic OC (EE 15 μg + gestodene 60 μg)/day	NA	12 months	ITT	69% of the women were satisfied or very satisfied with continuous low-dose OC treatment
Morelli *et al.*, 2013 [25]	Retrospective	92	Post-operative administration in	Continuous low-dose	LNG-IUD (*n* = 44)	24 months	Per-protocol	Higher satisfaction with treatment in

Source	Study design	Number of patients enrolled	Endometriosis location or stage[a]	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate[b]
			women with histologically proven endometriosis	multiphasic OC (DNG + E2V) /day (*n* = 48)				LNG-IUD users (98% vs 83% in OC users)[d]
Leone Roberti Maggiore *et al.*, 2014 [26]	PPT	143	Rectovaginal endometriosis	DSG 75 µg/day per os (*n* = 60)	Vaginal ring (EE 15 µg + etonogestrel 120 µg) (*n* = 83)	12 months	ITT	Higher patient satisfaction with treatment in DSG group (62% vs 36% in vaginal ring group)
Morotti *et al.*, 2014 [27]	PPT	144	Rectovaginal endometriosis	DSG 75 µg/day per os (*n* = 62)	Cyclic low-dose monophasic OC (EE 20 µg + DSG 150 µg)/day (*n* = 82)	6 months	ITT	Higher satisfaction with treatment in DSG group (61% vs 38% in OC group)
Harada *et al.*, 2017 [17]	RCT	312[e]	Not specified (most of the patients had a clinical diagnosis, with very few cases visually confirmed by laparoscopy)	Low-dose monophasic OC (EE 0.02 + DRSP 3 mg)/ day, $\text{Flexible}_{\text{MIB}}$ regimen[f] (*n* = 130)	Placebo (*n* = 129)	52 weeks[g]	ITT	Higher percentage of "very much satisfied/much satisfied/minimally satisfied" with treatment in OC group (75% vs 29% at week 24, and 83% vs 71% at week 52)[h]

[a] According to the revised American Fertility Society classification [28]

[b] Unless otherwise specified, satisfaction with treatment was based on a five-category scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied)

[c] Women with recurrent dysmenorrhea not responding to cyclic OC use

[d] Treatment satisfaction was defined by the percentage of women who successfully completed their treatment, without requiring suspension of the assigned regimen

[e] 53 women were randomized to an un-blinded reference arm (DNG 2 mg/day) in order to compare the vaginal bleeding pattern of $Flexible_{MIB}$

[f] The $Flexible_{MIB}$ regimen consists of a repeat cycle of 120 consecutive days of active tablet followed by a 4-day tablet-free interval, either after the 120 days or after ≥3 consecutive days of bleeding and/or spotting between days 25 and 120

[g] After 24 weeks, placebo recipients were changed to $Flexible_{MIB}$

[h] Treatment satisfaction was assessed through a seven-category scale (very much satisfied, much satisfied, minimally satisfied, neither satisfied nor dissatisfied, minimally dissatisfied, much dissatisfied, very much dissatisfied).

DNG, dienogest; DRSP, drospirenone; DSG, desogestrel; E2V, estradiol valerate; EE, ethinyl-estradiol; ITT, intention-to-treat; NA, not applicable; LNG-IUD, levonorgestrel-intrauterine device; NETA, norethisterone acetate; OC, oral contraceptive; PPT, patient preference trial; RCT, randomized controlled trial

Table 2. Hormonal activities of progestogens investigated for the treatment of endometriosis. Literature data, 2003-2015 [59-65].

Compound	***Progestogen activity***	***Androgenic activity***	***Anti-androgenic activity***	***Glucocorticoid activity***	***Anti-mineralcorticoid activity***	***Half-life (h)***
Cyproterone acetate	+	-	++	+	-	48-78.6
Dienogest	+	-	+	-	-	6-12
Levonorgestrel	++	+	-	-	-	9.9-26
Medroxyprogesterone acetate	++	±	-	+	-	24
Nomegestrol acetate	+	-	±	-	-	50
Norethisterone acetate	++	+	-	-	-	7-8

++ strong activity; + activity; +/- weak activity; - no activity

Table 3. Studies evaluating satisfaction with progestogens therapies for the treatment of symptomatic endometriosis (literature data, 1999–2017).[a]

Source	Study design	Number of patients enrolled	Endometriosis location or stage[b]	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate[c]
Vercellini *et al.*, 1999 [92]	Prospective non-comparative pilot study	20	Women with histologically proven endometriosis (stage not specified)	LNG-IUD	NA	12 months	ITT	75% of women were satisfied or very satisfied with LNG-IUD treatment
Vercellini *et al.*, 2003 [49]	RCT	40	Stage I *n* = 3; Stage II *n* = 6; Stage III *n* = 15; Stage IV *n* = 16	LNG-IUD (*n* = 20)	Expectant management after laparoscopic treatment of endometriotic lesions (*n* =20)	12 months	ITT	Higher satisfaction with treatment in LNG-IUD group (75% vs 50% in the expectant management group)
Lockhat *et al.*, 2004 [93]	Prospective non-comparative	34	Stage I *n* = 5; Stage II *n* = 15; Stage III *n* = 6; Stage IV *n* = 0	LNG-IUD	NA	6 months	Per protocol	66% of women were satisfied or very satisfied with LNG-IUD treatment
Ferrero *et al.*, 2009 [70]	PPT	82	Rectovaginal endometriosis	Letrozole 2.5 mg + NETA 2.5 mg/day per os (*n* = 41)	NETA 2.5 mg/day per os (*n* = 41)	6 months	ITT	Higher satisfaction with NETA treatment only (63% vs 56% in letrozole + NETA group)
Momoeda *et al.*, 2009 [51]	Prospective cohort study non-comparative	135	Ovarian endometriosis	DNG 2 mg/day per os	NA	52 weeks	Per protocol	High satisfaction with treatment (89%)[d]

Source	Study design	Number of patients enrolled	Endometriosis location or stage[b]	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate[c]
Walch *et al.*, 2009 [94]	RCT	41	Stage I *n* = 11; Stage II *n* = 15; Stage III *n* = 7; Stage IV *n* = 8	Etonogestrel 68 mg implant (*n* = 21)	DMPA 150 mg i.m. injections/90 days (*n* = 20)	12 months	ITT	Comparable satisfaction with treatment (57% in the implant group vs 55% in the DMPA group)
Ferrero *et al.*, 2010 [71]	Prospective non-comparative	40	Colorectal endometriosis (sigmoid colon *n* = 18; rectosigmoid junction *n* = 12; rectum *n* = 10)	NETA 2.5 mg/day per os[e]	NA	12 months	ITT	60% of the women were satisfied or very satisfied with NETA treatment
Ferrero *et al.*, 2010 [72]	Prospective non-comparative	6	Colorectal endometriosis (sigmoid colon *n* = 2; rectosigmoid junction *n* = 2; rectum *n* = 2)	Letrozole 2.5 mg/day + NETA 2.5 mg/day per os	NA	6 months	ITT	67% of the women were satisfied or very satisfied with NETA treatment
Vercellini *et al.*, 2012 [73]	PPT	154	Stage III *n* = 64; Stage IV *n* = 90 Rectovaginal endometriosis *n* = 59	NETA 2.5 mg/day per os (*n* = 103; rectovaginal endometriosis sub-group *n* = 35)	Second-line laparoscopic excision of endometriotic lesions (*n* = 51; rectovaginal endometriosis sub-group *n* = 24)	12 months	ITT	Higher satisfaction with treatment in NETA group (59% vs 43% in surgery group). In the sub-group of patients with rectovaginal endometriosis similar satisfaction rate (54% in surgery group vs 51% in NETA group)

Source	Study design	Number of patients enrolled	Endometriosis location or stage[b]	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate[c]
Morotti *et al.*, 2014 [95]	Open-label prospective study non-comparative[f]	25	Rectovaginal endometriosis	DNG 2 mg/day per os	NA	6 months	ITT	52% of the women were satisfied or very satisfied after 6 months of treatment with DNG
Vercellini *et al.*, 2016 [75]	Before-after study	90	Endometrioma *n* = 104 Deep endometriosis *n* = 108 (rectovaginal endometriosis *n* = 64; Douglas and parametria infiltrating lesions *n* = 39; bladder nodules *n* = 17; bowel nodules *n* = 7)[g]	DNG 2 mg/day per os (*n* = 90)	NETA 2.5 mg/day per os (*n* = 90)	6 months	ITT	Similar satisfaction with treatment (72% in DNG group vs 71% in NETA group). Comparable satisfaction in the sub-group of patients with rectovaginal endometriosis (68% in DNG group vs 67% in NETA group)
Morotti *et al.*, 2017 [76]	Retrospective non-comparative	103 (61 completed the 5-year follow-up)	Rectovaginal endometriosis	NETA 2.5 mg/day per os[e]	NA	5 years	ITT	41% of the women were satisfied or very satisfied with long term NETA treatment

[a] Seven studies comparing an estrogen-progestogen with a progestogen are included in Table 1 [Ref: 18,19,21,23,25-27]
[b] According to the revised American Fertility Society classification [28]
[c] Unless otherwise specified, satisfaction with treatment was based on a five-category scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied)
[d] Patient satisfaction with treatment as determined by interview was classified into four categories (certainly willing to use again, prefer to use again, hesitate to use again, and never willing to use again)
[e] In case of breakthrough bleeding, the dose of NETA was increased by 2.5 mg/day (maximum dose of 5 mg/day)

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

[g] 44 women had more than one lesion

DNG, dienogest; DSG; desogestrel; EE, ethinyl-estradiol; i.m., intramuscular; ITT, intention-to-treat; LNG-IUD, levonorgestrel-intrauterine device; NETA, norethisterone acetate; NA, not applicable; OC, oral contraceptive; PPT, patient-preference trial

HIGHLIGHTS

- Endometriosis is a chronic disorder requiring long-term adherence to treatment
- Individual response to drugs is variable and a stepwise approach is suggested
- Progestogens should be selected in case of deep lesions and severe deep dyspareunia