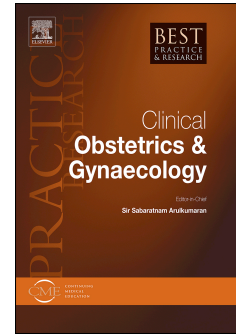


# Accepted Manuscript

Medical treatment of endometriosis related pain

Paolo Vercellini, M.D., Laura Buggio, M.D., Maria Pina Frattaruolo, M.D., Alessandra Borghi, M.D., Dhouha Dridi, M.D., Edgardo Somigliana, M.D.



PII: S1521-6934(18)30033-6

DOI: [10.1016/j.bpobgyn.2018.01.015](https://doi.org/10.1016/j.bpobgyn.2018.01.015)

Reference: YBEOG 1791

To appear in: *Best Practice & Research Clinical Obstetrics & Gynaecology*

Received Date: 20 December 2017

Accepted Date: 23 January 2018

Please cite this article as: Vercellini P, Buggio L, Frattaruolo MP, Borghi A, Dridi D, Somigliana E, Medical treatment of endometriosis related pain, *Best Practice & Research Clinical Obstetrics & Gynaecology* (2018), doi: 10.1016/j.bpobgyn.2018.01.015.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

## 1 MEDICAL TREATMENT OF ENDOMETRIOSIS RELATED PAIN

2

3

4 Paolo Vercellini, M.D.<sup>a,b</sup>

paolo.vercellini@unimi.it

5 Laura Buggio, M.D.<sup>a,b</sup>

buggiolaura@gmail.com

6 Maria Pina Frattaruolo, M.D.<sup>a,b</sup>

mp.frattaruolo@gmail.com

7 Alessandra Borghi, M.D.<sup>a,b</sup>

alessandra.borghi.92@gmail.com

8 Dhouha Dridi, M.D.<sup>a,b</sup>

dh.dridi2@gmail.com

9 Edgardo Somigliana, M.D.<sup>a,b</sup>

dadosomigliana@yahoo.it

10

11

12 From the <sup>a</sup>Department of Clinical Sciences and Community Health, Università degli Studi di Milano,13 <sup>b</sup>Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore

14 Policlinico, Via Commenda, 12 - 20122 Milan, Italy.

15

16

17

18 Correspondence: Paolo Vercellini, M.D.

19 Department of Clinical Sciences and Community Health, Università degli Studi di Milano and

20 Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore

21 Policlinico, Via Commenda, 12 - 20122 Milan, Italy

22 Tel: +39.02.5503.2917; fax: +39.02.50320264; e-mail: paolo.vercellini@unimi.it

23

## 24 ABSTRACT

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

36  
37 **KEYWORDS:** endometriosis, dysmenorrhoea, dyspareunia, pelvic pain, oral contraceptives,  
38 progestogens, dienogest, GnRH agonists, GnRH antagonists

39

## 40 1. INTRODUCTION: "GIMME SOME TRUTH"\*

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

42

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

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

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

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

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

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

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

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

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

121 In this regard, ideally our clinical goal is complete elimination of pain [16], provided this primary aim  
122 does not compromise safety, quality of life, and economic stability of women and their families.

123 Otherwise, a reasonable compromise between all of these factors could be preferable, especially when  
124 prolonged periods of treatment are foreseen. For this reason, in the present review particular emphasis  
125 has been put on the overall “therapeutic balance” of various medications, as well as on patient  
126 satisfaction, an important global patient reported outcome, rather than on pain score variation as an  
127 isolated measure of the effect size of treatments.

128

## 129 2. PROS AND CONS OF COMBINED ORAL CONTRACEPTIVES

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

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

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

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



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

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

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

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

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

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

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

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

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

208         Regarding the possible use of progestogens as first-line medical therapy in all women with  
209 endometriosis, in addition to the above psychological aspects, it should also be taken into account that  
210 treatments may be needed for years. Therefore, safety aspects are of utmost importance here. The  
211 progestogens most frequently studied in women with endometriosis are norethisterone acetate  
212 (NETA), and dienogest (DNG) [29]. Indeed, both progestogens are associated with potential safety  
213 drawbacks, as the former may modify serum cholesterol lipoprotein distribution [21,50], whereas the  
214 latter may decrease bone mineral content [51-53]. Whether these variations in surrogate markers might  
215 translate into increased incidence of cardio-vascular events or pathologic fractures is currently  
216 unknown, also considering that this information would be available in the distant future, given the  
217 young age of women who have used or are using these progestogens. Most low-dose OCs do not alter  
218 serum lipid profile and do not decrease bone mineral content, and may be safely used for many years.

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

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

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

234 Finally, Casper correctly maintains that the use of OCs for endometriosis is "off-label".  
235 Nonetheless, in several international guidelines issued by authoritative societies and professional  
236 organisations, OCs are included among the first-line medications to be used in symptomatic women  
237 [44,54-57]. In particular, recommendation #37 of the recent guideline NG73 "Endometriosis: diagnosis  
238 and management" issued by the NICE states "*Offer hormonal treatment (for example, the combined  
239 oral contraceptive pill or a progestogen) to women with suspected, confirmed or recurrent  
240 endometriosis*" [44]. At the same time, the Committee notes that "*At the time of publication (September  
241 2017), none of these medicines had UK marketing authorisations for this indication. The General  
242 Medical Council (GMC), in its Prescribing guidance: prescribing unlicensed medicines, states that  
243 although doctors should usually prescribe licensed medicines for their licensed indications, they may  
244 prescribe unlicensed medicines when it is necessary to do so to meet the specific needs of the patient.  
245 [...] It also states that when prescribing an unlicensed medicine is supported by authoritative clinical  
246 guidance (such as a NICE guideline), it may be sufficient to describe in general terms why the medicine  
247 is not licensed for the proposed use or patient population*" [44, page 238].

248

### 249 3. PROS AND CONS OF PROGESTOGENS

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

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

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

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

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

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

280 Advantages of the LNG-IUD include avoidance of daily drug intake and contraception.  
281 However, ovulation is not inhibited, except for the first few months after insertion. This constitutes an  
282 important disadvantage, because it has been demonstrated that ovarian endometriomas originates from  
283 haemorrhagic corpora lutea [81], and that the post-operative endometrioma recurrence rate is about  
284 10% per year for the first quinquennium of follow-up if ovulation is not suppressed [82,83]. The effect  
285 of the LNG-IUD in the prevention of postoperative endometrioma recurrence has been investigated in a  
286 RCT comparing two groups of 40 participants each allocated to receive the device or not after  
287 laparoscopic excision of endometriotic cysts [84]. The endometrioma recurrence rate did not differ  
288 significantly at 30 month-follow-up, being 25% in the LNG-IUD group and 37% in the control group.  
289 The authors concluded that long-term maintenance therapy using a LNG-IUD is not effective for  
290 preventing endometrioma recurrence. Therefore, the best candidate for the use of the LNG-IUD seems  
291 to be a parous woman with no further pregnancy desire and with dysmenorrhoea as her main or only  
292 pain symptom. The LNG-IUD may not have the same effect of other progestogens used systemically  
293 on deep dyspareunia.

294 Nomegestrol acetate is a progestogen used for the treatment of irregular uterine bleeding and  
295 dysmenorrhoea that has been tested in an animal model of endometriosis with favourable preliminary  
296 results [85]. Nomegestrol acetate has pharmacological and hormonal properties similar to dienogest  
297 [Table 2] and, when combined with oestradiol in an OC used cyclically (NOMAC, 2.5 mg; oestradiol,  
298 1 mg), was frequently associated with absence of withdrawal bleeding [37]. This progestogen is  
299 inexpensive and well tolerated, but further studies are needed in women with symptomatic  
300 endometriosis.

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

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

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

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

326

#### 327 4. CHOOSING GnRH AGONISTS AND ANTAGONISTS WISELY

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

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

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



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

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

360 Elagolix has been assessed versus an active comparator in a single, phase 2 multicentre RCT  
361 [68]. A daily elagolix dose of 150 mg was not inferior to a depot three-monthly subcutaneous MPA  
362 formulation in terms of BMD variation and pain symptom reduction. It is interesting to note that the  
363 effect of cheap DMPA was similar to that of the novel experimental drug. Three out of 168 participants  
364 (1.8%) allocated to elagolix got pregnant compared with none in the DMPA group.

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

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

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

391

## 392 5. SELECTIVE PROGESTERONE RECEPTOR MODULATORS FOR ENDOMETRIOSIS: A SAFE 393 OPTION?

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

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

403 The effect of asoprisnil was assessed in a double-blind, placebo-controlled, RCT conducted on  
404 130 participants [104]. The three doses studied (5, 10, 25 mg/day for 12 weeks) all reduced pain  
405 symptoms scores significantly and induced amenorrhoea in a dose dependent manner, with no effect on  
406 serum oestradiol levels [104]. However, the full report of this industry-sponsored trial does not seem to  
407 have been published in a peer-reviewed journal. Chwalisz *et al.* maintained that asoprisnil may provide  
408 a novel, tissue-selective approach to control endometriosis-related pain [101]. However, according to  
409 Tosti *et al.* [100] and Bedaiwy *et al.* [6], the trials on asoprisnil were stopped because of development  
410 of endometrial hyperplasia in some women. In our view, this is precisely the reason to be careful when  
411 hypothesizing the use of SPRM in women with endometriosis.

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

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

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

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

436

## 437 6. POSTOPERATIVE MEDICAL TREATMENT: ETHICS BEYOND EFFECTIVENESS

438 It has been repeatedly demonstrated that lesion and symptom recurrence after surgery is substantially  
439 higher in women who undergo postoperative expectant management compared with those who use  
440 postoperative medical treatment [83,110]. The recurrence rate in the former group of women is around  
441 10% a year for the first five years of follow-up [82]. Data for longer periods of follow-up are limited.  
442 Endometrioma recurrence is detrimental for future fertility, and cyst excision is associated with reduced  
443 ovarian reserve [111,112]. The likelihood of conception after second-line surgery for recurrent ovarian

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

449 It has been observed that ovarian endometriomas developed from haemorrhagic corpora lutea  
450 [81]. Moreover, suppressing ovulation by using OCs dramatically reduced the postoperative  
451 endometrioma recurrence rate [114]. This finding has been consistently and repeatedly confirmed by  
452 independent groups using different study designs [45,115,116]. The effect size appears unusually large,  
453 as the reduction in risk is over 80%. In a systematic literature review and meta-analysis, a recurrent  
454 endometrioma was identified in 8% of "always" OC users and in 34% women who underwent  
455 expectant management (pooled odds ratio 0.12; 95% C.I., 0.05 to 0.29). The effect of OC is strictly  
456 related to duration of use, as the risk increases soon after drug discontinuation. In fact, when "always"  
457 users were compared with "ever" users, and "ever" with "never" users, the pooled odds ratio was,  
458 respectively, 0.21 (95% confidence interval 0.11-0.40) and 0.39 (95% confidence interval 0.23-0.66),  
459 thus supporting the validity of the overall result [115]. The modality of OC use (i.e., cyclic vs  
460 continuous) does not seem to influence the outcome [45,115].

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

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

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

482

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

484 Variability in the response to medical treatments is observed among patients with symptomatic  
485 endometriosis. This may be due to several factors, including the different number of nerve fibres close  
486 to or within endometriotic lesions, various degrees of peripheral as well as central sensitisation (type  
487 and degree of excitatory neural response to stimuli and endogenous pain-modulatory processes),  
488 symptom characteristics (e.g., dysmenorrhoea vs deep dyspareunia), and psycho-social factors [3,46-  
489 48,117-119]. However, when trying to assess the phenotypic characteristics that are most predictive of  
490 individual variation in medical therapy outcomes, we suggest to give adequate weight to the type of  
491 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

516 above which surgery is deemed mandatory. Unfortunately, most guidelines on endometriosis are  
517 inconsistent or somewhat vague, as a cut-off of 3 cm, 4 cm, or no cut-off have all been indicated [55,  
518 56,125,126].

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

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

538 c. High-risk lesions



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

553

#### 554 8. A SYMPTOM BASED, STEPPED-CARE APPROACH

555 According to the guidelines on endometriosis management issued by major international scientific  
556 societies, different medications have substantially similar effects in terms of pain relief, but have  
557 different safety and tolerability profiles and sometimes very different costs. Consequently, safe, well-  
558 tolerated, and inexpensive OCs and progestogens are suggested as first-line treatments in symptomatic  
559 patients [44,54-57]. Based on a systematic critical appraisal of the evidence, the NICE Committee  
560 confirmed two fundamental principles: 1) "*all treatments led to a clinically significant reduction in*  
561 *pain on the VAS when compared to placebo. The magnitude of this treatment effect was similar for all*  
562 *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].

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

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

609

610 9. TAYLORING MEDICAL THERAPY TO PROVIDE MINIMALLY DISRUPTIVE  
611 ENDOMETRIOSIS MANAGEMENT

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

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

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

636 A minimally disruptive approach also seems aligned with the position of the Practice  
637 Committee of the American Society for Reproductive Medicine that indicates “*endometriosis should be*  
638 *viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the*  
639 *use of medical treatment and avoiding repeated surgical procedures” [56]. The same position is held in*  
640 *the NICE guideline NG73, when it states “the Committee agreed with the evidence and further*  
641 *highlighted that the benefit from hormonal treatments was due to their efficacy in stopping or reducing*  
642 *periods. There was a desire from the Committee to reduce the number of repeated operations for*  
643 *women with endometriosis, further supporting maintenance of pain relief using hormonal treatments*  
644 *wherever possible”. [44, page 236]*

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

647

#### 648 10. PROSPECTUS: MEASURING CLINICAL EFFECTIVENESS, COST-EFFECTIVENESS, AND 649 OPPORTUNITY COST

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

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

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

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

675 The thresholds for cost-effectiveness that should be accepted when considering the opportunity  
676 cost of using dienogest and GnRH agonists and antagonists extensively in women with severe pain  
677 symptoms, are currently scarcely or not yet defined. The combination of high thresholds combined with  
678 high frequency of the condition implies that costly medications for symptomatic endometriosis would  
679 have a substantial impact on health care system budgets and, therefore, a large opportunity cost.  
680 Evaluation of opportunity cost should be included in analyses of economic evaluation of cost of  
681 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

## 702 SUMMARY

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

721



722 **Acknowledgements:**

723 We are grateful to Professor Tasuku Harada, Tottori University, Japan, who provided additional  
724 information regarding the clinical global impression of improvement and the degree of satisfaction with  
725 treatment of women recruited in the study “Ethinylestradiol 20 µg/drospirenone 3 mg in a flexible  
726 extended regimen for the management of endometriosis-associated pelvic pain: a randomized  
727 controlled trial”. *Fertil Steril.* 2017 Sep 11. doi: 10.1016/j.fertnstert.2017.07.1165 (Ref. #17).

728

729 This article was financed by Italian fiscal contribution "5x1000" 2012- Ministero dell'Istruzione,  
730 dell'Università e della Ricerca - devolved to Fondazione Istituto di Ricovero e Cura a Carattere  
731 Scientifico Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy.

732

733 **Conflict of interest:**

734 P.V. is Associate Editor of *Human Reproduction Update*, has received royalties from Wolters Kluwer  
735 for a chapter on endometriosis management in the clinical decision support resource *UpToDate*, and  
736 undertakes both public and private gynaecological practice.

737 L.B., M.P.F., A.B., and D.D. have no conflicts of interest.

738 E.S. received grants from Ferring and Serono.

739 **Practice Points:**

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

751 **Research Agenda:**

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

762

## 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.

- 783 **\*[10] Guo SW, Evers JL. Lack of transparency of clinical trials on endometriosis. *Obstet***  
784 ***Gynecol.* 2013;121:1281-90.**
- 785 [11] Guo SW. An overview of the current status of clinical trials on endometriosis: issues and concerns.  
786 *Fertil Steril.* 2014;101:183-190.e4.
- 787 [12] Maret-Ouda J, Wahlin K, El-Serag HB, Lagergren J. Association Between Laparoscopic  
788 Antireflux Surgery and Recurrence of Gastroesophageal Reflux. *JAMA.* 2017;318:939-946.
- 789 [13] Spechler SJ. The Durability of Antireflux Surgery. *JAMA.* 2017;318:913-915.
- 790 [14] Garg SK, Gurusamy KS. Laparoscopic fundoplication surgery versus medical management for  
791 gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev.* 2015 Nov  
792 5;(11):CD003243.
- 793 **\*[15] Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, et al.**  
794 **Interpreting the clinical importance of group differences in chronic pain clinical trials:**  
795 **IMMPACT recommendations. *Pain.* 2009;146:238-44.**
- 796 [16] Taylor HS. Clinical diagnosis of endometriosis and optimal medical therapy. *Fertil Steril.* 2017  
797 Sep 30. doi: 10.1016/j.fertnstert.2017.09.005. In press.
- 798 **\*[17] Harada T, Kosaka S, Elliesen J, Yasuda M, Ito M, Momoeda M. Ethinylestradiol 20**  
799 **µg/drospirenone 3 mg in a flexible extended regimen for the management of endometriosis-**  
800 **associated pelvic pain: a randomized controlled trial. *Fertil Steril.* 2017 Sep 11. doi:**  
801 **10.1016/j.fertnstert.2017.07.1165. In press.**
- 802 [18] Vercellini P, De Giorgi O, Oldani S, Cortesi I, Panazza S, Crosignani PG. Depot  
803 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 norgestrel acetate/17 $\beta$ -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-](https://www.nice.org.uk/guidance/ng73/resources/patient-decision-aid-hormone-treatment-for-endometriosis-symptoms-what-are-my-options-pdf-4595573197)  
872 [endometriosis-symptoms-what-are-my-options-pdf-4595573197](https://www.nice.org.uk/guidance/ng73/resources/patient-decision-aid-hormone-treatment-for-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-](https://www.nice.org.uk/guidance/ng73/resources/patient-decision-aid-user-guide-hormone-therapy-for-endometriosis-symptoms-patient-decision-aid-user-guide-for-healthcare-professionals-pdf-4595573198)  
876 [hormone-therapy-for-endometriosis-symptoms-patient-decision-aid-user-guide-for-healthcare-](https://www.nice.org.uk/guidance/ng73/resources/patient-decision-aid-user-guide-hormone-therapy-for-endometriosis-symptoms-patient-decision-aid-user-guide-for-healthcare-professionals-pdf-4595573198)  
877 [professionals-pdf-4595573198](https://www.nice.org.uk/guidance/ng73/resources/patient-decision-aid-user-guide-hormone-therapy-for-endometriosis-symptoms-patient-decision-aid-user-guide-for-healthcare-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, Viganò 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 norgestrol 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, Konincks 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 antiprogestone 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-](https://www.tga.gov.au/sites/default/files/auspar-ulipristal-acetate-161019.pdf)  
1043 [ulipristal-acetate-161019.pdf](https://www.tga.gov.au/sites/default/files/auspar-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, Viganò 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.

- 1075 [119] Morotti M, Vincent K, Becker CM. Mechanisms of pain in endometriosis. *Eur J Obstet Gynecol*  
1076 *Reprod Biol.* 2017;209:8-13.
- 1077 [120] Evers JL. Is adolescent endometriosis a progressive disease that needs to be diagnosed and  
1078 treated? *Hum Reprod* 2013;28:2023.
- 1079 [121] Vercellini P, Giudice LC, Evers JL, Abrao MS. Reducing low-value care in endometriosis  
1080 between limited evidence and unresolved issues: a proposal. *Hum Reprod* 2015;30:1996–2004.
- 1081 [122] Meresman GF, Augé L, Barañao RI, Lombardi E, Tesone M, Sueldo C. Oral contraceptives  
1082 suppress cell proliferation and enhance apoptosis of eutopic endometrial tissue from patients with  
1083 endometriosis. *Fertil Steril.* 2002;77:1141-7.
- 1084 [123] Minami T, Kosugi K, Suganuma I, Yamanaka K, Kusuki I, Oyama T, et al. Antiproliferative and  
1085 apoptotic effects of norethisterone on endometriotic stromal cells in vitro. *Eur J Obstet Gynecol Reprod*  
1086 *Biol.* 2013;166:76-80.
- 1087 [124] Vercellini P, Fedele L, Arcaini L, Bianchi S, Rognoni MT, Candiani GB. Laparoscopy in the  
1088 diagnosis of chronic pelvic pain in adolescent women. *J Reprod Med.* 1989;34:827-30.
- 1089 [125] Kennedy S, Bergqvist A, Chapron C, D’Hooghe T, Dunselman G, Greb R, et al. ESHRE  
1090 guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005;20:2698–2704.
- 1091 **\*[126] American College of Obstetricians and Gynecologists’ Committee on Practice Bulletin-**  
1092 **Gynecology. Practice bulletin No. 174: evaluation and management of adnexal masses. *Obstet***  
1093 ***Gynecol* 2016;128:e210-26.**

- 1094 **\*[127] Glanc P, Benacerraf B, Bourne T, Brown D, Coleman BG, Crum C, et al. First**  
1095 **international consensus report on adnexal masses: management recommendations. J Ultrasound**  
1096 **Med 2017;36:849–63.**
- 1097 [128] Noël JC, Chapron C, Bucella D, Buxant F, Peny MO, Fayt I, et al. Estrogen and progesterone  
1098 receptors in smooth muscle component of deep infiltrating endometriosis. *Fertil Steril* 2010;93:1774-7.
- 1099 [129] Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill  
1100 for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial.  
1101 *Fertil Steril.* 2008;90:1583-8.
- 1102 [130] Yela DA, Kajikawa P, Donati L, Cursino K, Giraldo H, Laguna Benetti-Pinto C. Deep infiltrating  
1103 endometriosis treatment with dienogest: a pilot study. *Journal of Endometriosis and Pelvic Pain*  
1104 *Disorders* 2015; 7: 33-7.
- 1105 [131] Leonardo-Pinto JP, Benetti-Pinto CL, Cursino K, Yele DA. Dienogest and deep infiltrating  
1106 endometriosis: The remission of symptoms is not related to endometriosis nodule remission. *Eur J*  
1107 *Obstet Gynecol Reprod Biol* 2017; 211:108-11.
- 1108 [132] Schultze-Mosgau MH, Waellnitz K, Nave R, Klein S, Kraetzschmar J, Rautenberg T, Schmitz H,  
1109 Rohde B. Pharmacokinetics, pharmacodynamics, safety and tolerability of an intravaginal ring  
1110 releasing anastrozole and levonorgestrel in healthy premenopausal women: a Phase 1 randomized  
1111 controlled trial. *Hum Reprod.* 2016 Aug;31(8):1713-22.
- 1112 [133] Reinecke I, Schultze-Mosgau MH, Nave R, Schmitz H, Ploeger BA. Model-Based Dose  
1113 Selection for Intravaginal Ring Formulations Releasing Anastrozole and Levonorgestrel Intended for  
1114 the Treatment of Endometriosis Symptoms. *J Clin Pharmacol.* 2017 May;57(5):640-651.

- 1115 [134] Buggio L, Lazzari C, Monti E, Barbara G, Berlanda N, Vercellini P. "Per vaginam" topical use of  
1116 hormonal drugs in women with symptomatic deep endometriosis: a narrative literature review. Arch  
1117 Gynecol Obstet. 2017 Jun 29. doi: 10.1007/s00404-017-4448-z. In press.
- 1118 [135] Culley L, Law C, Hudson N, Denny E, Mitchell H, Baumgarten M, Raine-Fenning N. The social  
1119 and psychological impact of endometriosis on women's lives: a critical narrative review. Hum Reprod  
1120 Update 2013;19: 625–639.
- 1121 [136] Barbara G, Facchin F, Buggio L, Somigliana E, Berlanda N, Kustermann A, Vercellini P. What  
1122 Is Known and Unknown About the Association Between Endometriosis and Sexual Functioning: A  
1123 Systematic Review of the Literature. Reprod Sci. 2017. doi: 10.1177/1933719117707054. In press.
- 1124 [137] Barbara G, Facchin F, Meschia M, Berlanda N, Frattaruolo MP, Vercellini P. When love hurts. A  
1125 systematic review on the effects of surgical and pharmacological treatments for endometriosis on  
1126 female sexual functioning. Acta Obstet Gynecol Scand. 2017;96:668-687.
- 1127 [138] Buggio L, Barbara G, Facchin F, Frattaruolo MP, Aimi G, Berlanda N. Self-management and  
1128 psychological-sexological interventions in patients with endometriosis: strategies, outcomes, and  
1129 integration into clinical care. Int J Womens Health. 2017 2;9:281-293.
- 1130 **\*[139] Spencer-Bonilla G, Quiñones AR, Montori VM; International Minimally Disruptive**  
1131 **Medicine Workgroup. Assessing the Burden of Treatment. J Gen Intern Med. 2017 Jul 11. doi:**  
1132 **10.1007/s11606-017-4117-8. In press.**
- 1133 [140] Vercellini P, Facchin F, Buggio L, Barbara G, Berlanda N, Frattaruolo MP, et al. Management of  
1134 Endometriosis: Toward Value-Based, Cost-Effective, Affordable Care. J Obstet Gynaecol Can. 2017  
1135 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.

1153 Table 1. Studies evaluating satisfaction with estrogen-progestogens for the treatment of symptomatic endometriosis (literature data, 1996–  
 1154 2017).  
 1155

Source	Study design	Number of patients enrolled	Endometriosis location or stage <sup>a</sup>	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate <sup>b</sup>
Vercellini <i>et al.</i> , 1996 [18]	RCT	80	Stage I <i>n</i> = 14; Stage II <i>n</i> = 30; Stage III <i>n</i> = 21; Stage IV <i>n</i> = 15	DMPA 150 mg i.m. injections/3 months ( <i>n</i> = 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 ( <i>n</i> = 40)	12 months	ITT	Higher satisfaction with treatment in DMPA group (73% vs 58% in the OC group)
Vercellini <i>et al.</i> , 2002 [19]	RCT	90	Stage I <i>n</i> = 20; Stage II <i>n</i> = 19; Stage III <i>n</i> = 30; Stage IV <i>n</i> = 21	Continuous low-dose monophasic OC (EE 0.02 + DSG 0.15 mg)/day ( <i>n</i> = 45)	Cyproterone acetate 12.5 mg/day per os ( <i>n</i> = 45)	6 months	ITT	Slightly higher satisfaction with treatment in the cyproterone acetate group (73% vs 67% in the OC group)
Vercellini <i>et al.</i> , 2003 [20]	Prospective self-controlled	50 <sup>c</sup>	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 <i>et al.</i> , 2005 [21]	RCT	90	Rectovaginal endometriosis	Continuous low-dose monophasic OC (EE 0.01 + cyproterone acetate 3	NETA 2.5 mg/day per os ( <i>n</i> = 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 <sup>a</sup>	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate <sup>b</sup>
				mg)/day ( <i>n</i> =45)				
Vercellini <i>et al.</i> , 2010 [22]	PPT	207	Stage I <i>n</i> = 56; Stage II <i>n</i> = 45; Stage III <i>n</i> = 52; Stage IV <i>n</i> = 54  Rectovaginal endometriosis <i>n</i> = 59	Vaginal ring (EE 15 µg + etonogestrel 120 µg) ( <i>n</i> =123; rectovaginal endometriosis sub-group <i>n</i> = 38)	Transdermal patch (EE 20 µg + norelgestromin 150 µg) ( <i>n</i> = 84; rectovaginal endometriosis sub-group <i>n</i> = 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 <i>et al.</i> , 2012 [23]	RCT	84	Stage I <i>n</i> = 23; Stage II <i>n</i> = 15; Stage III <i>n</i> = 13; Stage IV <i>n</i> = 33	DMPA 150 mg i.m. injections/3 months ( <i>n</i> = 42)	Continuous mid-dose monophasic OC (EE 0.03 mg + gestodene 0.075 mg)/day ( <i>n</i> = 42)	24 weeks	ITT	Similar satisfaction rates (93% in DMPA group vs 88% in OC group)
Ferrari <i>et al.</i> , 2012 [24]	Prospective non-comparative	26	Colorectal endometriosis (medium-low rectum nodules <i>n</i> = 4; proximal rectum, <i>n</i> = 14; recto-sigmoid junction/sigmoid, <i>n</i> = 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 <i>et al.</i> , 2013 [25]	Retrospective	92	Post-operative administration in	Continuous low-dose	LNG-IUD ( <i>n</i> = 44)	24 months	Per-protocol	Higher satisfaction with treatment in

Source	Study design	Number of patients enrolled	Endometriosis location or stage <sup>a</sup>	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate <sup>b</sup>
			women with histologically proven endometriosis	multiphasic OC (DNG + E2V) /day ( <i>n</i> = 48)				LNG-IUD users (98% vs 83% in OC users) <sup>d</sup>
Leone Roberti Maggiore <i>et al.</i> , 2014 [26]	PPT	143	Rectovaginal endometriosis	DSG 75 µg/day per os ( <i>n</i> = 60)	Vaginal ring (EE 15 µg + etonogestrel 120 µg) ( <i>n</i> = 83)	12 months	ITT	Higher patient satisfaction with treatment in DSG group (62% vs 36% in vaginal ring group)
Morotti <i>et al.</i> , 2014 [27]	PPT	144	Rectovaginal endometriosis	DSG 75 µg/day per os ( <i>n</i> = 62)	Cyclic low-dose monophasic OC (EE 20 µg + DSG 150 µg)/day ( <i>n</i> = 82)	6 months	ITT	Higher satisfaction with treatment in DSG group (61% vs 38% in OC group)
Harada <i>et al.</i> , 2017 [17]	RCT	312 <sup>c</sup>	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, Flexible <sub>MB</sub> regimen <sup>f</sup> ( <i>n</i> = 130)	Placebo ( <i>n</i> = 129)	52 weeks <sup>g</sup>	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) <sup>h</sup>

1156 <sup>a</sup> According to the revised American Fertility Society classification [28]

1157 <sup>b</sup> Unless otherwise specified, satisfaction with treatment was based on a five-category scale (very satisfied, satisfied, uncertain, dissatisfied, very  
1158 dissatisfied)

1159 <sup>c</sup> Women with recurrent dysmenorrhea not responding to cyclic OC use

1160 <sup>d</sup> Treatment satisfaction was defined by the percentage of women who successfully completed their treatment, without requiring suspension of the  
1161 assigned regimen



1162 <sup>e</sup> 53 women were randomized to an un-blinded reference arm (DNG 2 mg/day) in order to compare the vaginal bleeding pattern of Flexible<sub>MIB</sub>  
1163 <sup>f</sup> The Flexible<sub>MIB</sub> regimen consists of a repeat cycle of 120 consecutive days of active tablet followed by a 4-day tablet-free interval, either after the  
1164 120 days or after  $\geq 3$  consecutive days of bleeding and/or spotting between days 25 and 120  
1165 <sup>g</sup> After 24 weeks, placebo recipients were changed to Flexible<sub>MIB</sub>  
1166 <sup>h</sup> Treatment satisfaction was assessed through a seven-category scale (very much satisfied, much satisfied, minimally satisfied, neither satisfied nor  
1167 dissatisfied, minimally dissatisfied, much dissatisfied, very much dissatisfied).  
1168  
1169 DNG, dienogest; DRSP, drospirenone; DSG, desogestrel; E2V, estradiol valerate; EE, ethinyl-estradiol; ITT, intention-to-treat; NA, not applicable;  
1170 LNG-IUD, levonorgestrel-intrauterine device; NETA, norethisterone acetate; OC, oral contraceptive; PPT, patient preference trial; RCT, randomized  
1171 controlled trial  
1172

1173 Table 2. Hormonal activities of progestogens investigated for the treatment of endometriosis. Literature data, 2003-2015 [59-65].

1174

1175

1176

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

1177

1178 ++ strong activity; + activity; +/- weak activity; - no activity

1179

1180

1181 Table 3. Studies evaluating satisfaction with progestogens therapies for the treatment of symptomatic endometriosis (literature data,  
 1182 1999–2017).<sup>a</sup>  
 1183

Source	Study design	Number of patients enrolled	Endometriosis location or stage <sup>b</sup>	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate <sup>c</sup>
Vercellini <i>et al.</i> , 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 <i>et al.</i> , 2003 [49]	RCT	40	Stage I <i>n</i> = 3; Stage II <i>n</i> = 6; Stage III <i>n</i> = 15; Stage IV <i>n</i> = 16	LNG-IUD ( <i>n</i> = 20)	Expectant management after laparoscopic treatment of endometriotic lesions ( <i>n</i> = 20)	12 months	ITT	Higher satisfaction with treatment in LNG-IUD group (75% vs 50% in the expectant management group)
Lockhat <i>et al.</i> , 2004 [93]	Prospective non-comparative	34	Stage I <i>n</i> = 5; Stage II <i>n</i> = 15; Stage III <i>n</i> = 6; Stage IV <i>n</i> = 0	LNG-IUD	NA	6 months	Per protocol	66% of women were satisfied or very satisfied with LNG-IUD treatment
Ferrero <i>et al.</i> , 2009 [70]	PPT	82	Rectovaginal endometriosis	Letrozole 2.5 mg + NETA 2.5 mg/day per os ( <i>n</i> = 41)	NETA 2.5 mg/day per os ( <i>n</i> = 41)	6 months	ITT	Higher satisfaction with NETA treatment only (63% vs 56% in letrozole + NETA group)
Momoeda <i>et al.</i> , 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%) <sup>d</sup>

Source	Study design	Number of patients enrolled	Endometriosis location or stage <sup>b</sup>	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate <sup>c</sup>
Walch <i>et al.</i> , 2009 [94]	RCT	41	Stage I <i>n</i> = 11; Stage II <i>n</i> = 15; Stage III <i>n</i> = 7; Stage IV <i>n</i> = 8	Etonogestrel 68 mg implant ( <i>n</i> = 21)	DMPA 150 mg i.m. injections/90 days ( <i>n</i> = 20)	12 months	ITT	Comparable satisfaction with treatment (57% in the implant group vs 55% in the DMPA group)
Ferrero <i>et al.</i> , 2010 [71]	Prospective non-comparative	40	Colorectal endometriosis (sigmoid colon <i>n</i> = 18; rectosigmoid junction <i>n</i> = 12; rectum <i>n</i> = 10)	NETA 2.5 mg/day per os <sup>e</sup>	NA	12 months	ITT	60% of the women were satisfied or very satisfied with NETA treatment
Ferrero <i>et al.</i> , 2010 [72]	Prospective non-comparative	6	Colorectal endometriosis (sigmoid colon <i>n</i> = 2; rectosigmoid junction <i>n</i> = 2; rectum <i>n</i> = 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 <i>et al.</i> , 2012 [73]	PPT	154	Stage III <i>n</i> = 64; Stage IV <i>n</i> = 90  Rectovaginal endometriosis <i>n</i> = 59	NETA 2.5 mg/day per os ( <i>n</i> = 103; rectovaginal endometriosis sub-group <i>n</i> = 35)	Second-line laparoscopic excision of endometriotic lesions ( <i>n</i> = 51; rectovaginal endometriosis sub-group <i>n</i> = 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 <sup>b</sup>	Study drug	Comparator	Treatment period	Type of analysis	Satisfaction rate <sup>c</sup>
Morotti <i>et al.</i> , 2014 [95]	Open-label prospective study non-comparative <sup>f</sup>	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 <i>et al.</i> , 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 $n = 7$ ) <sup>g</sup>	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 <i>et al.</i> , 2017 [76]	Retrospective non-comparative	103 (61 completed the 5-year follow-up)	Rectovaginal endometriosis	NETA 2.5 mg/day per os <sup>e</sup>	NA	5 years	ITT	41% of the women were satisfied or very satisfied with long term NETA treatment

1184 <sup>a</sup> Seven studies comparing an estrogen-progestogen with a progestogen are included in Table 1 [Ref: 18,19,21,23,25-27]

1185 <sup>b</sup> According to the revised American Fertility Society classification [28]

1186 <sup>c</sup> Unless otherwise specified, satisfaction with treatment was based on a five-category scale (very satisfied, satisfied, uncertain, dissatisfied, very  
1187 dissatisfied)

1188 <sup>d</sup> Patient satisfaction with treatment as determined by interview was classified into four categories (certainly willing to use again, prefer to use again,  
1189 hesitate to use again, and never willing to use again)

1190 <sup>e</sup> In case of breakthrough bleeding, the dose of NETA was increased by 2.5 mg/day (maximum dose of 5 mg/day)

1191 <sup>f</sup>This study specifically selected patients with symptomatic rectovaginal endometriosis who had pain persistence and were unsatisfied after 6-months  
1192 of treatment with NETA  
1193 <sup>g</sup>44 women had more than one lesion  
1194 DNG, dienogest; DSG; desogestrel; EE, ethinyl-estradiol; i.m., intramuscular; ITT, intention-to-treat; LNG-IUD, levonorgestrel-intrauterine device;  
1195 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