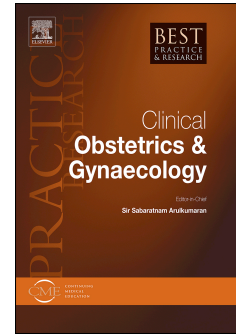# Accepted Manuscript

Medical treatment of endometriosis related pain

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1   MEDICAL TREATMENT OF ENDOMETRIOSIS RELATED PAIN

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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.

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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 hiatoplasty 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 ± 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 μg EE) is supraphysiologic, as 5 μg 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 μg of EE or 1.5 mg of 17 β-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 β-oestradiol and 2.5 mg

166 of nomegestrol 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 nor-ethisterone 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.

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.

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 Bullettin #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 6months 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. <u>High-risk lesions</u>

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

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.

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Practice Points:

- Available hormonal compounds for endometriosis are symptomatic and not curative

- As symptom recurrence is the rule at drug discontinuation, long periods of treatments should be planned in women not seeking pregnancy

- Medications for endometriosis have different safety and tolerability profiles and costs, but do not differ in terms of magnitude of the effect on pain

- Low-dose oral contraceptives and low-cost progestogens should be considered first-line medications

- High-cost compounds should be used only in women not responding or not tolerating first-line medications

Research Agenda:

- Non-teratogenic compounds that relieve pain without suppressing ovulation would allow treating also women seeking conception

- Only drugs with a selective cytoreductive effect on ectopic but not eutopic endometrium would consent the modification of the natural history of endometriosis without compromising fertility

- Epidemiological data are needed to define the potential long-term effects of prolonged use of different medications for endometriosis

- Pragmatic trials including low-dose oral contraceptives or low-cost progestogens as active comparators are needed to define the incremental benefit of novel experimental drugs

- Comparative effectiveness research on medications for endometriosis should include aspects of healthcare economic analysis such as quantification of opportunity costs

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

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

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

1156 [a] According to the revised American Fertility Society classification [28]

1157 [b] Unless otherwise specified, satisfaction with treatment was based on a five-category scale (very satisfied, satisfied, uncertain, dissatisfied, very

1158 dissatisfied)

1159 [c] Women with recurrent dysmenorrhea not responding to cyclic OC use

1160 [d] Treatment satisfaction was defined by the percentage of women who successfully completed their treatment, without requiring suspension of the

1161 assigned regimen

1162   [e] 53 women were randomized to an un-blinded reference arm (DNG 2 mg/day) in order to compare the vaginal bleeding pattern of Flexible$_{MIB}$

1163   [f] The Flexible$_{MIB}$ regimen consists of a repeat cycle of 120 consecutive days of active tablet followed by a 4-day tablet-free interval, either after the

1164   120 days or after ≥3 consecutive days of bleeding and/or spotting between days 25 and 120

1165   [g] After 24 weeks, placebo recipients were changed to Flexible$_{MIB}$

1166   [h] 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).

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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

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

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

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

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1181   Table 3. Studies evaluating satisfaction with progestogens therapies for the treatment of symptomatic endometriosis (literature data,
1182   1999–2017).[a]

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

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

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

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

1185   [b] According to the revised American Fertility Society classification [28]

1186   [c] Unless otherwise specified, satisfaction with treatment was based on a five-category scale (very satisfied, satisfied, uncertain, dissatisfied, very

1187   dissatisfied)

1188   [d] 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   [e] In case of breakthrough bleeding, the dose of NETA was increased by 2.5 mg/day (maximum dose of 5 mg/day)

1191   [f] 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   [g] 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