

1 IS SHIFTING TO A PROGESTIN WORTHWHILE WHEN ESTROGEN-PROGESTINS  
2 ARE INEFFICACIOUS FOR ENDOMETRIOSIS-ASSOCIATED PAIN?  
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4 **Running Head:** From estrogen-progestins to progestins for inefficacy on endometriosis-associated  
5 pain  
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## 26 ABSTRACT

27 The purpose of this study was to assess the proportion of patients satisfied with their treatment after  
28 a change from a low-dose oral contraceptive (OC) to norethisterone acetate (NETA) because of  
29 inefficacy of OC on pain symptoms.

30 To this end, prospective, self-controlled study was conducted on 153 women using OC as a  
31 treatment for endometriosis, and with persistence of one or more moderate or severe pain  
32 symptoms. At baseline and during 12 months after a shift from OC to oral NETA, 2.5 mg/day,  
33 pelvic pain was measured by means of a 0 to 10-point numerical rating scale and a  
34 multidimensional categorical rating scale. Variations in health-related quality of life, psychological  
35 status, and sexual function were also evaluated with validated scales. At the end of the study period  
36 participants indicated the degree of satisfaction with their treatment according to a 5-degree scale  
37 from very satisfied to very dissatisfied.

38 A total of 28 women dropped out of the study, the main reason being intolerable side effects  
39 ( $n=15$ ). At 12-month assessment, 70% of participants were very satisfied or satisfied with NETA  
40 treatment (intention-to-treat analysis). Statistically significant improvements were observed in  
41 health-related quality of life, psychological status, and sexual function. At per-protocol analysis,  
42 almost half of the patients (58/125) reported sub-optimal drug tolerability. However, complains  
43 were not severe enough to cause dissatisfaction, drug discontinuation, or request for surgery.  
44 These encouraging results could be used to counsel women with symptomatic endometriosis not  
45 responding to OC, and inform their decisions on modifications of disease management.

46

47 **KEYWORDS:** endometriosis; pelvic pain; medical treatment; combined oral contraceptives;  
48 progestins.

## 49 INTRODUCTION

50 Estrogen-progestins and progestins are currently considered as first-line treatments for symptomatic  
51 endometriosis in women not seeking pregnancy and without absolute surgical indications, such as  
52 adnexal masses of doubtful ultrasonographic appearance or large endometriomas, ureteral stenosis  
53 with hydronephrosis, and bowel stenosis causing persistent subocclusive symptoms.<sup>1-5</sup>

54 In women with endometriosis-associated pelvic pain, some authors suggest starting  
55 treatment with low-dose, combined, monophasic, oral contraceptive pills (OCs), and shifting to  
56 progestin monotherapy in case OCs are inefficacious or not tolerated.<sup>6</sup> This stepwise pharmacologic  
57 approach is based on metabolic, psychological, and practical considerations. Low-dose OCs have  
58 been proven safe when used in women without definite contraindications,<sup>7-9</sup> whereas the most  
59 popular progestins used for endometriosis treatment may alter the serum lipid profile<sup>10,11</sup> or affect  
60 bone mineralization.<sup>12-15</sup> As OCs are generally not perceived as medications for an illness, their use  
61 may limit the psychological burden of disease labelling.<sup>16,17</sup> Finally, when used continuously, OCs  
62 allow easy management of erratic bleeding through tailored cycling, whereas this modality may  
63 result less successful with progestin monotherapy.

64 However, this approach has been recently criticized as, based on published biological and  
65 clinical evidence, OCs might reveal less effective than progestins in controlling endometriosis,  
66 relieving associated pain symptoms, and preventing lesion progression.<sup>18</sup> Indeed, OCs have been  
67 indicated even as a risk factor for the development of deep, infiltrating lesions.<sup>19</sup> The issue here  
68 would be the supra-physiologic concentrations of estrogens contained in OCs, as 5 mg of ethinyl-  
69 estradiol (EE) are equivalent to around 1 mg of micronized estradiol or 0.625 mg of conjugated  
70 equine estrogen.<sup>18</sup> Thus, even low-dose OCs containing only 15-20 mg of EE would create a hyper-  
71 estrogenic environment resulting in suboptimal lesion and symptom control despite adequate  
72 combined progestin doses.<sup>18</sup>

73           Given this background, we deemed of interest to investigate which degree of pain symptom  
74 improvement and satisfaction with treatment could be obtained by shifting to a progestin  
75 monotherapy in women in whom low-dose OCs use did not relieve pain.

76

## 77 MATERIALS AND METHODS

78 The manuscript was prepared according to the Strengthening the Reporting of Observational studies  
79 in Epidemiology guidelines for reporting observational studies.<sup>20</sup> The main objective of the present  
80 study was to assess the proportion of patients satisfied with their treatment after a change from a  
81 low-dose, monophasic OC to norethisterone acetate (NETA) because of inefficacy of OC on pain  
82 symptoms (persistence of one or more moderate or severe pain symptoms, including dysmenorrhea,  
83 deep dyspareunia, non-menstrual pain, and dyschezia). Secondary objective was the evaluation of  
84 variations in pain symptoms, health-related quality of life, psychological status, and sexual function  
85 associated with the shift from OC to NETA.

86           The investigation was performed in an academic department, and the competent Institutional  
87 Review Board approved the study (Comitato Etico Fondazione IRCCS Ca' Granda - Ospedale  
88 Maggiore Policlinico, determination #786/2013). Patients signed an informed consent form before  
89 enrolment. Women who denied their consensus were excluded.

90

### 91 **Design**

92 A prospective, self-controlled study design was adopted with the objective of assessing within-  
93 person comparisons before and after the shift from OC to NETA. With this study design each  
94 participant acts as her own control, in order to avoid the inherent biases caused by differences  
95 between patients.<sup>21</sup> In fact, the objective of the study was to assess variations in efficacy when  
96 shifting to NETA not in a general population of patients taking OC, but specifically in those  
97 patients who were dissatisfied because of inefficacy of OC and that would have otherwise  
98 discontinued medical therapy.

99 **Study participants**

100 We considered 18- to 40-year old women, not seeking conception, with a surgical diagnosis  
101 of endometriosis in the previous 24 months or with a current non-surgical diagnosis of  
102 endometriosis,<sup>22</sup> and using an OC for pelvic pain, but unwilling to continue or modify (change of  
103 OC type or modality of assumption) the current treatment because of inefficacy on symptoms and  
104 overall dissatisfaction with OCs.

105 Non-surgical diagnoses were based on ultrasonographic criteria in patients with ovarian  
106 endometriomas;<sup>23,24</sup> on visual inspection of the posterior fornix and biopsy of vaginal lesions in  
107 those with rectovaginal endometriosis;<sup>10,25</sup> on ultrasonographic criteria,<sup>26</sup> cystoscopic findings, and  
108 biopsy of vesical lesions in those with bladder detrusor endometriosis; on physical signs at recto-  
109 vaginal examination and ultrasonographic criteria<sup>27,28</sup> in those with deep lesions infiltrating the  
110 Douglas pouch and parametria; and on ultrasonographic criteria<sup>23,28</sup> double contrast barium enema  
111 and rectosigmoidoscopy or colonoscopy findings in those with full-thickness bowel lesions.  
112 Magnetic resonance imaging was performed in selected circumstances.

113 Women were referred or self-referred to our tertiary-care outpatient clinic for the treatment  
114 of endometriosis. Patients were excluded in case of use of drugs that interfere with ovarian steroid  
115 metabolism; allergy to components of the study medication or to NSAIDs; abnormal findings at  
116 breast examination and mammary ultrasound scan; an abnormal cervical smear; a diagnosis of  
117 concomitant disorders that may cause pelvic pain independently of endometriosis presence (e.g.,  
118 pelvic inflammatory disease or pelvic varices or genital malformations at previous surgery; known  
119 urologic and orthopedic diseases); psychiatric disturbances; and history of drug or alcohol abuse.  
120 Participants were recruited during the period August 2014 – July 2015.

121 Women were informed that OCs are considered by some authors as the first-line treatment  
122 for endometriosis-associated pelvic pain, but that further medical therapy steps are available in case  
123 of inefficacy. They were also informed that medical therapies for endometriosis are usually  
124 effective in reducing various types of pain in more than two thirds of patients.<sup>29-31</sup> However, drugs

125 induce only temporary relief, are not expected to be definitively curative, and may cause several  
126 side effects (listed, with percentages derived from previous studies conducted in our centre).  
127 Finally, when hormonal treatments are to be continued for long periods, estrogen-progestins and  
128 progestins appear to be among the compounds that most favourably balance benefits, harm and  
129 costs.<sup>17,32-34</sup>

130 In case of pain persistence, it was explained that the estrogen included in OCs on one hand  
131 may prevent potentially detrimental effects of hypo-estrogenizing treatments (e.g., decrease in bone  
132 mineral density and unfavourable modifications in serum lipid pattern), but on the other hand may  
133 limit the therapeutic efficacy on endometriotic implants that, being estrogen-sensitive, may retain  
134 part of their metabolic activity. Women were informed that other drugs for symptomatic  
135 endometriosis were available but, owing to severe untoward effects and/or high costs, generally  
136 they were not suggested for prolonged treatment periods. Finally, patients were also informed that  
137 laparoscopic surgery was a reasonable alternative in case they declined switching from a OC to a  
138 progestin, but that pain and lesion recurrence was about 10% a year without long-term  
139 postoperative medical therapy.<sup>35,36</sup>

140

## 141 **Treatments**

142 The OCs used in our centre were monophasic formulations containing ethinyl-estradiol 0.015 mg  
143 and gestodene 60 mg or, in case of spotting, ethinyl-estradiol 0.02 mg and desogestrel 150 mg. In  
144 smokers and in those with a BMI  $\geq$  30, a combination of ethinyl-estradiol 0.02 mg and  
145 levonorgestrel 100 mg was prescribed.

146 Norethisterone acetate, a 19-nortestosterone derivative progestin, has been repeatedly  
147 evaluated in women with endometriosis,<sup>37-43</sup> and has been routinely used in our referral centre for  
148 several years.<sup>6,10,25,44</sup> Norethisterone acetate is approved by the FDA and the Italian Ministry of  
149 Health for the treatment of endometriosis and is reimbursed by the Italian National Health System.  
150 Norethisterone acetate was prescribed at the dose of 2.5 mg once a day, *per os*. The progestin was

151 started after 4-7 days since OC discontinuation, depending on the type of OC previously used, and  
152 it was continued without preplanned time limits. However, for the purpose of the present study,  
153 only the first 12 months of use have been evaluated. In case of prolonged spotting ( $\geq 7$  days) or  
154 breakthrough bleeding, the patients were advised to discontinue treatment for one week. When  
155 needed, naproxen sodium was the standard non-steroidal anti-inflammatory drug prescribed (one  
156 550-mg tablet twice a day unless contraindicated).

157

### 158 **Measurements**

159 All patients assisted in our centre systematically undergo clinical and ultrasonographic evaluation  
160 every six months. On these occasions, women are routinely asked to complete five questionnaires,  
161 two on pain (a numerical rating scale, NRS; and a multi-dimensional categorical rating scale,  
162 MCRS), one on quality of life (the Short Form-12 questionnaire, SF-12), one on psychological  
163 status (the Hospital Anxiety and Depression scale, HADS), and one on sexual functioning (the  
164 Female Sexual Function Index, FSFI). Women are also asked to indicate drug tolerability using a  
165 NRS and to rate the degree of satisfaction with their treatment.

166 The above scales and questionnaires have been described previously in detail.<sup>6,10,25,44,45</sup> The  
167 presence and severity of dysmenorrhea, deep dyspareunia, non-menstrual pelvic pain, and  
168 dyschezia were assessed using an 11-point NRS, with 0 indicating absence of pain and 10 pain as  
169 bad as it could be. Patients were also asked to grade the severity of the above symptoms using a 0-  
170 to 3-point MCRS modified from that devised by Biberoglu and Behrman.<sup>46</sup> Irregular bleeding  
171 during treatment was defined as spotting (scanty bleeding requiring  $\leq 1$  pad or tampon per day) or  
172 breakthrough bleeding (light or moderate bleeding requiring  $\geq 2$  pads or tampons per day). Pain  
173 during spotting or breakthrough bleeding was considered as dysmenorrhea.

174 The SF-12 health survey, developed from the original SF-36 questionnaire,<sup>47,48</sup> is a well  
175 know, validated self-administered 12-item instrument. It measures health dimensions covering  
176 functional status, well-being, and overall health. Information from the 12 items is used to construct

177 physical (PCS-12) and mental (MCS-12) component summary measures,<sup>49,50</sup> with higher scores  
178 indicating better health perception.

179 The HADS questionnaire is a self-assessment mood scale specifically designed for use in  
180 non-psychiatric hospital outpatients to determine states of anxiety and depression. It comprises 14  
181 questions, 7 for the anxiety subscale and 7 for the depression subscale. Lower scores indicate better  
182 psychological status.<sup>51</sup>

183 The FSFI questionnaire is a 19-item, multidimensional, self-report instrument for evaluating  
184 the main categories of female sexual dysfunction and sexual satisfaction.<sup>52-54</sup> The transformed  
185 maximum score for each domain is 6, and the maximum (best) transformed full-scale score is 36,  
186 with a minimum full-scale score of 2.0.

187 Occurrence of side effects associated with medical treatments is actively investigated in our  
188 endometriosis outpatient clinic, and the overall tolerability of hormonal therapies is measured using  
189 a 0- to 10-point NRS, with 0 indicating absolutely intolerable untoward effects and 10 absence of  
190 adverse effects. Scores are then categorized, with 9-10 indicating that a drug is very well tolerated;  
191 7-8, well tolerated; 5-6, moderately tolerated; 3-4, poorly tolerated; 0-2, not tolerated.<sup>6</sup>

192 Patients rated the degree of satisfaction after the modification of their treatment according to  
193 a five-category scale (very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very  
194 dissatisfied) by answering the following question: "Taking into consideration the variations  
195 occurred in pain symptoms, overall physical and psychological well-being, health-related quality of  
196 life, and sexual functioning, how would you define the level of satisfaction with your current  
197 treatment?" For this study, only women that were dissatisfied or very dissatisfied with their OC  
198 treatment because of inefficacy on pain (one or more persistent pain symptom > 5 points as  
199 measured by the NRS) were considered. In order to limit the potential effect of confounding,  
200 satisfaction with treatment, the main study outcome, was dichotomized into "satisfied" (very  
201 satisfied plus satisfied) and "dissatisfied" (neither satisfied nor dissatisfied plus dissatisfied plus  
202 very dissatisfied).



## 203 **Data management**

204 The focus of the investigation was not a head-to-head comparison between OC and NETA but,  
205 instead, quantification of the proportion of women who were satisfied with NETA treatment 12  
206 months after OC discontinuation because of inefficacy. No study is available to define the potential  
207 benefits of progestins over OCs in this clinical condition. Therefore, a pre-planned power  
208 calculation was not performed, and we decided to include all the eligible patients evaluated in a 1-  
209 year period.

210 Data were archived using Excel 2003 (Microsoft Corporation, Redmond, Washington,  
211 U.S.A.) and exported in SPSS 18.0 (SPSS, Inc, Chicago, IL, U.S.A.) or SAS software 9.4 (SF-12  
212 data; SAS Institute Inc., Cary, NC, U.S.A.) for statistical analysis. Estimate of patient satisfaction  
213 rate was performed according to the intention-to-treat principle, considering as dissatisfied all  
214 patients who dropped out of the study for any reason except conception seeking, thus including  
215 request for surgery and lost to follow-up. Variations in pelvic pain symptoms, health-related quality  
216 of life, psychological status, sexual functioning, and drug tolerability between baseline and 12-  
217 month values were evaluated by using the paired Student *t* test for normally distributed data, the  
218 non-parametric Wilcoxon matched pairs test for non-normally distributed data, the McNemar test  
219 for categorical variables, and the Fisher Exact test in case of cells without numerical data.

220 Determinants of satisfaction with treatment were investigated with unpaired tests (Student *t* test for  
221 normally distributed continuous variables, Wilcoxon test for non-normally distributed continuous  
222 variables, and the chi-squared test for categorical variables). All statistical tests were two-sided. A *P*  
223 value < 5% was considered statistically significant. When appropriate, 95% confidence intervals  
224 (CIs) of proportions were calculated by applying a binomial distribution model.

225

## 226 **RESULTS**

227 A total of 153 women evaluated during the recruitment period were enrolled in the study (Figure 1).  
228 The baseline demographic and clinical characteristics of the patients are shown in Table 1. Two

229 thirds of women previously underwent surgery for endometriosis, and all had stage III-IV disease  
230 according to the revised American Society for Reproductive Medicine (ASRM) classification<sup>55</sup>,  
231 except one patient who had stage II endometriosis. A total of 116 (76%) patients had deep  
232 endometriotic lesions, and 91 (60%) had ovarian endometriomas. The median [interquartile range,  
233 IQR] duration of previous OC use was 9 [5–24] months. One hundred-two women (67%) were  
234 using OC cyclically and 51 (33%) continuously. Sixty-four subjects (42%) were dissatisfied with  
235 OC use also because of side effects in addition to inefficacy on pain symptoms. However,  
236 inefficacy was the main reason for dissatisfaction also in these 64 subjects independently of  
237 intolerance. The most frequent side effects were headache (15%) and spotting/breakthrough  
238 bleeding (15%).

239 A total of 125 women completed the preplanned 12-month study period, whereas 28 (18%)  
240 dropped out of the study before the 6-month follow-up evaluation ( $n = 2$ ), or between the 6- and the  
241 12-month assessment ( $n = 26$ ; Figure 1). Overall, 15 women referred one or more intolerable side  
242 effects with NETA as the reason for abandoning the study (headache  $n = 7$ ; erratic bleeding,  $n = 6$ ;  
243 weight increase,  $n = 4$ ; abdominal bloating,  $n = 4$ ; acne,  $n = 2$ ; mood nausea, decreased libido,  
244 vaginal dryness, breast tenderness, depressed mood,  $n = 1$  each).

245 A significant reduction in symptoms' severity as measured by both the NRS and the MCRS  
246 scales was observed when comparing baseline and 12-month measurements (Table 2). Median  
247 [IQR] dysmenorrhea NRS scores decreased from 8 [6-9] to 0 [0-0] after 1 year of NETA treatment.  
248 According to the MCRS, menstrual pain was moderate or severe in 94/125 (75%) women at  
249 baseline evaluation, but in only one at 12-month follow-up assessment. The variations in deep  
250 dyspareunia, non-menstrual pain, and dyschezia followed a similar pattern. In particular, median  
251 [IQR] deep dyspareunia NRS scores, evaluated in the 114 women who were sexually active both at  
252 baseline and 12-month follow-up, decreased from 7 [1-8] to 0[0-5]. According to the MCRS 54/114  
253 (47%) women suffered from moderate-to severe pain at intercourse at baseline, compared with  
254 15/114 (13%) after 1 year of NETA treatment (Table 2).

255           Only the physical component of the SF-12 improved at the end of the study period, whereas  
256 no substantial variation was observed in the mental component of the health-related quality of life  
257 questionnaire (Table 2). However, when the psychological status was evaluated by means of  
258 HADS, significant reductions were observed in the scores of both anxiety and depression  
259 questionnaire components. According to the FSFI, a statistically significant amelioration of sexual  
260 functioning was observed in the 114 sexually active women at baseline and end of follow-up (Table  
261 2).

262           At final per-protocol analysis, almost half of the patients (58/125) reported sub-optimal drug  
263 tolerability. However, complains were not severe enough to cause dissatisfaction, drug  
264 discontinuation, or request for surgery. Side effects referred at baseline and at 12-month evaluation  
265 are shown in Table 3. After switching from OC to NETA, the prevalence of headache, spotting, and  
266 nausea decreased significantly. The mean  $\pm$  SD tolerability score as assessed by the NRS increased  
267 from  $5.4 \pm 2.6$  during OC use to  $6.9 \pm 2.5$  after 12 months of NETA treatment. Overall, 34%  
268 (42/125) women scored their tolerability as good or very good ( $\text{NRS} \geq 7$ ), compared with 54%  
269 (67/125) at 12-month assessment.

270           When evaluating the degree of satisfaction with NETA treatment at the end of the study  
271 period, four women who discontinued the drug between 6- and 12-month follow-up visits because  
272 of pregnancy desire were excluded, as variation in satisfaction with treatment during time is  
273 unpredictable. Eventually, 105/149 patients (70%; 95% C.I., 63% to 77%) were satisfied or very  
274 satisfied with NETA treatment, whereas 44/149 (30%; 95% C.I., 23% to 37%) were neither  
275 satisfied nor dissatisfied, dissatisfied, or very dissatisfied. The baseline demographic and clinical  
276 characteristics of the 105 patients satisfied with NETA treatment and those of the 44 dissatisfied  
277 ones were substantially similar. A statistically significant difference was observed only for non-  
278 menstrual pain, which was more severe at both the NRS and the MCRS in the group of dissatisfied  
279 patients (Supplemental Tables 1 and 2).

280 The impact of the two potentially relevant variables, i.e., the modality of OC use (cyclic  
281 versus continuous) before switching to NETA, and type of endometriotic lesions (deep lesions  
282 versus ovarian endometriomas) was investigated. The proportion of satisfied patients was 24/33  
283 (73%; 95% C.I., 57% to 86%) in women with deep lesions and previous continuous OC use; 54/80  
284 (68%; 95% C.I., 57% to 77%) in those with deep lesions and previous cyclic OC use; 11/17 (65%;  
285 95% C.I., 42% to 84%) in those with ovarian endometriosis and previous continuous OC use; and  
286 16/19 (84%; 95% C.I., 64% to 96%) in those with ovarian endometriosis and previous cyclic OC  
287 use.

288

## 289 DISCUSSION

290 According to the results of the present study, slightly more than two thirds of women with  
291 endometriosis experiencing pelvic pain symptoms despite OC use were satisfied one year after  
292 shifting to NETA treatment. The satisfaction rate at the end of the study period was not significantly  
293 influenced neither by the modality of previous OC use, nor by the type of endometriotic lesion  
294 present, thus supporting the consistency of the general results. However, with one exception, all the  
295 patients who underwent previous surgery had ASRM stage III-IV endometriosis, and all those who  
296 were recruited based on non-surgical criteria had ovarian endometriomas or deep infiltrating  
297 lesions. Therefore, our results may not be generalizable to women with early stage disease.

298 Pain symptoms' scores decreased during NETA treatment. The reduction of dysmenorrhea  
299 scores was expected as most participants experienced progestin-induced amenorrhea. The effect of  
300 NETA on deep dyspareunia is worthier of note and confirms our previous findings on patients with  
301 severe pain at intercourse.<sup>25,44</sup> Only a tiny minority of women referred moderate or severe non-  
302 menstrual pain and dyschezia at the end of the study period. Overall, except some women with deep  
303 dyspareunia as their main complaint, the shift from an OC to NETA was of substantial benefit for  
304 patients who were still moderately or severely symptomatic despite OC use. This seems important  
305 because, in similar circumstances, this “third way” can be chosen as an alternative to stepping-up by

306 using drugs with less favorable therapeutic profiles (e.g., GnRH agonists and danazol) or  
307 undertaking surgery. Moreover, this finding supports the view that, in some women, the estrogen  
308 component of OCs may not allow sufficient inhibition of ectopic endometrium metabolism, thus  
309 occasionally limiting the efficacy of these medications in relieving endometriosis-associated pelvic  
310 pain symptoms.<sup>18</sup>

311 Also the increased tolerability of NETA compared with that of OC may have influenced the  
312 likelihood of being satisfied with the treatment received. Indeed, as medical therapy for  
313 endometriosis is not definitively curative, the issue of tolerability, in addition to that of safety and  
314 efficacy, is crucial, because long periods of treatment should be foreseen. The reduction in the  
315 frequency of nausea and headache after shifting from OC to NETA was expected, as these side  
316 effects are typically associated with estrogens.<sup>56</sup> The decrease in the frequency of spotting confirms  
317 the good control of NETA on erratic uterine bleeding.<sup>6,10,39,40,43</sup>

318 Nevertheless, slightly less than half of the patients who completed the study period (per-  
319 protocol analysis) referred that NETA was moderately, poorly, or not tolerable, although not to the  
320 point of causing dissatisfaction, drug discontinuation, or request for surgery. Moreover, the majority  
321 of participants who dropped out of the study did so because of side effects. Tolerance is a  
322 determinant of patient compliance and adherence to drugs, and should receive more focus in future  
323 trials on medical treatment for endometriosis. In fact, according to major international guidelines,  
324 the efficacy of various hormonal compounds on pain is similar, whereas side effects vary.<sup>1-4</sup>

325 The physical component of the SF-12 questionnaire improved significantly during NETA  
326 treatment, whereas the mental component did not. This last finding is at odds with the ameliorations  
327 observed in both the anxiety and depression dimensions of the HADS scale. We do not have an  
328 explanation for this apparent discrepancy, and random fluctuation of data, or incapacity of the SF-  
329 12 scale to capture differences in this particular domain, cannot be excluded.

330 Also sexual function, as measured by the FSFI, improved significantly. However, as  
331 repeatedly observed,<sup>6,44,57</sup> the mean score remained well below the cut-off for a physiologic

332 condition. We have previously interpreted this finding as a demonstration that impacting on a single  
333 dimension, i.e., pain at intercourse, of a multifactorial experience such as sexual life, may not  
334 completely restore a complex physiological function. Moreover, NETA reduced libido and  
335 lubrication in some women. However, also it may not be excluded that the FSFI cut-off may be  
336 inappropriate for a population of endometriosis patients. Therefore, observing the overall trend in  
337 FSFI scores' variation during treatment might be more opportune than focusing on the achievement  
338 of the exact and potentially arbitrary cut-off score of 26.55.

339         The self-controlled design may appear as a limitation of our study. However, this model was  
340 chosen because our aim was not to compare OC and NETA in a parallel-group, randomized,  
341 controlled trial (RCT), but rather to evaluate sequentially the effect of NETA used as a second-line  
342 treatment modality specifically in a selected group of non-responders to OC. In this setting,  
343 recruited patients acted as their own control, thus limiting the effect of confounding inherent to  
344 other designs. In fact, relevant characteristics that can influence study outcomes may differ between  
345 patients.<sup>21</sup> The use of multivariable analyses should account for these differences in observational  
346 studies, but residual confounding may not be excluded. Moreover, the intention-to-treat analysis  
347 adopted to investigate patient satisfaction included all drop-outs except women who discontinued  
348 treatment to seek a conception. Thus, overoptimistic results should have been avoided. Moreover,  
349 even if a placebo effect cannot be excluded, it is presumably limited given that this is a population  
350 of women who already experienced a treatment failure and were thus presumably less prone to a  
351 placebo effect. Noteworthy, given the pragmatic approach of this study, i.e., reflecting real world  
352 clinical management, the existence of a placebo component in the determinisms of the observed  
353 findings would not invalidate the general conclusions.

354         However, the "regression toward the mean" phenomenon could theoretically explain at least  
355 partly the results observed in a self-controlled study. In fact, extreme values are likely unduly  
356 influenced by random variation and, when re-measured, they tend to be closer to the mean of the  
357 original population from which the study subjects were drawn.<sup>58,59</sup> Therefore, when the patients'

358 conditions are worse than average and they are enrolled in a self-controlled study of a new therapy  
359 because standard regimens seem to have lost efficacy, some general amelioration may occur that  
360 has nothing to do with improved treatment.<sup>58</sup> Despite this, the impact of regression toward the mean  
361 should have been limited in our study, as we considered patients complaining of chronic and fairly  
362 stable pain symptoms that were measured on more than one occasion during the pre-enrollment  
363 phase.<sup>58</sup>

364         Observational studies are not suited to assess efficacy, that is whether a new, experimental  
365 treatment can work. For this purpose, the explanatory RCT is the standard investigational modality.  
366 However, observational studies can be used to assess whether interventions that have already been  
367 proven to work under ideal circumstances, work also in real life.<sup>60,61</sup> Therefore, observational  
368 studies are useful to evaluate effectiveness and efficiency and, in case of medical treatment for  
369 endometriosis, to define the prospective role of the available medications in different clinical  
370 conditions.<sup>61</sup>

371         A pre-planned power analysis was not performed, but the sample size of our study was  
372 larger than that theoretically required to detect as statistically significant the observed difference  
373 between baseline and 12-month follow-up values in most outcome measures. The relatively high  
374 dropout rate (28/153, 18%) was not surprising, given that the study population was generally at  
375 unfavourable prognosis considering the persistence of moderate to severe pain symptoms despite  
376 OC use, and the related patient dissatisfaction status. In this regard, it may be hypothesized that the  
377 use of dienogest instead of NETA could have led to greater efficacy<sup>57</sup> and/or better tolerability,<sup>6</sup> and  
378 thus higher degree of satisfaction with treatment. However, we have selected NETA because many  
379 patients in our centre cannot afford the much higher cost of dienogest.<sup>6</sup> In fact, our general policy is  
380 to prescribe dienogest only in case of intolerance to NETA.

381         In our opinion, the results of the present study should not lead to systematic prescription of  
382 progestins as the first-line treatment for endometriosis, but should rather be used when counselling  
383 non-respondents to OCs. Progestin treatment for years may raise some safety concerns.<sup>11,14-16,62,63</sup>

384 Therefore, these drugs should be chosen to step-up when OC are not effective on pain (or not  
385 tolerated or contraindicated), or in presence of severely infiltrating lesions, when a more profound  
386 inhibition of ectopic endometrium metabolism is desirable. More in general, we believe that the  
387 current approach to management of endometriosis, characterized by selection, among available  
388 alternatives, of the purportedly most efficacious intervention on the basis of head-to-head  
389 comparisons, should be substituted by a stepwise approach that takes into consideration not only  
390 absolute efficacy, but also safety, tolerability, and costs, in order to define an overall therapeutic  
391 profile. Medications with the most favorable therapeutic profile should be chosen first, stepping-up,  
392 in non-responders only, to medications that, although with a less favourable overall therapeutic  
393 profile, are more effective on pain.<sup>16</sup>

394 We are convinced that women suffering from endometriosis badly need answers to  
395 questions that matter to them. These questions are those that physicians face in their everyday  
396 practice. Performance of RCTs is nowadays problematic for independent investigators, owing to  
397 unreasonable increase in administrative bureaucracy and often unaffordable insurance costs.<sup>61</sup> On  
398 the other hand, industry supported, explanatory RCTs have almost exclusively registration purposes  
399 and may not provide those answers that are important to patients.<sup>34,64,65</sup> Indeed, we are not aware of  
400 RCTs investigating medical or surgical alternatives specifically for symptomatic women not  
401 responding to OC use. With this study we have tried to provide a pragmatic description of what  
402 could be obtained by simply shifting from an OC to an inexpensive progestin. In this frequently  
403 encountered clinical situation, two out of three patients benefitted from this change of medication,  
404 and were satisfied with the new treatment after one year of use. Precisely because our investigation  
405 was not conducted under ideal experimental conditions, our data should be generalizable and could  
406 be used to counsel non-responders to OC, in order to help informing their decisions on how to  
407 modify the management of their disease.

408



## 409 AUTHOR CONTRIBUTIONS

410 PV: conception and design of the study, manuscript preparation; FO, MPF, and LB: acquisition and  
411 analysis of data; AR: analysis and interpretation of health-related quality of life data; ES:  
412 conception and design of the study, analysis and interpretation of data; all the authors: critical  
413 revision of the article for important intellectual content, and approval of the final version of the  
414 manuscript.

415

## 416 FUNDING

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

420

## 421 CONFLICT OF INTEREST

422 PV, FO, MPF, LB, and AR declare that there is no conflict of interest. ES received grants from  
423 Ferring and Serono.

424

## 425 ETHICAL APPROVAL

426 All procedures performed in this study involving human participants were in accordance with the  
427 ethical standards of the institutional and/or national research committee and with the 1964 Helsinki  
428 declaration and its later amendments or comparable ethical standards.

429 FIGURE LEGENDS

430 Figure 1. Flow-chart showing recruitment and progression through the study of women who shifted  
431 from OC to NETA because of inefficacy on pain symptoms.

432

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Table 1. Distribution of baseline demographic and clinical characteristics of women who shifted to norethisterone acetate for inefficacy of low-dose oral contraceptive ( $n = 153$ ).

Characteristic	Enrolled patients ( $n = 153$ )
Age (years)	33.4 $\pm$ 5.4
BMI (Kg/m <sup>2</sup> )	21.4 $\pm$ 3.7
Smoking	31 (20.3%)
Previous deliveries	37 (24%)
Previous interventions for endometriosis <sup>a</sup>	
None	51 (33%)
1	79 (52%)
2	18 (12%)
$\geq 3$	5 (3%)
Endometriotic lesion type <sup>b</sup>	
Deep infiltrating endometriosis	116 (76%)
Ovarian endometriomas	91 (60%)
Estroprogestin use	
Duration [months]	9 [5-24]
Continuous use	51 (33%)
Cyclic use	102 (67%)

Data is reported as mean  $\pm$  SD, or number (percentage), or median [interquartile range].

BMI = body mass index.

<sup>a</sup> A total of 101/102 of the women who underwent previous surgery had stage III-IV endometriosis according to the revised American Society for Reproductive Medicine classification<sup>55</sup>.

<sup>b</sup>The sum does not add to the total as some women had both lesion types.

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**Table 2.** Per-protocol analysis<sup>a</sup> of pain symptoms, health-related quality of life, psychological status, and sexual functioning scores variation between baseline and 12-month evaluation in patients ( $n = 125$ ) shifting from low-dose oral contraceptive to norethisterone acetate for inefficacy on pain.

Symptoms / Questionnaires	Baseline	12 months	<i>P</i>
<b>Dysmenorrhea</b>			
NRS	8 [6-9]	0 [0-0]	<0.001
MCRS $\geq 2$	94 (75%)	1 (1%)	<0.001
<b>Deep dyspareunia<sup>b</sup></b>			
NRS	7 [1-8]	0 [0-5]	<0.001
MCRS $\geq 2$	54 (47%)	15 (13%)	<0.001
<b>Non-menstrual pelvic pain</b>			
NRS	5 [0-7]	0 [0-2]	<0.001
MCRS $\geq 2$	48 (38%)	4 (3%)	<0.001
<b>Dyschezia</b>			
NRS	4 [0-7]	0 [0-0]	<0.001
MCRS $\geq 2$	52 (42%)	5 (4%)	<0.001
<b>SF-12</b>			
Physical component	30.7 $\pm$ 11.0	53.4 $\pm$ 6.7	<0.001
Mental component	45.0 $\pm$ 9.7	46.3 $\pm$ 9.9	NS
<b>HADS</b>			
Anxiety	12.3 $\pm$ 6.6	9.5 $\pm$ 6.4	<0.001
Depression	6.2 $\pm$ 3.3	5.0 $\pm$ 3.2	0.001
Total	6.1 $\pm$ 3.6	4.5 $\pm$ 3.6	<0.001
FSFI total score <sup>b</sup>	21.4 $\pm$ 6.3	24.5 $\pm$ 6.4	<0.001

Data is reported as mean  $\pm$  SD, or number (percentage), or median [interquartile range].

NRS = 0-10-point Numerical rating scale. MCRS = 0-3-point multidimensional categorical rating scale modified from that devised by Biberoglu and Behrman<sup>46</sup>. SF-12 = Short Form-12<sup>50</sup>. HADS = Hospital Anxiety and Depression Scale<sup>51</sup>. FSFI = Female Sexual Function Index<sup>52,53</sup>. NS = not significant.

<sup>a</sup>Women who withdrew before 12-month follow-up assessment ( $n = 28$ ) were excluded.

<sup>b</sup>Eleven women did not have sexual intercourses either at baseline and/or at 12-month evaluation.

Table 3. Per-protocol analysis of frequency of side effects reported at baseline and at 12-month evaluation by patients ( $n = 125$ ) shifting from oral contraceptive to norethisterone acetate.

Side effects <sup>a</sup>	Baseline	12 months	<i>P</i>
Headache	42 (34%)	28 (22%)	0.03
Spotting	39 (31%)	11 (9%)	<0.001
Breakthrough bleeding	4 (3%)	0 (0%)	NS
Weight gain	32 (26%)	38 (30%)	NS
Nausea	11 (9%)	2 (2%)	0.001
Decreased libido	35 (28%)	45 (36%)	NS
Vaginal Dryness	37 (30%)	44 (35%)	NS
Bloating or swelling	17 (14%)	13 (10%)	NS
Breast tenderness	6 (5%)	5 (4%)	NS
Acne	1 (1%)	3 (2%)	NS
Alopecia	0 (0%)	3 (2%)	NS
Mood disorders	9 (7%)	17 (14%)	NS
Others	13 (10%)	14 (11%)	NS

<sup>a</sup>Some women reported more than one side effect.

Data are number (percentage).

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**Supplemental Table 1.** Comparison of the baseline demographic and clinical characteristics of women who were satisfied and women who were not satisfied after 12 months of treatment with norethisterone acetate ( $n = 149$ ).

Characteristic	Satisfied $n = 105$	Not satisfied $n = 44$	<i>P</i>
Age (years)	33.4 ± 5.5	33.5 ± 5.4	NS
BMI (Kg/m <sup>2</sup> )	21.3 ± 3.6	21.4 ± 4.3	NS
Smoking	20 (69%)	9 (31%)	NS
Previous deliveries	25 (67%)	12 (33%)	NS
Previous interventions for endometriosis <sup>a</sup>	75 (74%)	26 (26%)	NS
Endometriotic lesion type <sup>b</sup>			
Deep infiltrating endometriosis	78 (69%)	35 (31%)	NS
Ovarian endometriomas	68 (76%)	21 (24%)	NS
Estroprogestin use			
Duration [months]	9 [6-14]	10 [4-24]	NS
Continuous use	35 (70%)	15 (30%)	NS
Cyclic use	70 (71%)	29 (29%)	
Pain symptoms			
Dysmenorrhea	83 (71%)	33 (29%)	NS
Deep dyspareunia <sup>c</sup>	57 (70%)	24 (30%)	NS
Non-menstrual pelvic pain	59 (68%)	28 (32%)	NS
Dyschezia	37 (66%)	19 (34%)	NS
Side effects (in addition to pain)	44 (70%)	19 (30%)	NS

Data is reported as mean ± SD, or median [interquartile range], or number (percentage). Row percentages are reported.

BMI = body mass index. NS = not significant.

Women who withdrew for seeking pregnancy ( $n=4$ ) were excluded.

Women who withdrew before the 12-month follow-up were considered as not satisfied ( $n=24$ ).

<sup>a</sup>A total of 100/101 of the women who underwent previous surgery had stage III-IV endometriosis according to the revised American Society for Reproductive Medicine classification<sup>55</sup>.

<sup>b</sup>The sum does not add to the total as some women had both lesion types.

<sup>c</sup>Eleven women did not have sexual intercourses either at baseline and/or at 12-month evaluation.

**Supplemental Table 2.** Comparison of baseline clinical assessment of women who were satisfied and women who were not satisfied after 12 months of treatment with norethisterone acetate ( $n = 149$ ).

Symptoms / Questionnaires	Satisfied $n = 105$	Not satisfied $n = 44$	<i>P</i>
<b>Dysmenorrhea</b>			
NRS	8 [6-9]	7 [5-8]	NS
MCRS $\geq 2$	80 (76%)	31 (70%)	NS
<b>Deep dyspareunia <sup>a</sup></b>			
NRS	7 [0-8]	8 [4-9]	NS
MCRS $\geq 2$	46 (45%)	25 (61%)	NS
<b>Non-menstrual pelvic pain</b>			
NRS	5 [0-7]	7 [5-8]	0.002
MCRS $\geq 2$	37 (35%)	25 (57%)	0.015
<b>Dyschezia</b>			
NRS	4 [0-7]	6 [0-8]	NS
MCRS $\geq 2$	44 (42%)	23 (52%)	NS
<b>SF-12</b>			
Physical component	30.1 $\pm$ 10.3	31.3 $\pm$ 12.8	NS
Mental component	45.4 $\pm$ 9.6	44.2 $\pm$ 9.9	NS
<b>HADS</b>			
Anxiety	6.0 $\pm$ 3.2	6.2 $\pm$ 3.3	NS
Depression	6.0 $\pm$ 3.5	6.5 $\pm$ 4.0	NS
Total	12.0 $\pm$ 6.4	12.7 $\pm$ 7.0	NS
FSFI total score <sup>a</sup>	21.5 $\pm$ 6.2	21.2 $\pm$ 6.4	NS
<b>Tolerability<sup>b</sup></b>			
NRS	5.4 $\pm$ 2.5	5.9 $\pm$ 2.9	NS
Well tolerated (NRS $\geq 7$ )	35 (33%)	18 (41%)	NS

Data is reported as mean  $\pm$  SD, or median [interquartile range], or number (percentage).

NRS = 0-10-point Numerical rating scale. MCRS = 0-3-point multidimensional categorical rating scale modified from

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that devised by Biberoglu and Behrman<sup>46</sup>. SF-12 = Short Form-12<sup>50</sup>. HADS = Hospital Anxiety and Depression

Scale<sup>51</sup>. FSFI = Female Sexual Function Index<sup>52,53</sup>. NS = not significant.

Women who withdrew for seeking pregnancy (n=4) were excluded.

Women who withdrew before the 12-month evaluation were considered as not satisfied (n=24).

<sup>a</sup>Refers to 99 satisfied women and 41 not satisfied women.

<sup>b</sup>Assessed using a 0 to 10-point numeric scale and a 5-category scale: very well tolerated, well tolerated, moderately tolerated, poorly tolerated, not tolerated.