

1 MEDICAL TREATMENT OR SURGERY FOR COLORECTAL ENDOMETRIOSIS?
2 RESULTS OF A SHARED DECISION MAKING APPROACH

3
4 **Running title:** Progestins or surgery for colorectal endometriosis

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28 ABSTRACT

29 **Study question:** Which is the degree of patient satisfaction in women with symptomatic colorectal
30 endometriosis who choose medical or surgical treatment after a shared decision making (SDM)
31 process?

32 **Summary answer:** The degree of satisfaction with treatment was high both in women who chose
33 medical treatment with a low-dose oral contraceptive (OCP) or a progestin, and in those who chose
34 to undergo surgical resection of bowel endometriosis.

35 **What is known already:** Hormonal therapies and surgery for colorectal endometriosis have been
36 investigated in non-comparative studies with inconsistent results.

37 **Study design, size, duration:** Parallel cohort study conducted on 87 women referring to our centre
38 with an indication to surgery for colorectal endometriosis. A standardised SDM process was
39 adopted, allowing women to choose their preferred treatment. Median follow-up was 40 [18-60]
40 months in the medical therapy group and 45 [30-67] in the surgery group.

41 **Participants, setting, methods:** Patients with endometriosis infiltrating the proximal rectum, the
42 rectosigmoid junction, and the sigmoid, not causing severe sub-occlusive symptoms were enrolled.
43 A total of 50 patients chose treatment with an OCP ($n = 12$) or a progestin ($n = 38$), whereas 37
44 women confirmed their previous indication to surgery. Patient satisfaction was graded according to
45 a five-category scale. Variations in bowel and pain symptoms were measured by means of a 0 to 10
46 numeric rating scale. Constipation was assessed with the Knowles-Eccersley-Scott Symptom
47 Questionnaire (KESS), health-related quality of life with the Short Form-12 questionnaire (SF-12),
48 psychological status with the Hospital Anxiety and Depression scale (HADS), and sexual
49 functioning with the Female Sexual Function Index (FSFI).

50 **Main results and the role of chance:** Six women in the medical therapy group requested surgery
51 because of drug inefficacy ($n = 3$) or intolerance ($n = 3$). Seven major complications were observed
52 in the surgery group (19%). At 12-month follow-up, 39 (78%) women in the medical therapy group
53 were satisfied with their treatment, compared with 28 (76%) in the surgery group (adjusted OR,

54 1.37; 95% CI, 0.45 to 4.15; intention-to-treat analysis). Corresponding figures at final follow-up
55 assessment were 72% in the former group and 65% in the latter one (adjusted OR, 1.74; 95% CI,
56 0.62 to 4.85). The 60-month cumulative proportion of dissatisfaction-free participants was 71% in
57 the medical therapy group compared with 61% in the surgery group ($P = 0.61$); the Hazard
58 incidence rate ratio was 1.21 (95% CI, 0.57 to 2.62). Intestinal complaints were ameliorated by both
59 treatments. Significant between-group differences in favour of medical treatment were observed at
60 12-month follow-up in diarrhoea, dysmenorrhoea, non-menstrual pelvic pain, and SF-12 physical
61 component scores. The total HADS score improved significantly in both groups, whereas the total
62 FSFI score improved only in women who chose medical therapy.

63 **Limitations, reasons for caution:** As treatments were not randomly assigned, selection bias and
64 confounding are likely. The small sample size exposes to the risk of type II errors.

65 **Wider implications of the findings:** When adequately informed and empowered through a SDM
66 process, most patients with non-occlusive colorectal endometriosis who had already received a
67 surgical indication, preferred medical therapy. The possibility of choosing the preferred treatment
68 may allow maximisation of the potential effect of the interventions.

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76 **KEYWORDS:** endometriosis, colorectal endometriosis, constipation, surgery, medical treatment.

77

78 INTRODUCTION

79 Deep bowel endometriosis, i.e., endometriosis infiltrating at least the intestinal muscular layer
80 (Chapron *et al.*, 2006), appears to affect about one tenth of woman with endometriotic disease
81 (Koninckx *et al.*, 2012; Abrão *et al.*, 2015). When endometriosis causes evident bowel obstruction,
82 emergency surgery and segmental resection is the only reasonable choice.

83 However, most patients with deep bowel endometriosis complain of cyclic and non-cyclic
84 symptoms, such as abdominal bloating, intestinal cramping, diarrhoea, and constipation, without
85 obvious obstruction to stool passage. Symptoms may be associated not only with the degree of
86 endometriotic infiltration and bowel lumen restriction, but also with lesion localization (Chapron *et*
87 *al.*, 2006; Roman *et al.*, 2012). The rectosigmoid colon is the most frequently involved intestinal
88 tract, followed by isolated nodules of the proximal sigmoid, and by lesions of the terminal ileus and
89 cecum (Vercellini *et al.*, 2004; Abrão *et al.*, 2015; Roman *et al.*, 2017a).

90 According to some authors, excisional surgery is the best solution for women with
91 symptomatic intestinal endometriosis, as medical treatments may exert an effect on the endometrial
92 and smooth muscle component of the nodule, but not on the extensive fibrotic component, thus
93 providing limited benefit (Remorgida *et al.*, 2007; Minelli *et al.*, 2009; Abrão *et al.*, 2015; Milone
94 *et al.*, 2015). However, several investigators observed substantial improvements of bowel
95 symptoms during treatment with low-dose, monophasic oral contraceptive pills (OCP) or progestins
96 (Ferrero *et al.*, 2010a, 2010b; Ferrari *et al.*, 2012; Yela *et al.*, 2015; Leonardo-Pinto *et al.*, 2017).
97 Egekvist *et al.* (2017) reported that 56% of 238 women with symptomatic rectosigmoid
98 endometriosis eventually avoided surgery by using OCPs or progestins.

99 Disentangling the uncertainties on the role of medical therapy in women with this
100 infiltrating endometriosis form is exceedingly important, as excisional procedures with opening of
101 the bowel lumen are generally effective in relieving intestinal symptoms, but are also associated
102 with severe short- and long-term complications.

103 Only non-comparative studies are available on treatment of intestinal endometriosis with
104 either medical therapy or surgery. Participants are being recruited in a French randomised,
105 controlled trial comparing medical and surgical treatment for rectal endometriosis, but results will
106 be available at the end of 2019
107 ([https://www.clinicaltrials.gov/ct2/show/NCT01973816?term=endometriosis+AND+France&draw](https://www.clinicaltrials.gov/ct2/show/NCT01973816?term=endometriosis+AND+France&draw=4&rank=24)
108 [=4&rank=24](https://www.clinicaltrials.gov/ct2/show/NCT01973816?term=endometriosis+AND+France&draw=4&rank=24). Accessed on October 1, 2017).

109 In our centre, a consistent shared decision making (SDM) approach is systematically applied
110 whenever a complex choice should be made between medical and surgical treatment in the absence
111 of robust evidence demonstrating definite advantages of one therapeutic balance over the other.
112 Therefore, we deemed it important to evaluate the impact of this process on patients who had
113 already received an indication for excision of deep endometriosis infiltrating the rectosigmoid
114 colon, and to assess the effectiveness of hormonal manipulation and surgery in relieving bowel
115 symptoms in women who chose their preferred option.

116 The primary end-point of the study was patient satisfaction with treatment. Variations in
117 intestinal and pain symptoms, sexual functioning, psychological status, and health-related quality of
118 life were also assessed.

119

120 MATERIALS AND METHODS

121 This parallel cohort study evaluated the medium- (12 months) and long-term outcomes (> 12
122 months) of two therapeutic alternatives, that is, long-term treatment with a low-dose, monophasic
123 OCP or a progestin, and excisional surgery, for symptomatic deep bowel endometriosis infiltrating
124 the sigmoid colon, the rectosigmoid junction or the proximal rectum. The study was conducted
125 retrospectively on prospectively and systematically recorded data. The investigation, performed in
126 an academic department specialising in endometriosis management, was approved by the local
127 institutional review board (Comitato di Etica Milano Area B; determination #1123/2017). All
128 patients signed a written consent for participation in the study.

129 **Study population**

130 We considered 18–50-year-old women not wanting pregnancy, who received an indication
131 for surgical excision of intestinal endometriosis, and were referred to our centre between January
132 2011 and January 2016 for an expert opinion or for performing the surgical procedure. The
133 diagnosis of deep intestinal endometriosis was based on rectal endosonography to define the level
134 of rectal involvement and to determine the depth of rectal wall infiltration; double-contrast barium
135 enema to ascertain the presence and degree of colorectal stenosis; colonoscopy or sigmoidoscopy to
136 exclude chronic inflammatory bowel diseases and malignancies and investigate additional proximal
137 localisations in selected circumstances; and magnetic resonance imaging and CT colonography to
138 better define the overall anatomic conditions of the affected bowel tract and associated
139 endometriotic pelvic lesions in some women. The diagnostic work-up includes kidney and urinary
140 tract ultrasonography to rule out hydro-utereronephrosis and bladder nodules.

141 Subjects with persistent, cyclic or non-cyclic intestinal symptoms of more than 6
142 months' duration, and an instrumental diagnosis of endometriosis infiltrating the muscular layer of
143 the proximal rectal tract (≥ 8 cm from the anal verge), the rectosigmoid junction (13 to 15 cm from
144 the anal verge) and the sigmoid (> 15 cm from the anal verge) were deemed eligible for the study.
145 Nodules of the distal rectum (within 8 cm from the anal verge) were not included, as generally they
146 are part of rectovaginal endometriosis forms and, in our opinion, should be considered separately.
147 (Vercellini *et al.*, 2009a). Exclusion criteria were: bowel stenosis associated with obstinate sub-
148 occlusive symptoms (e.g., nausea and vomiting not limited to the days of menstruation, frequent
149 episodes of colicky pain with abdominal distension (> 1 per month), habitual emission of small-
150 calibre stool); detection of $\geq 60\%$ stenosis of the bowel lumen independently of subocclusive
151 symptoms (Figure 1); previous surgery for intestinal endometriosis; previous endoscopy-based
152 diagnosis of chronic inflammatory bowel diseases (Crohn's disease; ulcerative colitis); evidence of
153 complex adnexal cysts or an ovarian endometrioma of diameter > 4 cm at vaginal ultrasonography;
154 the typical contraindications to oestrogen-progestins; and unwillingness to tolerate menstrual

155 changes. Previous surgery for endometriosis not involving the bowel was not considered an
156 exclusion criterion.

157 **Treatments**

158 In case of symptomatic bowel endometriosis, women are informed that data supporting the
159 efficacy of hormonal therapies for the relief of intestinal symptoms, although generally favourable,
160 do not allow to draw conclusions on long-term outcomes, as they are derived from non-comparative
161 observational studies with short periods of treatment. They are also informed that medical therapies
162 for endometriosis induce only temporary relief, are not expected to be definitively curative, and
163 may cause several side effects. Finally, when hormonal treatments are to be continued for long
164 periods, oestrogen-progestins and progestins appear to be among the compounds that most
165 favourably balance benefits, harm and costs (Vercellini *et al.*, 2011).

166 Patients are informed that surgery is currently considered the standard treatment for severely
167 symptomatic bowel endometriosis; according to published evidence, excision of the affected
168 intestinal area and segmental colorectal resection substantially improve bowel complaints and
169 health-related quality of life, but are associated with major complications.

170 For the present study, two groups of participants with deep intestinal endometriosis were
171 eventually generated in whom motivational factors were optimized by allowing them to receive
172 their preferred treatment. Thus, the selected therapeutic modality was not by random allocation. In
173 women opting for medical therapy, the SDM process remained open during the treatment period,
174 allowing women to request surgery at any time.

175 Participants who chose hormonal treatment were instructed to take a low-dose, monophasic
176 OCP or a progestin starting on the first day of menstruation. In case an OCP was chosen, a
177 combination containing ethinylestradiol 0.015 mg and gestodene 60 mg per pill was prescribed.
178 Women were instructed to use the OCP continuously. In case a progestin was preferred, oral
179 norethisterone acetate (NETA), 2.5 mg once a day (Ferrero *et al.*, 2010b), or oral dienogest, 2 mg
180 once a day, was administered. In case of prolonged spotting (≥ 7 days) or breakthrough bleeding

181 during continuous hormonal therapy, the women were advised to discontinue treatment for 4 days
182 (OCP users) or 1 week (NETA users). They were also allowed to use psyllium twice a day and to
183 take NSAIDs when needed.

184 Surgical procedures were performed at laparoscopy or laparotomy based on the caring
185 abdominal surgeon's advice and according to previously described standard techniques (Fedele *et*
186 *al.*, 2004; Vercellini *et al.*, 2009b). Segmental resection was generally preferred in patients with
187 extensive intestinal infiltration, limiting disk excision to cases of small or well-defined nodules. The
188 decision to carry out a diverting ostomy was taken intra-operatively and based on individual bowel
189 anatomic conditions. Gynaecologists treated associated pelvic endometriotic lesions as usual
190 (Vercellini *et al.*, 2009b). After surgery, patients were advised to use postoperative medical therapy
191 with a low-dose OCP or a progestin with the objective of limiting the risk of symptom and lesion
192 recurrence (Seracchioli *et al.*, 2009).

193 **Measurements**

194 In all patients referring to our centre, demographic information and a medical history are
195 systematically obtained at baseline screening. Follow-up clinical and ultrasonographic evaluation
196 are scheduled every 6 months. On these occasions, women are routinely asked to complete several
197 questionnaires. For this study, two were on intestinal symptomatology (a numeric rating scale,
198 NRS; and the Knowles-Eccersley-Scott Symptom Questionnaire, KESS), one on pain (a NRS), one
199 on quality of life (the Short Form-12 questionnaire, SF-12), one on psychological status (the
200 Hospital Anxiety and Depression scale, HADS), and one on sexual functioning (the Female Sexual
201 Function Index, FSFI).

202 With the first questionnaire on intestinal symptoms, originally published by Ferrero *et al.*
203 (2010b), the severity of each symptom is assessed by a 11-point numeric rating scale, with 0
204 indicating absence of symptom, and 10 symptom that is as severe as it can be.

205 The KESS questionnaire (Knowles *et al.*, 2000, 2002) is a well-recognised, validated, self-
206 report, multidimensional, instrument, originally developed to diagnose constipation, that allows to

207 discriminate among pathophysiological sub-groups. The questionnaire is composed of 11 questions
208 with four or five mutually exclusive answers and corresponding 0 to 3 or 0 to 4 scores. Item scores
209 are summed to deliver a total score ranging from 0 to 39, with higher scores indicating higher
210 symptom severity. A score of 10 or over indicates the existence of constipation (Knowles *et al.*,
211 2000).

212 Patients are also asked to complete a questionnaire on the presence and severity of
213 dysmenorrhoea, deep dyspareunia, non-menstrual pelvic pain, and dyschesia using an 11-point
214 numeric rating scale, with 0 indicating the absence of pain and 10 indicating pain that is as bad as it
215 can be. A score of 1 to 5 is considered mild pain, from 6 to 8 moderate pain, and over 8 severe pain.
216 The SF-12, HADS, and FSFI have been described previously in detail (Vercellini *et al.*, 2016).

217 Briefly, the SF-12 health survey, developed from the original SF-36 questionnaire (Ware
218 and Sherbourne, 1992; McHorney *et al.*, 1993), is a well know, validated self-administered 12-item
219 instrument. It measures health dimensions covering functional status, well-being, and overall health
220 to construct physical (PCS-12) and mental (MCS-12) component summary measures (Ware *et al.*,
221 1996; Gandek *et al.*, 1998), with higher scores indicating better health perception.

222 The HADS questionnaire is a self-assessment mood scale to determine states of anxiety and
223 depression. It comprises 14 questions, 7 for the anxiety subscale and 7 for the depression subscale.
224 Lower scores indicates better psychological status (Zigmond and Snaith, 1983).

225 The FSFI questionnaire is a 19-item, multidimensional, self-report instrument for evaluating
226 the main categories of female sexual dysfunction and sexual satisfaction (Rosen *et al.*, 2000;
227 Meston, 2003; Wiegel *et al.*, 2005). The maximum (best) transformed full-scale score is 36, with a
228 minimum full-scale score of 2.0.

229 Women using hormone therapies are asked to indicate the occurrence of side effects.
230 Irregular bleeding during medical treatment is defined as spotting (scanty bleeding requiring ≤ 1
231 pads or tampons per day) or breakthrough bleeding (light or moderate bleeding requiring ≥ 2 pads

232 or tampons per day). Pain during spotting or breakthrough bleeding is considered to be
233 dysmenorrhea.

234 At each follow-up visit, patients routinely rate the degree of satisfaction with their treatment
235 according to a 5-category scale (very satisfied, satisfied, neither satisfied nor dissatisfied,
236 dissatisfied, or very dissatisfied) by answering the following question: “Taking into consideration
237 the variations that occurred in intestinal and pain symptoms, overall physical and psychological
238 well-being, health-related quality of life, and sexual functioning, how would you define the level of
239 satisfaction with your current treatment?”

240 **Data management**

241 Data were archived using Excel 2003 (Microsoft Corporation, Redmond, Washington, U.S.A.) and
242 exported in SPSS 18.0 (SPSS, Inc, Chicago, IL, U.S.A.) or SAS software 9.4 (SF-12 data; SAS
243 Institute Inc., Cary, NC, U.S.A.) for statistical analysis. The focus of the investigation was not on a
244 head-to-head comparison between the two treatment alternatives. The study question was "how
245 many women with a surgical indication for symptomatic deep bowel endometriosis chose medical
246 therapy instead of surgery after undergoing a shared decision making process, and how many of
247 these are satisfied with their treatment at long-term follow-up evaluation?" As treatment allocation
248 was based on patient preference, distribution of participants between the two study groups was
249 expectedly unbalanced (Vercellini *et al.*, 2012). Moreover, no comparative studies on the effect of
250 medical therapy and surgery for symptomatic bowel endometriosis have yet been published.

251 Available case series demonstrated substantially similar benefits of the two therapeutic alternatives
252 (Ferrero *et al.*, 2010a e 2010b; Minelli *et al.*, 2009; Darai *et al.*, 2010), thus impeding the definition
253 of a clinically important between-group difference in the main outcome. For these reasons, a pre-
254 planned power calculation was not performed, and we decided to include all the eligible patients
255 evaluated in a quinquennium.

256 In order to estimate the effect of treatment on patient satisfaction, a dichotomization of the
257 outcome into treatment success (very satisfied plus satisfied subjects) and treatment failure (neither

258 satisfied nor dissatisfied plus dissatisfied plus very dissatisfied subjects) was done. The statistical
259 significance of differences in patient satisfaction rates was compared using Fisher's exact test, and
260 the analysis was performed according to the intention-to-treat principle. Dropouts were considered
261 as treatment failures (dissatisfied) and included in this analysis. A logistic regression model
262 including terms for age, previous surgery for endometriosis, the number and dimension of the
263 endometriotic lesions and characteristics found to differ ($P < 0.05$) at baseline univariate analysis,
264 were used to calculate the adjusted odds ratio (OR) for being dissatisfied (very dissatisfied,
265 dissatisfied, or neither satisfied nor dissatisfied) with the use of medical therapy compared with
266 surgery. Time to dissatisfaction with the treatment chosen was analysed with the product limit
267 method and the curves obtained were compared by the log-rank test. Subjects deciding to seek
268 conception were censored. The event data used in computing time to dissatisfaction with treatment
269 were the date of medical therapy commencement or surgery, and the date of study questionnaires
270 completion with indication of dissatisfaction or uncertainty, or last follow-up visit.
271 Baseline characteristics of the patients were compared using Fisher's exact test, Mann-Whitney test,
272 or unpaired Student's *t*-test, as appropriate. The distribution of the studied variables was assessed
273 using the Shapiro-Wilk test. Normally distributed variables were reported as mean \pm SD and
274 compared using unpaired Student *t*-test, paired Student *t*-test or ANOVA for repeated measures, as
275 appropriate. Non-normally distributed variables were reported as median (interquartile range) and
276 compared using Mann-Whitney test, paired Wilcoxon test and Friedman test, as appropriate. All
277 statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

278

279 RESULTS

280 In the quinquennium 2011-2016, 146 patients with symptomatic colorectal endometriosis were
281 evaluated and counselled in our centre. A total of 59 women were excluded for various reasons
282 (Figure 3). After the completion of the SDM process, 50 (57%) patients decided not to undergo
283 surgery and try medical treatment, whereas 37 (43%) confirmed their preference for the previously

284 received surgical indication. The median [interquartile range] follow-up period was 40 [18-60]
285 months for women who chose medical therapy and 45 [30-67] months for those who chose surgery.
286 Recruitment and women's progress through the study is shown in Figure 2. The demographic and
287 clinical characteristics of participants in the two study groups are shown in Table I. The distribution
288 of the considered variables was similar. In the majority of cases the endometriotic nodule infiltrated
289 the rectosigmoid junction and in four women out of ten the upper rectum. An isolated sigmoid
290 nodule was identified in only 6 patients. More than one nodule was detected in one fifth of the
291 participants. The mean diameter of the largest nodule was slightly over 3 cm in the medical
292 treatment group, and 3.5 cm in the surgery group ($P = 0.15$). Additional major endometriotic
293 lesions (uterosacral, rectovaginal and bladder nodules, ovarian endometriomas) were present in 21
294 (42%) women in the medical treatment group and in 13 (35%) in the surgery group ($P = 0.51$).

295 A total of 12 (24%) women who chose medical therapy used the low-dose OCP, and 38
296 (76%) a progestin (NETA, $n = 29$; dienogest, $n = 9$). Side effects were very common, and were
297 experienced by 37 (74%) women. The most frequently reported untoward effects were weight gain
298 ($n = 16$), decreased libido ($n = 9$), bloating ($n = 8$), vaginal dryness ($n = 8$), headache ($n = 5$), and
299 mood changes ($n = 2$). However, side effects were severe enough to cause withdrawal from the
300 study in only three women (weight gain, $n = 1$; headache, $n = 1$; mood changes, $n = 1$).

301 Surgery was performed at laparoscopy in nine women (24%) and at laparotomy in 28 (76%).
302 The vast majority of patients (92%) underwent segmental resection (Supplementary Table S I). The
303 mean length of the resected bowel segment was 13 ± 6 cm. Two distinct intestinal tracts were
304 resected in seven women. An end-to-end, and end-to-side anastomosis was performed in,
305 respectively, 91% and 9%, of the cases. Disk excision was performed in only 3 women. A diverting
306 ileostomy has been created in three patients, and a colostomy in two. Additional endometriotic
307 lesions were excised in all subjects. Histology confirmed endometriotic infiltration of the muscular
308 layer in 27 patients, of the sub-mucosal layer in 8, and of the intestinal mucosa in 2. No major intra-
309 operative complications occurred. Six (16%) major post-operative complications were observed

310 necessitating immediate (intestinal anastomosis dehiscence, $n = 2$; haemoperitoneum, $n = 2$) or
311 delayed (rectovaginal fistula formation, $n = 1$; colostomy occlusion, $n = 1$) re-intervention. One
312 woman developed severe dysfunctional constipation caused by iatrogenic splanchnic denervation.
313 Twenty women (54%) used prolonged postoperative medical treatment (OCP, $n = 8$; NETA, $n = 9$;
314 dienogest, $n = 3$).

315 **Satisfaction with treatment**

316 Seven women in the medical treatment group and one in the surgery group withdrew from the study
317 for various reasons (Figure 2). All these women, including one in the former group that
318 discontinued therapy to seek a conception, were considered as failures (dissatisfied) in the
319 evaluation of satisfaction with treatment, the primary end-point of our study.

320 At 12-month follow-up, 11 (22%) women in the medical therapy group were very satisfied
321 with their treatment, 28 (56%) satisfied, 4 (8%) neither satisfied nor dissatisfied, 6 (12%)
322 dissatisfied, and 1 (2%) very dissatisfied. Corresponding figures in the surgery group were,
323 respectively, 11 (30%), 17 (46%), 3 (8%), 1 (3%), and 5 (13%). Overall, at 12-month follow-up
324 78% of women who chose medical therapy was satisfied or very satisfied with the treatment
325 received, compared with 76% of those who chose surgery (OR, 1.14; 95% CI, 0.42 to 3.12.
326 Adjusted OR, 1.37; 95% CI, 0.45 to 4.15). Corresponding figures at final follow-up assessment
327 were 72% in the medical treatment group (very satisfied, $n = 14$; satisfied, $n = 22$; neither satisfied
328 nor dissatisfied, $n = 5$; dissatisfied, $n = 7$; very dissatisfied, $n = 2$), and 65% in the surgery group
329 (very satisfied, $n = 11$; satisfied, $n = 13$; neither satisfied nor dissatisfied, $n = 4$; dissatisfied, $n = 6$;
330 very dissatisfied, $n = 3$) (OR, 1.39; 95% CI, 0.56 to 3.48. Adjusted OR, 1.74; 95% CI, 0.62 to 4.85).

331 Dissatisfaction-free survival analysis is shown in Figure 3. The 60-month cumulative
332 proportion of subjects free from dissatisfaction (satisfied with the treatment received) was 71% in
333 the medical therapy group, compared with 61% in the surgery group (log-rank test, $\chi^2_1 = 0.25$; $P =$
334 0.61). The incidence rate ratio (IRR) of dissatisfaction in operated women was 1.21 (95% CI, 0.57
335 to 2.62).

336 Effect on bowel symptoms

337 At baseline, diarrhoea, catamenial diarrhoea, and intestinal cramping NRS scores were significantly
338 higher in the surgery group compared to the medical treatment group (Table II). These variables
339 were included in the multivariable model used to analyse the primary outcome. The frequency of
340 the remaining bowel symptoms did not differ between the study groups.

341 All studied symptoms significantly improved in both study groups with the exception of
342 diarrhoea in operated women ($P = 0.10$). At 12-month follow-up and at the end of the follow-up the
343 NRS scores of the studied symptoms were similar between women choosing for medical therapy
344 and those opting for surgery with, again, the exception of diarrhoea that resulted worse in operated
345 women (Table II).

346 Considering the KESS score, a significantly improvement occurred in both groups (Table
347 III). Moreover, we failed to identify any significant difference between the two groups at study
348 entry, at 12-month follow-up and at the last assessment.

349 Effect on pain, health-related quality of life, psychological status, and sexual functioning

350 Dysmenorrhoea, deep dyspareunia, non-menstrual pelvic pain and dyschesia did not differ between
351 the study groups at baseline evaluation (Table IV). All these symptoms improved in both treatments
352 groups. However, the magnitude of the beneficial effects was more pronounced in women choosing
353 medical therapy, in particular for dysmenorrhoea and for non-menstrual pain. At baseline, 94% of the
354 women in the medical treatment group used non-opioid analgesics compared with 84% in the
355 surgery group. The respective proportions at 12-month and last follow-up assessment were 24% and
356 23% in the medical treatment group, and 51% and 47% in the surgery group ($P = 0.02$).

357 Mean SF-12 scores increased (improved) significantly in both groups at both 12-month and
358 last follow-up evaluation (Table III). Also psychological status improved in both groups without
359 significant between-group difference (Supplementary Table S II). Minor variations were observed
360 in the mean total FSFI score. However, in both study groups the mean total FSFI score was well

361 below the physiologic cut-off score (26.55) at both 12-month and last follow-up evaluation
362 (Supplementary Table S II).

363

364 DISCUSSION

365 More than two thirds of women who chose long-term medical therapy were satisfied with their
366 treatment after a median follow-up of more than three years, a proportion similar to that observed in
367 women who chose surgery. Including one woman lost to follow-up, only 6/50 (12%) patients
368 requested surgery because of inefficacy of ($n = 3$), or intolerance to OCP and progestins ($n = 3$).
369 Another 7 (14%) women were not satisfied with their therapy, but preferred to continue their
370 medications instead of undergoing surgery.

371 It would had been of importance to ask the patients also whether their overall health became
372 better or worse since last time they answered the questionnaires. However, the question on which
373 the participants formulated their judgment on the degree of satisfaction with treatment at each
374 follow-up visit was inclusive of variations in intestinal and pain symptoms, overall physical and
375 psychological well-being, health-related quality of life, and sexual functioning.

376 Most women with symptomatic bowel endometriosis, when thoroughly informed on
377 potential benefits, risks, and drawbacks of medical and surgical treatment, expressed their
378 preference for the former option, thus confirming that patients who engage in SDM tend to choose
379 nonsurgical treatment alternatives (Vercellini *et al.*, 2012; Spatz *et al.*, 2017). It may not be
380 excluded that, had they not already received a surgical indication, the proportion of patients
381 choosing medical therapy could have been even higher. On the other hand, the opposite could have
382 been true, had colorectal resection be systematically offered at laparoscopy instead of laparotomy.

383 The incidence of side effects reported by women who chose OCP and progestins was
384 unusually high. However, only 3/50 women requested surgery because of drug intolerance. Also the
385 incidence of surgical complications was high, as six women underwent repeat surgery and one
386 developed permanent severe iatrogenic constipation. Thus, the potential benefits and potential

387 harms of the two options depict very different therapeutic balances, thus suggesting that, in women
388 with colorectal endometriosis not seeking pregnancy, "*surgery is the therapy of choice for*
389 *symptomatic patients when deep lesions do not improve with a medical treatment*" (Abrão *et al.*,
390 2015).

391 Owing to the intrinsic methodological limitations of the design of the present study, we are
392 unable to accurately define and reliably compare the respective effect size of the two treatment
393 options. Taking this shortcoming into account, low-dose, monophasic OCPs and progestins
394 successfully controlled symptoms associated with infiltrating colorectal endometriosis in the
395 majority of patients who preferred a conservative approach, and this result appears aligned with the
396 priorities and expectations of these women. What we have observed could be considered the
397 maximum possible effect obtainable in similar clinical conditions when using medical therapy in
398 those patients that have chosen their treatment.

399 However, it should be emphasized that, precisely in everyday practice, the alternative
400 between medical and surgical treatment could be proposed in only about two thirds of patients with
401 colorectal endometriosis, as 37 could not choose because of severe intestinal stenosis. Moreover,
402 six of the 50 women who chose hormonal treatments discontinued them owing to drug inefficacy or
403 intolerance. This means that medical therapy could be used successfully in no more than half of the
404 women with colorectal endometriosis evaluated in our centre during the index period. In addition,
405 the population enrolled in our study was rather young. Elderly women may bleed more frequently
406 under medical treatment, likely owing to adenomyosis, and be more prone to ask a surgical option
407 after several months of medical treatment.

408 In comparison with recently published evidence, in our study laparoscopy and disk excision
409 were underused. The decision between laparoscopy and laparotomy, as well as on the type of bowel
410 procedure to perform, were taken by abdominal surgeons based on their knowledge, experience,
411 and advice. The rate of open surgery in our series was very high, and it may not be excluded that
412 with a systematic laparoscopic approach the incidence of complications and the proportion of

413 satisfied patients could have been better. On the other hand, the majority of women who underwent
414 surgery, also used long-term postoperative medical therapy with OCP or progestins. Therefore, the
415 effect of surgery on intestinal and pelvic pain symptoms was likely overestimated, as it is not
416 possible to discriminate between the effect of the two therapeutic components when they are
417 combined.

418 Medical treatment improved irritative-type symptoms and also constipation, although to a
419 lesser extent. The resolution of cyclic inflammation due to intra- and peri-lesional micro-
420 haemorrhages may explain the effect of hormonal compounds on irritative complaints. In fact, the
421 responsiveness of deep intestinal lesions to progestins is supported by demonstration of
422 progesterone receptors in ectopic glands infiltrating the muscular layer of the bowel wall (Noël *et*
423 *al.*, 2010). In theory, constipation may originate from fibrosis, which should be unresponsive to
424 medical therapy, but also from altered innervation, which cannot be restored (or may even be
425 worsened) by surgery (Milone *et al.*, 2015). In these cases, also surgery seems less effective on
426 constipation than on other types of bowel symptoms (Roman *et al.*, 2013a, 2016, 2017b). According
427 to Roman *et al.* (2013a; 2013b), here colorectal resection may not substantially improve bowel
428 complaints (Riiskjaer *et al.*, 2016), and Kupelian and Cutner (2016) suggest that surgeons should
429 not offer segmental resection based on the expectation that digestive outcomes will improve.

430 A possible explanation for the somewhat unexpected effect of medical therapy on
431 constipation observed in our study, might be a decrease in nodule size that may partially relieve the
432 reduction in lumen caliber of the affected bowel tract (Ferrari *et al.*, 2012). In this regard, our
433 experience is not fully consistent with that of other authors (Ferrero *et al.*, 2010b; Leonardo-Pinto *et*
434 *al.*, 2017).

435 The observed larger effect of OCP and progestins over surgery on dysmenorrhoea was
436 expected, as menstruations were abolished in most women who chose medical therapy. However,
437 dysmenorrhoea is a non-specific symptom, and it is not a reliable parameter to assess the efficacy of
438 surgery for colorectal endometriosis. More interesting is the effect of medical therapy on deep

439 dyspareunia that confirms our previous findings in patients suffering from severe pain at intercourse
440 (Vercellini *et al.*, 2012). Improvements in health-related quality of life, psychological status, and
441 sexual function were similar in the two study groups, but it may not be excluded that surgical
442 outcomes could have been better if all the procedures had been performed at laparoscopy.

443 In conclusion, long-term treatment with a low-dose OCP or a progestin should be
444 systematically included among the therapeutic options for women not seeking a conception with
445 bowel endometriosis and without persistent and severe sub-occlusive symptoms. Surgery should be
446 considered as a second-line treatment reserved to those patients not responding to, not tolerating, or
447 with contraindications to low-dose OCP and progestins. However, the final decision should be
448 made together with the woman, respecting her priorities and preferences.

449 AUTHOR'S ROLES

450 P.V. conceived and designed the study and drafted the original version of the manuscript; M.P.F.
451 acquired and analysed data; R.R. interpreted data; D.D., and O.D.G. acquired data; A.R. and P.M.
452 analysed and interpreted health-related quality of life data; F.M.C. acquired, analysed, and
453 interpreted pathology data; E.S. participated in the conception and design of the study and analysed
454 and interpreted data; all the authors revised critically the article for important intellectual content,
455 and approved the final version of the manuscript to be published.

456

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461

462 CONFLICT OF INTEREST

463 P.V., M.P.F., R.R., D.D., A.R., P.M. O.D.G., and M.C. declare that they have no conflicts of
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577 37.
- 578

579 FIGURE LEGENDS

580

581 Figure 1. Barium enema demonstrating deep endometriotic infiltration of the rectosigmoid
582 junction with lumen stenosis (*arrow*).

583

584 Figure 2. Flow chart showing recruitment and women's progress through the study.

585

586 Figure 3. Sixty-month dissatisfaction-free survival analysis according to the treatment
587 modality adopted: (*solid line*) oral contraceptive or progestin ($n = 50$); (*dashed line*) surgery ($n =$
588 37) (log-rank test, $\chi^2_1 = 0.25$; $P = 0.61$). Vertical tick marks are censored observations.