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Medical treatment or surgery for colorectal endometriosis? Results of a shared decision-making approach

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STUDY QUESTION: What is the degree of patient satisfaction in women with symptomatic colorectal endometriosis who choose medical or surgical treatment after a shared decision-making (SDM) process?

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

WHAT IS KNOWN ALREADY: Hormonal therapies and surgery for colorectal endometriosis have been investigated in non-comparative studies with inconsistent results.

STUDY DESIGN, SIZE, DURATION: Parallel cohort study conducted on 87 women referring to our centre with an indication to surgery for colorectal endometriosis. A standardised SDM process was adopted, allowing women to choose their preferred treatment. Median follow-up was 40 [18–60] months in the medical therapy group and 45 [30–67] in the surgery group.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Patients with endometriosis infiltrating the proximal rectum, the rectosigmoid junction, and the sigmoid, not causing severe sub-occlusive symptoms were enroled. A total of 50 patients chose treatment with an OCP ($n = 12$) or a progestin ($n = 38$), whereas 37 women confirmed their previous indication to surgery. Patient satisfaction was graded according to a 5-category scale. Variations in bowel and pain symptoms were measured by means of a 0–10 numeric rating scale. Constipation was assessed with the Knowles–Eccersley–Scott Symptom Questionnaire (KESS), health-related quality of life with the Short Form-12 questionnaire (SF-12), psychological status with the Hospital Anxiety and Depression scale (HADS) and sexual functioning with the Female Sexual Function Index (FSFI).

MAIN RESULTS AND THE ROLE OF CHANCE: Six women in the medical therapy group requested surgery because of drug inefficacy ($n = 3$) or intolerance ($n = 3$). Seven major complications were observed in the surgery group (19%). At 12-month follow-up, 39 (78%) women in the medical therapy group were satisfied with their treatment, compared with 28 (76%) in the surgery group (adjusted odds ratio (OR), 1.37; 95% confidence interval (CI), 0.45–4.15; intention-to-treat analysis). Corresponding figures at final follow-up assessment were 72% in the former group and 65% in the latter one (adjusted OR, 1.74; 95% CI, 0.62–4.85). The 60-month cumulative proportion of dissatisfaction-free participants was 71% in the medical therapy group compared with 61% in the surgery group ($P = 0.61$); the Hazard incidence rate ratio was 1.21 (95% CI, 0.57–2.62). Intestinal complaints were ameliorated by both treatments. Significant between-group differences in favour of medical treatment were observed at 12-month follow-up in diarrhoea, dysmenorrhoea, non-menstrual pelvic pain and SF-12 physical component scores. The total HADS score improved significantly in both groups, whereas the total FSFI score improved only in women who chose medical therapy.

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LIMITATIONS REASONS FOR CAUTION: As treatments were not randomly assigned, selection bias and confounding are likely. The small sample size exposes to the risk of type II errors.

WIDER IMPLICATIONS OF THE FINDINGS: When adequately informed and empowered through a SDM process, most patients with non-occlusive colorectal endometriosis who had already received a surgical indication, preferred medical therapy. The possibility of choosing the preferred treatment may allow maximisation of the potential effect of the interventions.

STUDY FUNDING/COMPETING INTEREST(S): This study was financed by Italian fiscal contribution '5 × 1000'—Ministero dell'Istruzione, dell'Università e della Ricerca—devolved to Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy. 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 interest. E.S. received grants from Ferring and Serono.

Key words: endometriosis / colorectal endometriosis / constipation / surgery / medical treatment

Introduction

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

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

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

Disentangling the uncertainties on the role of medical therapy in women with this infiltrating endometriosis form is exceedingly important, as excisional procedures with opening of the bowel lumen are generally effective in relieving intestinal symptoms, but are also associated with severe short- and long-term complications. Only non-comparative studies are available on treatment of intestinal endometriosis with either medical therapy or surgery. Participants are being recruited in a French randomised, controlled trial comparing medical and surgical treatment for rectal endometriosis, but results will be available at the end of 2019 (https://www.clinicaltrials.gov/ct2/show/NCT01973816?term=endometriosis+AND+France&draw=4&rank=24. Accessed on 1 October 2017).

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

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

Materials and Methods

Study design

This parallel cohort study evaluated the medium- (12 months) and long-term outcomes (>12 months) of two therapeutic alternatives; long-term treatment with a low-dose, monophasic OCP or a progestin, and excisional surgery, for symptomatic deep bowel endometriosis infiltrating the sigmoid colon, the rectosigmoid junction or the proximal rectum. The study was conducted retrospectively on prospectively and systematically recorded data.

Ethical approval

The investigation, performed in an academic department specialising in endometriosis management, was approved by the local institutional review board (Comitato di Etica Milano Area B; determination #1123/2017). All patients signed a written consent for participation in the study.

Study population

We considered 18–50-year-old women not wanting pregnancy, who received an indication for surgical excision of intestinal endometriosis, and were referred to our centre between January 2011 and January 2016 for an expert opinion or for performing the surgical procedure. The diagnosis of deep intestinal endometriosis was based on rectal endosonography to define the level of rectal involvement and to determine the depth of rectal wall infiltration; double-contrast barium enema to ascertain the presence and degree of colorectal stenosis; colonoscopy or sigmoidoscopy to exclude chronic inflammatory bowel diseases and malignancies and

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investigate additional proximal localisations in selected circumstances; and magnetic resonance imaging and computerised tomography (CT) colonography to better define the overall anatomic conditions of the affected bowel tract and associated endometriotic pelvic lesions in some women. The diagnostic work-up includes kidney and urinary tract ultrasonography to rule out hydro-utereronephrosis and bladder nodules.

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

Treatments

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

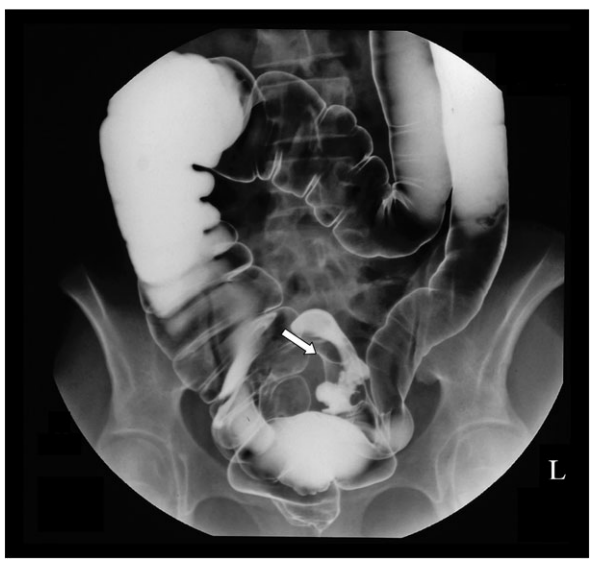

Figure 1 Barium enema demonstrating deep endometriotic infiltration of the rectosigmoid junction with lumen stenosis (*arrow*). L, left side.

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

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

Participants who chose hormonal treatment were instructed to take a low-dose, monophasic OCP or a progestin starting on the first day of menstruation. In case an OCP was chosen, a combination containing ethinylestradiol 0.015 mg and gestodene 60 mg per pill was prescribed. Women were instructed to use the OCP continuously. In case, a progestin was preferred, oral norethisterone acetate (NETA), 2.5 mg once a day (Ferrero *et al.*, 2010b), or oral dienogest, 2 mg once a day, was administered. In case of prolonged spotting (≥7 days) or breakthrough bleeding during continuous hormonal therapy, the women were advised to discontinue treatment for 4 days (OCP users) or 1 week (NETA users). They were also allowed to use psyllium twice a day and to take non-steroidal anti-inflammatory drugs (NSAIDs) when needed.

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

Measurements

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

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

The KESS questionnaire (Knowles *et al.*, 2000, 2002) is a well-recognised, validated, self-report, multidimensional, instrument, originally developed to diagnose constipation that allows to discriminate among pathophysiological sub-groups. The questionnaire is composed of 11 questions with 4 or 5 mutually exclusive answers and corresponding 0–3 or 0–4 scores. Item scores are summed to deliver a total score ranging from 0 to 39, with higher scores indicating higher symptom severity. A score of 10 or over indicates the existence of constipation (Knowles *et al.*, 2000).

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

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

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

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

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

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

Data management

Data were archived using Excel 2003 (Microsoft Corporation, Redmond, WA, USA) and exported in SPSS 18.0 (SPSS, Inc., Chicago, IL, USA.) or SAS software 9.4 (SF-12 data; SAS Institute Inc., Cary, NC, USA) for statistical analysis. The focus of the investigation was not on a head-to-head comparison between the two treatment alternatives. The study question was 'how many women with a surgical indication for symptomatic deep bowel endometriosis chose medical therapy instead of surgery after undergoing a SDM process, and how many of these are satisfied with their treatment at long-term follow-up evaluation?' As treatment allocation was based on patient preference, distribution of participants between the two study groups was expectedly unbalanced (Vercellini *et al.*, 2012). Moreover, no comparative studies on the effect of medical therapy and surgery for symptomatic bowel endometriosis have yet been published. Available case series demonstrated substantially similar benefits of the two therapeutic alternatives (Minelli *et al.*, 2009; Daraï *et al.*, 2010; Ferrero *et al.*, 2010a,b), thus impeding the definition of a clinically important between-group difference in the main outcome. For these reasons, a pre-planned power calculation was not performed, and we decided to include all the eligible patients evaluated in a quinquennium.

In order to estimate the effect of treatment on patient satisfaction, a dichotomisation of the outcome into treatment success (very satisfied plus satisfied subjects) and treatment failure (neither satisfied nor dissatisfied plus dissatisfied plus very dissatisfied subjects) was done. The statistical significance of differences in patient satisfaction rates was compared using Fisher's exact test, and the analysis was performed according to the intention-to-treat principle. Dropouts were considered as treatment failures (dissatisfied) and included in this analysis. A logistic regression model including terms for age, previous surgery for endometriosis, the number and dimension of the endometriotic lesions and characteristics found to differ ($P < 0.05$) at baseline univariate analysis, were used to calculate the adjusted odds ratio (OR) for being dissatisfied (very dissatisfied, dissatisfied or neither satisfied nor dissatisfied) with the use of medical therapy compared with surgery. Time to dissatisfaction with the treatment chosen was analysed with the product limit method and the curves obtained were compared by the log-rank test. Subjects deciding to seek conception were censored. The event data used in computing time to dissatisfaction with treatment were the date of medical therapy commencement or surgery, and the date of study questionnaires completion with indication of dissatisfaction or uncertainty, or last follow-up visit.

Baseline characteristics of the patients were compared using Fisher's exact test, Mann–Whitney test or unpaired Student's *t*-test, as appropriate. The distribution of the studied variables was assessed using the Shapiro–Wilk test. Normally, distributed variables were reported as mean ± standard deviation (SD) and compared using unpaired Student *t*-test, paired Student *t*-test or analysis of variance for repeated measures, as appropriate. Non-normally distributed variables were reported as median (interquartile range) and compared using Mann–Whitney test, paired Wilcoxon test and Friedman test, as appropriate. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

In the quinquennium 2011–2016, 146 patients with symptomatic colorectal endometriosis were evaluated and counselled in our centre. A total of 59 women were excluded for various reasons (Fig. 2). After the completion of the SDM process, 50 (57%) patients decided not to undergo surgery and try medical treatment, whereas 37 (43%) confirmed their preference for the previously received surgical indication. The median [interquartile range] follow-up period was 40 [18–60] months for women who chose medical therapy and 45 [30–67] months for those who chose surgery. Recruitment and women's progress through the study are shown in Fig. 2. The demographic and clinical characteristics of participants in the two study groups are shown in Table I. The distribution of the considered variables was similar. In the majority of cases, the endometriotic nodule infiltrated the rectosigmoid junction and in 4 women out of 10 the upper rectum. An isolated sigmoid nodule was identified in only six patients. More than one nodule was detected in one-fifth of the participants. The mean diameter of the largest nodule was slightly over 3 cm in the medical treatment group, and 3.5 cm in the surgery group ($P = 0.15$). Additional major endometriotic lesions (uterosacral, rectovaginal and bladder nodules, ovarian endometriomas) were present in 21 (42%) women in the medical treatment group and in 13 (35%) in the surgery group ($P = 0.51$).

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

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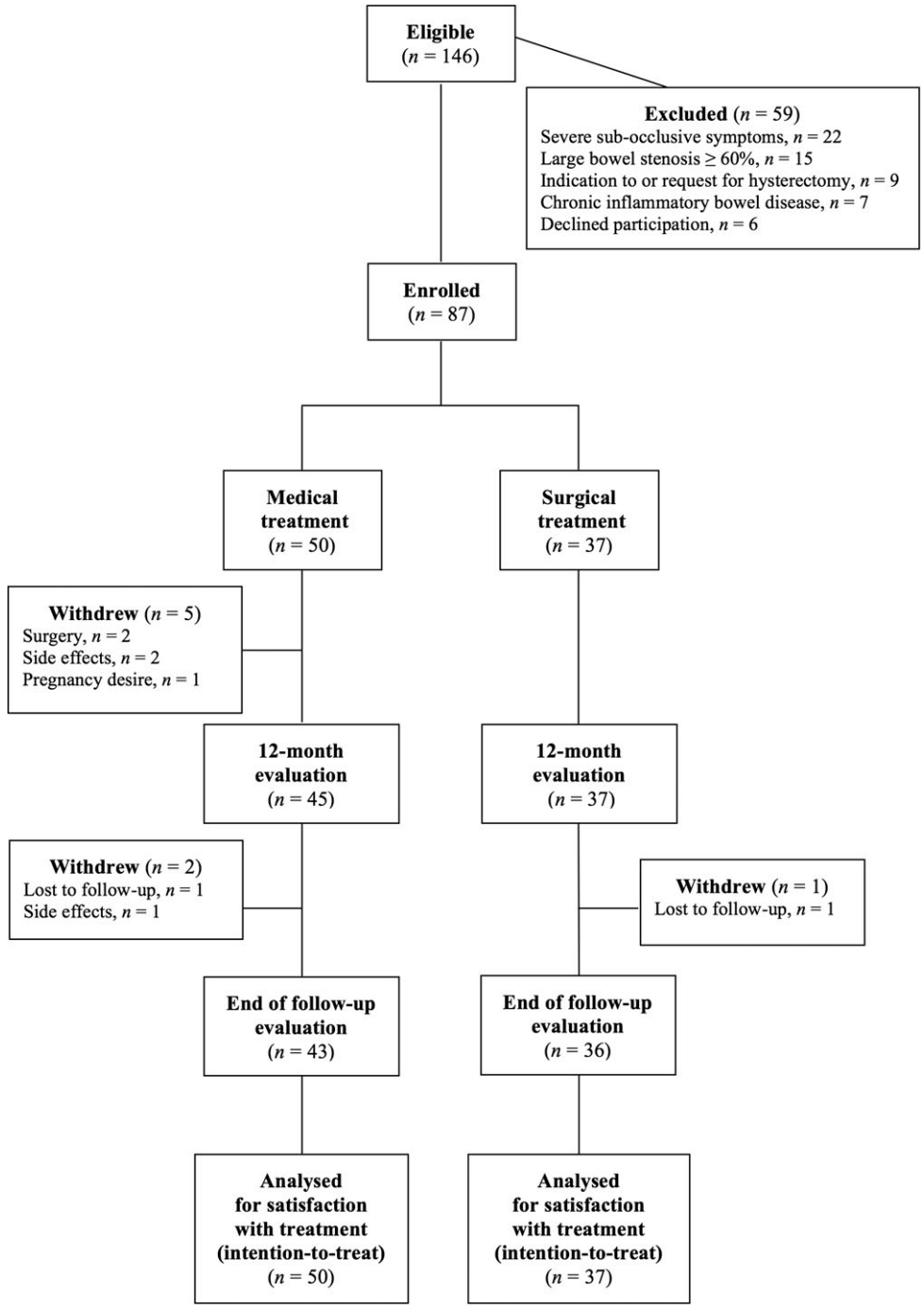

Figure 2 Flow chart showing recruitment and women's progress through the study.

the study in only three women (weight gain, *n* = 1; headache, *n* = 1 and mood changes, *n* = 1).

Surgery was performed at laparoscopy in 9 women (24%) and at laparotomy in 28 (76%). The vast majority of patients (92%) underwent segmental resection (Supplementary Table SI). The mean length of the resected bowel segment was 13 ± 6 cm. Two distinct intestinal tracts were resected in seven women. An end-to-end, and end-to-side anastomosis was performed in, respectively, 91% and 9%, of the cases. Disk excision was performed in only three women. A diverting ileostomy has been created in three patients, and a colostomy in two. Additional endometriotic lesions were excised in all subjects. Histology confirmed endometriotic infiltration of the muscular layer in 27 patients, of the sub-mucosal layer in 8 and of the intestinal mucosa in 2. No major intra-operative complications occurred. Six (16%) major post-operative complications were observed necessitating immediate (intestinal anastomosis dehiscence, *n* = 2; haemoperitoneum, *n* = 2) or delayed (rectovaginal fistula

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Table I Baseline demographic and clinical characteristics of women included in the two study groups.

Characteristics	Medical treatment ($n = 50$)	Surgical treatment ($n = 37$)	P
Age (y)	33.8 ± 5.8	33.1 ± 4.3	0.54
BMI (kg/m^2)	22.4 ± 3.5	23.0 ± 3.6	0.52
Smoking	11 (22%)	4 (11%)	0.18
Parous	13 (26%)	12 (32%)	0.54
Previous surgery for endometriosis			0.15
1	29 (58%)	15 (40%)	
≥2	8 (16%)	5 (14%)	
Number of bowel endometriotic lesions			0.91
1	40 (80%)	30 (81%)	
≥2	10 (20%)	7 (19%)	
Site of largest bowel endometriotic lesion			0.52
Sigmoid colon	2 (4%)	4 (11%)	
Rectosigmoid junction	28 (56%)	18 (49%)	
Upper rectum	20 (40%)	15 (40%)	
Diameter of largest bowel endometriotic lesion (cm)	3.0 ± 1.4	3.5 ± 1.8	0.15
Follow-up period [months]	40 [18–60]	45 [30–67]	0.06

Data are reported as mean ± SD, or number (percentage), or median [interquartile range].
Between-group differences were tested using unpaired Student *t*-test.
BMI, body mass index.

formation, $n = 1$; colostomy occlusion, $n = 1$) re-intervention. One woman developed severe dysfunctional constipation caused by iatrogenic splancnic denervation. Twenty women (54%) used prolonged post-operative medical treatment (OCP, $n = 8$; NETA, $n = 9$ and dienogest, $n = 3$).

Satisfaction with treatment

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

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

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

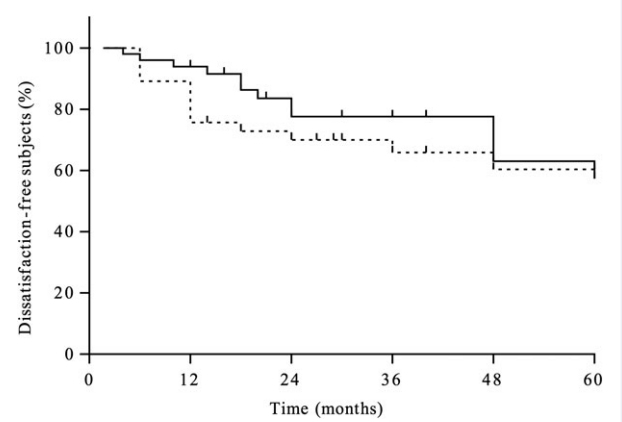

Figure 3 Sixty-month dissatisfaction-free survival analysis according to the treatment modality adopted: (*solid line*) oral contraceptive or progestin ($n = 50$); (*dashed line*) surgery ($n = 37$) (log-rank test, $\chi^2_1 = 0.25$; $P = 0.61$). Vertical tick marks are censored observations.

Effect on bowel symptoms

At baseline, diarrhoea, catamenial diarrhoea and intestinal cramping NRS scores were significantly higher in the surgery group compared with the medical treatment group (Table II). These variables were

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Table II Variation of bowel symptoms during treatment in the two study groups as assessed by a 0–10 points numeric rating scale.

Variables	Medical treatment	Surgical treatment	*P*
Diarrhoea			
Basal	1.5 [1.0–3.0]	3.0 [1.0 – 7.5]	0.04
12 months	1.0 [0.0–2.0]	2.0 [1.0–5.0]	0.03
End of follow-up	1.0 [0.0–2.0]	2.0 [1.0–5.0]	0.005
P	0.001	0.10	
Catamenial diarrhoea			
Basal	3.0 [1.0–5.0]	4.0 [1.0 – 8.5]	0.04
12 months	0.0 [0.0–1.0]	1.0 [0.0–2.0]	0.055
End of follow-up	0.0 [0.0–1.0]	0.5 [0.0–2.0]	0.14
P	<0.001	<0.001	
Constipation			
Basal	6.0 [2.0–8.0]	6.0 [2.0 – 8.5]	0.68
12 months	4.0 [1.0–6.0]	4.0 [1.0–7.0]	0.85
End of follow-up	3.0 [1.0–6.0]	5.0 [1.0–7.0]	0.77
P	<0.001	0.01	
Catamenial constipation			
Basal	7.5 [2.7–9.0]	7.0 [2.5–9.0]	0.76
12 months	0.0 [0.0–2.0]	1.0 [0.0–6.0]	0.054
End of follow-up	0.0 [0.0–1.0]	1.0 [0.0–7.0]	0.06
P	<0.001	<0.001	
Intestinal cramping			
Basal	6.0 [3.0–8.0]	8.0 [4.0–9.0]	0.05
12 months	2.0 [1.0–4.0]	2.0 [1.0–6.0]	0.39
End of follow-up	2.0 [1.0–5.0]	2.0 [1.0–6.5]	0.39
P	<0.001	0.01	
Abdominal bloating			
Basal	8.0 [3.7–8.2]	8.0 [5.0–9.0]	0.35
12 months	4.0 [2.0–7.0]	6.0 [2.0–8.0]	0.17
End of follow-up	4.0 [1.7–7.0]	5.5 [2.0–8.0]	0.27
P	<0.001	0.006	
Feeling of incomplete evacuation			
Basal	7.0 [4.0–8.0]	6.0 [3.0–9.0]	0.95
12 months	2.0 [2.0–5.0]	4.0 [1.0–8.0]	0.37
End of follow-up	2.0 [1.0–5.0]	4.5 [1.0–7.0]	0.20
P	<0.001	<0.001	
Passage of mucus			
Basal	4.0 [1.0–7.0]	5.0 [0.0–8.0]	0.44
12 months	1.0 [0.0–3.0]	1.0 [0.0–4.5]	0.85
End of follow-up	1.0 [0.0–3.0]	1.0 [0.0–4.0]	0.96
P	<0.001	<0.001	
Catamenial haematochezia			
Basal	1.0 [1.0–6.2]	1.0 [0.0–8.0]	0.85
12 months	1.0 [0.0–1.0]	1.0 [0.0–1.0]	0.88
End of follow-up	1.0 [0.0–1.0]	1.0 [0.0–1.0]	0.94
P	<0.001	<0.001	

Data are reported as median [interquartile range]. Within-group comparisons were tested with the non-parametric Friedman test for repeated measures. Between-group differences were tested using the non-parametric Mann–Whitney test.
In the medical therapy group, data are available for 50, 45 and 43 women at baseline, 12 months and end of follow-up, respectively.
In the surgical group, data are available for 37, 37 and 36 women at baseline, 12 months and end of follow-up, respectively.

included in the multivariable model used to analyse the primary outcome. The frequency of the remaining bowel symptoms did not differ between the study groups.

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

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

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

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

Mean SF-12 scores increased (improved) significantly in both groups at both 12-month and last follow-up evaluation (Table III). Also psychological status improved in both groups without significant between-group difference. The mean total HADS questionnaire score reduction (improvement) was -5.2 ± 8.9 in the medical therapy group and -3.7 ± 8.6 in the surgery group ($P = 0.45$). Variations in anxiety and depression sub-scores showed similar trends (Supplementary Table SII). Minor variations were observed in the mean total FSFI score. However, in both study groups the mean total FSFI score was well below the physiologic cut-off score (26.55) at both 12-month and last follow-up evaluation (Supplementary Table SII).

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Table III Variation of KESS and SF-12 scores during treatment in the two study groups.

Variables	Medical treatment	Surgical treatment	P
KESS score			
Basal	13.8 ± 6.4	13.2 ± 4.9	0.63
12 months	8.4 ± 5.7	10.1 ± 6.9	0.22
End of follow-up	9.3 ± 6.3	10.3 ± 7.4	0.52
P	<0.001	0.003	
SF-12: physical component			
Basal	38.5 ± 9.4	35.3 ± 7.7	0.10
12 months	48.8 ± 7.6	41.6 ± 10.4	<0.01
End of follow-up	48.8 ± 8.0	45.6 ± 10.0	0.07
P	<0.001	<0.001	
SF-12: mental component			
Basal	37.2 ± 10.4	35.2 ± 8.3	0.38
12 months	43.6 ± 10.4	42.9 ± 10.0	0.76
End of follow-up	42.3 ± 10.4	42.2 ± 10.4	0.97
P	<0.001	<0.001	

KESS, Knowles–Eccersley–Scott Symptom; SF-12, Short Form-12.
Data are reported as mean ± SD.
Within-group comparisons were tested with one-way analysis of variance for repeated measures. Between-group differences were tested using the Student *t*-test.
In the medical therapy group, data are available for 50, 45 and 43 women at baseline, 12 months and end of follow-up, respectively.
In the surgical group, data are available for 37, 37 and 36 women at baseline, 12 months and end of follow-up, respectively.

Table IV Variation of endometriosis-associated pelvic pain symptoms during treatment in the two study groups as assessed by a 0–10 points numeric rating scale.

Variables	Medical treatment	Surgical treatment	P
Dysmenorrhoea			
Basal	9.0 [8.0–9.2]	9.0 [8.0–10.0]	0.54
12 months	0.0 [0.0–1.0]	2.0 [0.0–6.5]	<0.001
End of follow-up	0.0 [0.0–12.0]	1.0 [0.0–6.7]	0.005
P	<0.001	<0.001	
Dyspareunia			
Basal	7.0 [4.0–9.0]	6.0 [4.0–7.0]	0.21
12 months	3.5 [1.0–6.0]	3.5 [1.2–6.7]	0.65
End of follow-up	3.0 [1.0–5.0]	3.5 [1.2–6.7]	0.20
P	<0.001	0.001	
Non-menstrual pelvic pain			
Basal	6.0 [2.0–7.0]	6.0 [4.0 – 8.0]	0.26
12 months	1.0 [0.0–3.0]	4.0 [2.0–7.0]	<0.001
End of follow-up	1.0 [0.0–4.0]	3.5 [1.0–7.0]	0.002
P	<0.001	<0.001	
Dyschesia			
Basal	7.5 [3.0–9.0]	8.0 [5.0–9.0]	0.27
12 months	2.0 [1.0–4.0]	3.0 [1.0–6.0]	0.22
End of follow-up	1.0 [1.0–4.0]	4.0 [1.0–6.0]	0.054
P	<0.001	<0.001	

Data are reported as median [interquartile range]. Within-group comparisons were tested with the non-parametric Friedman test for repeated measures. Between-group differences were tested using the non-parametric Mann–Whitney test.
In the medical therapy group, data are available for 50, 45 and 43 women at baseline, 12 months and end of follow-up, respectively (for dyspareunia, the number of women is 47, 38 and 36, respectively, because not all women engaged in sexual activity).
In the surgical group, data are available for 37, 37 and 36 women at baseline, 12 months and end of follow-up, respectively (for dyspareunia, the number of women is 32, 29 and 29, respectively, because not all women engaged in sexual activity).

Discussion

More than two-thirds of women who chose long-term medical therapy were satisfied with their treatment after a median follow-up of more than 3 years, a proportion similar to that observed in women who chose surgery. Including 1 woman lost to follow-up, only 6/50 (12%) patients requested surgery because of inefficacy of ($n = 3$), or intolerance to OCP and progestins ($n = 3$). Another 7 (14%) women were not satisfied with their therapy, but preferred to continue their medications instead of undergoing surgery.

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

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

The incidence of side effects reported by women who chose OCP and progestins was unusually high. However, only 3/50 women requested surgery because of drug intolerance. Also the incidence of surgical complications was high, as six women underwent repeat surgery and one developed permanent severe iatrogenic constipation. Thus, the potential benefits and potential harms of the two options depict very different therapeutic balances, thus suggesting that, in women with colorectal endometriosis not seeking pregnancy, 'surgery is the therapy of choice for symptomatic patients when deep lesions do not improve with a medical treatment' (Abrão *et al.*, 2015).

Owing to the intrinsic methodological limitations of the design of the present study, we are unable to accurately define and reliably compare the respective effect size of the two treatment options. Taking this shortcoming into account, low-dose, monophasic OCPs and progestins successfully controlled symptoms associated with infiltrating colorectal endometriosis in the majority of patients who preferred a conservative approach, and this result appears aligned with the priorities and expectations of these women. What we have observed could be considered the maximum possible effect obtainable in similar

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clinical conditions when using medical therapy in those patients that have chosen their treatment.

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

In comparison with recently published evidence, in our study laparoscopy and disk excision were underused. The decision between laparoscopy and laparotomy, as well as on the type of bowel procedure to perform, was taken by abdominal surgeons based on their knowledge, experience and advice. The rate of open surgery in our series was very high, and it may not be excluded that with a systematic laparoscopic approach the incidence of complications and the proportion of satisfied patients could have been better. On the other hand, the majority of women who underwent surgery, also used long-term post-operative medical therapy with OCP or progestins. Therefore, the effect of surgery on intestinal and pelvic pain symptoms was likely overestimated, as it is not possible to discriminate between the effect of the two therapeutic components when they are combined.

Medical treatment improved irritative-type symptoms and also constipation, although to a lesser extent. The resolution of cyclic inflammation due to intra- and peri-lesional micro-haemorrhages may explain the effect of hormonal compounds on irritative complaints. In fact, the responsiveness of deep intestinal lesions to progestins is supported by demonstration of progesterone receptors in ectopic glands infiltrating the muscular layer of the bowel wall (Noël *et al.*, 2010). In theory, constipation may originate from fibrosis, which should be unresponsive to medical therapy, but also from altered innervation, which cannot be restored (or may even be worsened) by surgery (Milone *et al.*, 2015). In these cases, also surgery seems less effective on constipation than on other types of bowel symptoms (Roman *et al.*, 2013a; 2016, 2017b). According to Roman *et al.* (2013a,b), here colorectal resection may not substantially improve bowel complaints (Riiskjaer *et al.*, 2016), and Kupelian and Cutner (2016) suggest that surgeons should not offer segmental resection based on the expectation that digestive outcomes will improve. A possible explanation for the somewhat unexpected effect of medical therapy on constipation observed in our study might be a decrease in nodule size that may partially relieve the reduction in lumen calibre of the affected bowel tract (Ferrari *et al.*, 2012). In this regard, our experience is not fully consistent with that of other authors (Ferrero *et al.*, 2010b; Leonardo-Pinto *et al.*, 2017).

The observed larger effect of OCP and progestins over surgery on dysmenorrhoea was expected, as menstruations were abolished in most women who chose medical therapy. However, dysmenorrhoea is a non-specific symptom, and it is not a reliable parameter to assess the efficacy of surgery for colorectal endometriosis. More interesting is the effect of medical therapy on deep dyspareunia that confirms our previous findings in patients suffering from severe pain at intercourse (Vercellini *et al.*, 2012). Improvements in health-related quality of life, psychological status and sexual function were similar in the two study groups, but it may not be excluded that surgical outcomes could have been better if all the procedures had been performed at laparoscopy.

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

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

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

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Conflict of interest

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

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