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Medical treatment in the management of deep endometriosis infiltrating the proximal rectum and sigmoid colon: a comprehensive literature review

Running headline: Medical therapy for bowel endometriosis

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Abstract

A comprehensive literature review was performed to evaluate the effect of various hormonal therapies, in terms of variations of intestinal and pain complaints and of patient satisfaction with treatment, in women with symptomatic, non-severely sub-occlusive endometriosis infiltrating the proximal rectum and sigmoid colon. A MEDLINE search through PubMed from 2000 to 2018 was conducted to identify all original English language articles published on medical treatment for colorectal endometriosis. Additional reports were identified by systematically reviewing reference lists and using the "similar articles" function in PubMed. A total of 420 women with colorectal endometriosis treated with combined oral contraceptives, progestins, gonadotropin releasing-hormone (GnRH) agonists, and aromatase inhibitors have been described in eight case series, two retrospective cohort studies, and four case reports. Published data consistently suggest that several hormonal medications can control most symptoms associated with intestinal endometriosis, provided the relative bowel lumen stenosis is less than 60%. Patients with irritative-type symptoms appear to respond better than those with constipation. Overall, about two thirds of women were satisfied with the treatment received, independently of the drug used. Progestins are the compound supported by the largest body of evidence. The addition of aromatase inhibitors or, alternatively, the use of GnRH agonists, do not seem to be associated with better outcomes. Long-term treatment with a progestin should be proposed as an alternative to surgery to patients with non-severely sub-occlusive endometriosis infiltrating the proximal rectum and sigmoid colon not seeking conception. The final decision should be shared together with the woman, respecting her preferences and priorities.

Key words:

endometriosis; bowel endometriosis; colorectal endometriosis; pelvic pain; medical therapy; oral contraceptives; progestins.

Abbreviations

GnRH = gonadotropin releasing-hormone;

NETA = nor-ethisterone acetate;

OC = oral contraceptive.

Key message

According to the findings of case series and cohort studies, low-dose estrogen-progestins and progestins relieved intestinal symptoms in around two thirds of women with non-severely sub-occlusive colorectal endometriosis, thus constituting an alternative to surgery in selected women not seeking conception.

Introduction

Deep bowel endometriosis, i.e., endometriosis infiltrating the intestinal muscular layer (1), appears to affect about one tenth of women with the endometriotic disease (2,3). When endometriosis causes bowel obstruction or severe sub-occlusion, surgery is the only reasonable choice. However, most patients with deep bowel endometriosis complains of cyclic and non-cyclic symptoms, such as abdominal bloating, intestinal cramping, diarrhea, and constipation, without obvious obstruction to stool passage (Figures 1 and 2). Symptoms may be associated not only with the degree of endometriotic infiltration and bowel lumen restriction, but also with lesion localization (1,4). 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 cecum (3,5,6).

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 (3,7-9). However, several investigators observed substantial improvements of bowel symptoms during hormonal treatment (10-14). Disentangling the uncertainties on the role of medical therapy in women with infiltrating bowel endometriosis seems 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 in about one patient out of 10 (e.g., intestinal leakage, anastomosis dehiscence, septic peritonitis, rectovaginal fistula formation, bowel anastomosis stenosis, iatrogenic neurologic bladder dysfunction with need for long periods of self-catheterization, and postoperative constipation and de-novo rectal dysfunction) (16-25). The incidence of some complications is associated also with the distance between the lower margin of resection and the anal verge (9,26). Thus, defining the localization of the lesion is important for limiting selection bias when comparing treatments in a research setting, and for counselling women when taking a decision in a clinical setting (9,15-20,26,27).

Given this background and the lack of consensus regarding the role of hormonal treatments for bowel endometriosis, we deemed opportune to synthesize the available evidence on the outcome of various medical therapies that have been used in patients with symptomatic, non-severely sub-occlusive lesions. As hormonal treatments for endometriosis generally suppress ovulation (28), the findings presented in this review may be used to inform and counsel specifically women not seeking conception.

Material and methods

The objective of the present comprehensive review was the evaluation of the effect of various hormonal therapies, in terms of variations of intestinal and pain complaints as well as of patient satisfaction with treatment, in women with symptomatic colorectal endometriosis.

The aim was to identify reports of studies including patients with an instrumental diagnosis of endometriosis infiltrating the muscular layer of the proximal rectal tract (≥ 8 cm from the anal verge), the rectosigmoid junction (13 to 15 cm from the anal verge) and the sigmoid (> 15 cm from the anal verge). Studies focusing specifically on nodules of the distal rectum (within 8 cm from the anal verge) were not considered, as these lesions constitute part of rectovaginal endometriotic plaques (29). Stenotic occlusion of the rectal ampulla is exceedingly rare, due to its large caliber and distensibility. Moreover, differently from the proximal third of the rectum (upper rectum), the mid-rectum, that corresponds to the Douglas' pouch, only has an anterior peritoneal covering. This renders sharp angulation, a determinant of bowel occlusion caused by endometriosis, mechanically unlikely if not impossible (15). In addition, the symptoms associated with endometriotic nodules of the mid- low-rectum are dyschezia and tenesmus, which are specific of lesions of the ampulla (30). Owing to the clinical differences with other endometriotic lesions of the proximal large bowel tract, the effect of medical therapies on nodules of the distal rectum has been already reported separately in another review (31).

A MEDLINE search through PubMed from January 2000 to January 2018 was conducted using combinations of medical subject heading terms "colorectal endometriosis", "intestinal endometriosis", "bowel endometriosis", "medical treatment", "combined oral contraceptives", "progestins", "GnRH agonists", "danazol", and "aromatase inhibitors". Only articles written in English and published in peer-reviewed journals were included, and the relative reference lists were systematically reviewed in order to identify further reports. Additional articles were searched using the "similar articles" function in PubMed. Information was extracted on study design, number of

treated patients, type of intestinal lesions, type of hormonal drugs used, treatment period, adverse events, types of questionnaires administered to assess bowel symptoms and function, and overall clinical outcome.

Results

A total of 420 women with large bowel endometriosis treated with combined oral contraceptives (OC), progestins, gonadotropin releasing-hormone (GnRH) agonists, and aromatase inhibitors have been described in 14 articles published in the period 2000-2018. Eight studies were case series (seven prospective, one retrospective) (10-14,32-34), two were retrospective cohort studies (29,35), and four were case reports (36-39) (Table 1). The precise location of lesions has not been systematically specified, and sometimes what was exactly intended with "colorectal endometriosis" is unclear. This terminology appears to have been used for different clinical situations, and not exclusively in cases of sigmoid and recto-sigmoid junction endometriosis, but also in cases of rectal nodules, which should be more properly included in the category of rectovaginal lesions or Douglas pouch lesions infiltrating the anterior rectal wall (15,29,31). The duration of medical treatment was three months in two studies, six months in three, 12 months in five, and > 12 months in four, including the two cohort studies.

Estrogen-progestins and progestins

Ferrari *et al.* (12) treated 26 patients with colorectal endometriotic lesions infiltrating the tunica muscularis with a low-dose, monophasic OC used continuously for 12 months. The lesion, as assessed at rectal endoscopic ultrasonography, was within 5 cm from the anal rim in 4 cases, between 5 and 10 cm in 14, and above 10 cm in eight. Women with an intestinal lumen stenosis more than 50% were excluded. Symptoms progressively improved and the nodule volume decreased by 62% at the end of the study. At 1-year evaluation, 18 patients (69%) were satisfied or very satisfied with their treatment, four were uncertain, and four were dissatisfied or very dissatisfied. Millochau *et al.* (38) reported the case of a woman treated with estrogen-progestin combinations for an isolated nodule of the sigmoid colon that grew during a 4-year medical treatment causing occlusive symptoms and necessitating surgery.

Egekvist *et al.* (35) conducted a retrospective cohort study in one of the two Danish tertiary referral centers in which treatment of advanced endometriosis is allowed by the national health authority. Patients treated medically or surgically for rectosigmoid lesions were identified in the electronic patient record system according to ICD10 codes for endometriosis affecting the rectosigmoid, vagina or the rectovaginal septum. Of the 238 women with rectosigmoid

endometriosis verified by transvaginal ultrasonography and/or magnetic resonance imaging, 78 (33%) underwent immediate surgery, whereas 160 were treated medically with OCs, a levonorgestrel-releasing- intra-uterine device, or oral progestins. After a median follow-up of 22 months, 27 of the 160 (17%) patients initially treated medically necessitated surgery. Overall, 133/238 (56%) women with rectosigmoid endometriosis could be managed successfully with hormone manipulation, and about four out of five women (133/160; 83%) for whom a medical treatment was decided at baseline evaluation, eventually avoided surgery.

The largest evidence on the effect of progestins for bowel endometriosis is derived from studies on the use of nor-ethisterone acetate (NETA) and dienogest. Ferrero *et al.* (11) enrolled 40 patients with nodules infiltrating the sigmoid ($n = 18$), the recto-sigmoid junction ($n = 12$), and the rectum ($n = 10$). The diagnosis was based on multidetector computed tomography enteroclysis, and women with a stenosis of the bowel lumen greater than 60% were excluded. Nor-ethisterone acetate determined relief from symptoms related to the menstrual cycle, including constipation, diarrhea, and cyclical rectal bleeding. The severity of diarrhea, intestinal cramping and passage of mucus also significantly improved during treatment. However, progestin therapy did not substantially ameliorate constipation, abdominal bloating and feeling of incomplete evacuation after bowel movements. Overall 21/40 patients (53%) referred some improvement in gastrointestinal symptoms. At 1-year evaluation, 60% of participant were satisfied or very satisfied with their treatment, 20% were uncertain, and 20% were either dissatisfied or very dissatisfied.

The effect of dienogest in patients with bowel endometriosis was assessed by the same research group in two case series. Yela *et al.* (13) treated 16 women with rectovaginal or bowel endometriosis with dienogest, 2mg/day for six months. All participants had already used other progestins without improvement of pain. It is unclear whether all the participants had intestinal lesions and which was the exact lesion location. The mean volume of the intestinal nodule decreased from 3.4 cc at baseline to 1.6 cc at the end of treatment. A significant reduction in defecation pain, referred by 69% of the patients at baseline, was observed from the second month of therapy.

Leonardo-Pinto *et al.* (14) evaluated the effect of dienogest prescribed for 12 months in 30 women with rectovaginal and bowel endometriosis. At baseline, participants referred persistent pain complaints despite medical treatment with other progestins for at least six months. Also in this case, whether all the patients had intestinal lesions and at which level was not specified. Intestinal pain decreased significantly during the study period but, at odds with their previous experience (35), the authors did not observe a significant reduction in bowel lesions size.

Dienogest was used also by Tamura *et al.* (37) and Ng *et al.* (39) in two women with endometriosis located at the proximal rectum and rectosigmoid junction. Substantial bowel symptom improvement and lesion size reduction were observed in both patients after, respectively, 22- and six-month progestin treatment.

A parallel cohort study was conducted on 87 women with colorectal endometriosis not causing persistent and severe sub-occlusive symptoms, to investigate whether an OC or a progestin are a satisfactory alternative to surgery in women who choose their treatment after a standardized shared decision-making process (29). A total of 50 patients chose treatment with a low-dose, monophasic OC ($n = 12$) or a progestin (nor-ethisterone acetate, 2.5 mg/day or dienogest, 2 mg/day; $n = 38$), whereas 37 women confirmed their previous indication to surgery. Six women in the medical treatment group requested surgery because of drug inefficacy or intolerance. Seven major complications (19%) were observed in the surgery group. At 12-month follow-up, 39 (78%) women in the OC/progestin group were satisfied with their treatment, compared with 28 (76%) in the surgery group (intention-to-treat analysis). Corresponding figures after a median follow-up of, respectively, 40 and 45 months, were 72% in the former group and 65% in the latter one. The 60-month cumulative proportion of dissatisfaction-free participants was 71% in the OC/progestin group compared with 61% in the surgery group. Bowel symptoms were improved by both treatments.

GnRH agonists

Porpora *et al.* (36) treated with leuprolide acetate in a monthly depot formulation, a woman with sigmoid endometriosis and observed symptom remission and lesion disappearance at 6-month follow-up colonoscopy.

The effect of a GnRH agonist (triptorelin in a depot 3-monthly formulation) with add-back therapy (oral tibolone, 2.5 mg/day) for 12 months was assessed by Ferrero *et al.* (10) in 18 women with endometriotic nodules infiltrating the sigmoid ($n = 9$), the recto-sigmoid junction ($n = 5$), and the rectum ($n = 4$). The larger colorectal nodule had a mean diameter of 2.2 ± 0.6 cm and the mean degree of stenosis of the bowel lumen was $42.0\% \pm 9.7\%$. Intestinal symptoms improved during treatment in 11 (61%) women, whereas in 7 (39%) the intestinal function did not change. In particular, patients with symptoms mimicking diarrhea-predominant irritable bowel syndrome benefitted more from GnRH agonist treatment compared with those complaining of symptoms mimicking constipation-predominant irritable bowel syndrome. In fact, abdominal bloating, intestinal cramping, and passage of mucus improved, but feeling of incomplete evacuation did not vary. At 1-year evaluation, 13 (72%) women were satisfied with their treatment.

Roman *et al.* (34) evaluated the effect of one i.m. depot injection of triptorelin 11.25 mg plus one daily dose of percutaneous estradiol 0.1% as a preoperative measure in 70 patients with an endometriotic rectal nodule infiltrating at least the muscular layer and up to 15 cm above the anus. The rectal lesions were identified at endo-rectal ultrasonography, and a computed tomography-based virtual colonoscopy was performed to identify bowel lumen stenosis and additional intestinal tract localizations. After three months of therapy, cyclic digestive complaints were relieved in more than half of the women (defecation pain, 57%; abnormal frequency of bowel movements, 43%; bloating, 36%), whereas constipation and non-cyclic symptoms were improved in less than a third of patients. Subjective improvement was unrelated with rectal nodule volume.

Aromatase inhibitors

An aromatase inhibitor was used by Ferrero *et al.* (32) in six women with bowel nodules infiltrating at least the tunica muscularis, but with lumen stenosis less than 60%. Four patients complained of intestinal cramping, three of abdominal bloating, three of symptoms mimicking irritable bowel syndrome (e.g., diarrhea), two of constipation, two of passage of mucus in the stools, and one of cyclic rectal bleeding. The patients received oral letrozole (2.5 mg/day) combined with NETA (2.5 mg/day) to prevent ovarian stimulation. All symptoms improved during the 6-month treatment, except constipation. At final assessment, four women (67%) were satisfied with the treatment received and declared that gastrointestinal symptoms were improved.

Discussion

Compared with superficial peritoneal endometriosis, deep endometriosis has a distinct histological characteristic as, in addition to the ectopic endometrial-like mucosa (endometrial epithelium and stroma), and the fibrotic component deriving from inflammation (caused by the metabolic activity of the ectopic endometrium and repeated micro-hemorrhages), smooth muscle fibers are also present (44). This is expected because the so-called deep endometriosis infiltrates the wall of hollow viscera such as the bowel, the bladder, the ureter, and the vagina. The result is a sort of desmoplastic lesion in the form of nodules or plaques comprising the three constituents, the mucosal, the fibrotic, and the smooth muscular one (44). If the smooth muscular component is the histologic hallmark of deep endometriosis, we consider as “deep” those forms of bowel endometriosis that infiltrate at least the muscular layer of the considered intestinal tract (1).

Responsiveness to gonadal steroids of the endometrium within deep bowel lesions is the prerequisite for medical therapy aimed at inducing metabolic quiescence of ectopic glands. Noël *et al.* demonstrated that progesterone receptors were present in major histologic components of colon endometriosis, including the smooth muscle fibers (45). Thus, hormonal treatments should exert an effect on two out of the three components of deep endometriosis, that is, the ectopic endometrial mucosa, and the smooth muscle fibers infiltrated by it. On the other hand, a major effect of medical therapies on the fibrotic component appears unlikely, although an influence of progestins on fibrosis remodeling during time cannot be excluded, due to their demonstrated anti-inflammatory properties (46,47).

Two pathogenic mechanisms explain pain associated with deep endometriotic lesions, i.e., chronic inflammation deriving from the metabolic activity of ectopic endometrium, and secondary fibrosis with embedding of endometriotic glands into scar tissue (15,30). Recurring release of mediators of inflammation, such as prostaglandins and cytokines, may cause a functional-type, mostly cyclic pain, such as irritative-type intestinal symptoms, whereas occlusive-type intestinal symptoms are generally the mechanical consequence of fibrotic tissue retraction, but they may be influenced also by inflammatory changes of bowel wall nodules (3,6,7).

Overall, the quality of the evidence on the effect of hormonal therapies as an alternative to surgery for symptomatic bowel endometriosis is suboptimal. Mainly non-comparative studies are available. Moreover, diverse compounds or combination of compounds have been used with very different durations of treatment. The exact location of intestinal endometriosis was not systematically indicated. Outcomes have been measured using different questionnaires and scales, thus rendering comparisons difficult. Scoring systems to measure pelvic dysfunction and quality of life in women with endometriosis should be standardized (48). Good-quality, comparative effectiveness research is seriously needed to more precisely define the respective impact of medical treatment and extirpative surgery in the long-term management of patients with symptomatic bowel endometriosis. In the words of Riiskjær *et al.* (48) "*the indication for surgery in bowel endometriosis is almost always relative*" and "*this makes selection of indications for surgery and comparison of treatment modalities and results important*".

To this aim, randomized, controlled trials may appear preferable, but adequately designed, prospective parallel cohort studies may also be conducted, especially when women are not prone to receive randomly such diverse treatments, and prefer to take part in the medical decision by choosing their preferred alternative based on their priorities after detailed and impartial information (29,49). In fact, the two options cannot be put on the same level, because the respective balances

between potential benefits and potential harms are hardly comparable in the absence of severe sub-occlusion, thus questioning the therapeutic equipoise that is ethically needed for randomization. On the other hand, the shared decision-making may be unduly influenced by physician's empathy, own beliefs, and *a priori* conviction, thus potentially undermining the scientific foundation on which the process should be based.

In everyday practice the real query may not be which of the two treatments is more effective in absolute terms, but instead to what extent a satisfactory improvement of bowel symptoms is achievable with medical therapy when surgery is considered the standard treatment and, consequently, which is the probability of undergoing surgery anyway because of failure of hormonal manipulation. In this regard, the cohort studies by Egekvist *et al.* (35) and Vercellini *et al.* (29) are encouraging, as the majority of patients who used hormonal medications on a long-term basis eventually avoided surgery and were satisfied with their treatment as pain and bowel symptoms substantially improved.

In spite of the limited quantity and quality of the findings provided in published reports, and while waiting for future better-designed studies, the data included in the present review constitute the only available evidence on which patients and caring gynecologists can base their shared decisions now. Medical treatment for bowel endometriosis may constitute a therapeutic alternative when established intestinal fibrotic stenosis with severely sub-occlusive symptoms are absent (2,3,6). Bowel occlusion is likely when wall infiltration is associated with intestinal fixed, strict angulation, or when the lumen is intrinsically narrow, such as in cases of involvement of the last ileal loop and the ileocecal valve (50,51). The practical issue here is defining when medical therapy is advantageous over surgery, taking into consideration that, if chosen, hormonal treatments should be continued for many years, as drugs control endometriosis but do not definitively cure it (28,31). In this regard, the untoward effects of different medications should be adequately described. As an example, progestins are frequently associated with bloating, weight gain, and irregular bleeding, especially in women with uterine adenomyosis. This may adversely impact on treatment adherence and, on the long term, induce patients to request surgery. This important aspect must be clarified during counseling, together with the fact that also conservative surgery as an isolated measure does not guarantee definitive symptoms relief (19,20,52).

Published data consistently suggest that several hormonal medications can control most symptoms associated with colorectal endometriosis, provided the relative bowel lumen stenosis is less than 60% (10-12,29,32). In particular, patients with irritative-type symptoms appear to respond significantly better than those with constipation, which may originate also from altered innervation.

The resolution of cyclic inflammation due to intra- and peri-lesional micro-hemorrhages may explain the effect on irritative complaints, whereas the observed decrease in nodule size under medical treatment may partially relieve the reduction in lumen caliber of the affected bowel tract. Overall, about two thirds of women were satisfied with the treatment received, independently of the drug used. Progestins are the compound supported by the largest body of evidence. The addition of aromatase inhibitors or, alternatively, the use of GnRH agonists, do not seem to be associated with better outcomes. Given the similar efficacy of the various drugs evaluated in women with colorectal endometriosis, priority should be given to safety, tolerability, and costs when choosing among different medical alternatives. In this regard, progestins appear to offer the best overall therapeutic profile, especially considering that medications may be used for very long periods of time.

Recently Casper questioned the role of OCs in the management of endometriosis based on the hypothesis that, owing to the supra-physiologic estrogen content, these combinations may not adequately suppress lesions and control symptoms (46). Although some literature data suggest that OCs may be safely used in women with colorectal endometriosis (12,29), bowel occlusion during treatment with estrogen-progestin combinations has been reported (38). Therefore, when treating women with symptomatic intestinal endometriosis, it may be wiser to use progestin monotherapies rather than OCs in order to minimize the risk of occlusion, (31). An algorithm for the management of non-occlusive colorectal endometriosis is suggested (Figure 3), based on the idea that, in women not seeking a natural conception, medical treatment may be considered as the first line of treatment, with surgery reserved to those patients not responding to, not tolerating, or with contraindications to progestins.

Medical therapy must be evaluated with caution when managing women who will seek a conception in the short term. In fact, some cases of large bowel occlusion or perforation as well as hydroureteronephrosis have been reported during pregnancy (53-55). Thus, the hormonal milieu of gestation may not guarantee the same lesion control usually observed during medical treatment. Surgery should be discussed also before undertaking in-vitro fertilization, as similar complications have been observed during ovarian stimulation (56,57). Abdominal procedures for complicated colorectal endometriosis in presence of a gravid uterus may reveal technically demanding and risky for both the mother and the fetus (58,59). Thus, women with sub-occlusive forms seeking pregnancy in the future should be thoroughly informed about the risks of not undergoing prior bowel surgery, and should be referred to tertiary care endometriosis centers where expert abdominal surgeons are available for pre-conception evaluation and advice. Unfortunately, except bowel occlusion, there is

currently no robust evidence demonstrating that prophylactic surgery reduces substantially the risk of other major complications during in-vitro fertilization and pregnancy.

In conclusion, long-term treatment with a progestin should always be included among the therapeutic options for women with non-severely sub-occlusive bowel endometriosis not seeking a conception. Given the dramatically different safety profiles, medical treatment and surgery may not be proposed as an “either/or” decision, but rather as a “step-up” decision, where surgery may be indicated as a second step only in those patients not responding to, not tolerating, or with contraindications to progestins. Women should be informed in detail about the potential benefits and potential harms of undergoing surgical removal of intestinal endometriosis and of attempting long-term lesion and symptom control with medical therapies (60). The final decision should be shared together with the woman, respecting her preferences and priorities.

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FIGURE LEGENDS

Table 1. Effect of aromatase inhibitors, estrogen-progestins, gonadotropin releasing hormone agonists (GnRHa) and progestins as assessed in studies on the treatment of bowel endometriosis (literature data, 2000–2018)^a.

Figure 1. Double-contrast barium enema showing an endometriotic stenosis of the recto-sigmoid junction (arrows).

Figure 2. Colonoscopy showing an endometriotic nodule infiltrating the sigmoid wall and protruding into the bowel lumen.

Figure 3. Suggested algorithm for a symptom-based management of large bowel endometriosis in women not seeking a natural conception. US = ultrasonography; MRI = magnetic resonance imaging; CT = computed tomography; GI = gastrointestinal

Table 1. Effect of aromatase inhibitors, estrogen-progestins, gonadotropin releasing hormone agonists (GnRHa) and progestins as assessed in studies on the treatment of bowel endometriosis (literature data, 2000–2018) ^a

Source	Study design	Patients enrolled (<i>n</i>)	Location of bowel endometriotic nodules	Study drug	Treatment period	Adverse effects (%)	Questionnaires adopted to evaluate bowel symptoms	Outcome
Porpora <i>et al.</i> , 2006 (36)	Case report	1	Sigmoid lesion	Leuprolide acetate 3.75 mg/28 days i.m.	3 months	NR	NR	Disappearance of symptoms after the first injection. At 6-months follow-up colonoscopy disappearance of bowel lesion. No recurrence of bowel lesion at follow-up colonoscopy (performed every year for 2 years)
Ferrero <i>et al.</i> , 2010 (10)	Prospective case series	18	Proximal rectum (<i>n</i> = 4); rectosigmoid junction (<i>n</i> = 5); sigmoid lesion (<i>n</i> = 9)	Triptorelin 11.25 mg/3 months i.m. + tibolone 2.5 mg/day per os	12 months	Hot flushes (33) Vaginal bleeding (33) Sweating episodes (17) Vaginal dryness and superficial dyspareunia (11) Nervousness and	Patient self judgements of changes in gastrointestinal symptoms using a 5-point Likert scale (significantly improved, improved, unchanged,	Significant improvement of pain symptoms. Improvement in intestinal function in patients with symptoms mimicking IBS-D. At 12-month assessment 13 (72%) women were very satisfied or satisfied, 2

Source	Study design	Patients enrolled (<i>n</i>)	Location of bowel endometriotic nodules	Study drug	Treatment period	Adverse effects (%)	Questionnaires adopted to evaluate bowel symptoms	Outcome
						irritability (11) Weight gain (11) Sleeplessness (6) Fatigue (6) Difficulty in concentration (6)	worsened, significantly worsened)	(11%) were uncertain, and 3 (17%) were dissatisfied
Ferrero <i>et al.</i> , 2010 (11)	Prospective case series	40	Proximal rectum (<i>n</i> = 10); rectosigmoid junction (<i>n</i> = 12); sigmoid lesion (<i>n</i> = 18)	NETA 2.5 mg/day per os ^b	12 months	Worsening of constipation (7.5) Breakthrough bleeding (5) Weight gain (5) Spotting (2.5) Depression (2.5) Migraine attacks (2.5)	Symptom analogue scale questionnaire (1 indicated the absence of the symptom; 10 indicated the highest severity of the symptom) regarding each gastrointestinal symptom.	Significant improvement of dysm, dysp, CPP, dyschezia and diarrhea. No significant improvement in patients with constipation, abdominal bloating and feeling of incomplete evacuation after bowel movements. 60% of patients were satisfied or very satisfied with the treatment.

Source	Study design	Patients enrolled (n)	Location of bowel endometriotic nodules	Study drug	Treatment period	Adverse effects (%)	Questionnaires adopted to evaluate bowel symptoms	Outcome
Ferrero <i>et al.</i> , 2010 (32)	Prospective case series	6	Proximal rectum (n = 2); rectosigmoid junction (n = 2); sigmoid lesion (n = 2)	Letrozole 2.5 mg/day + NETA 2.5 mg/day per os	6 months	Breakthrough bleeding (17) Weight gain (17) Joint pain (17) Decreased libido (17)	Symptom analogue scale questionnaire (1 indicated the absence of the symptom; 10 indicated the highest severity of the symptom) regarding each gastrointestinal symptom.	Significant improvement of dysm, dysp, CPP, and gastrointestinal symptoms. High satisfaction rate at the end of study period (67% of women were satisfied or very satisfied). No changes in BMD were identified.
Harada <i>et al.</i> , 2011 (33)	Retrospective case series	4	Rectosigmoid junction (n = 4)	DNG 2 mg/day per os	12 months	Spotting (75) Hot Flushes (50) Gastralgia (25) Depression (25)	NR	Significant improvement of pain symptoms and reduction in nodule size.
Ferrari <i>et al.</i> , 2012 (12)	Prospective case series	22 ^c	Proximal rectum, n = 14; recto-sigmoid junction/sigmoid, n = 8	Continuous low-dose monophasic OC (EE 15 µg + gestodene 60 µg)/day	12 months	Breakthrough bleeding (38) Weight gain (23) Headache (12) Decreased libido (8)	Dyschezia was assessed by 0-10 visual analog pain scale (0 indicated the absence of the symptom; 10 indicated the	Significant improvement of dysm, dysp, CPP, and dyschezia. Significant reduction of nodule size after 12 months of treatment.

Source	Study design	Patients enrolled (n)	Location of bowel endometriotic nodules	Study drug	Treatment period	Adverse effects (%)	Questionnaires adopted to evaluate bowel symptoms	Outcome
							highest severity of the symptom)	High satisfaction rate at the end of study period (69% of women were satisfied or very satisfied).
Tamura <i>et al.</i> , 2013 (37)	Case report	1	Proximal rectum and rectosigmoid junction	Cyclic DNG 2 mg/day per os	22 months	Spotting	NR	Significant improvement of pain and gastrointestinal symptoms. Disappearance of bowel lesion at biopsy. Reduction of CA-125 serum levels.
Roman <i>et al.</i> , 2015 (34)	Prospective case series	70	Lesions located within 15 cm from the anal verge.	Triptorelin acetate 1.25 mg i.m. + estradiol 0.1%/day percutaneous	3.4 ± 1.8 months	NR	GIQLI (ref. 40), Bristol stool scale (ref. 41), KESS (ref. 42), Fecal Incontinence Quality of Life index (ref. 43)	Improvement of cyclic digestive complaints in more than half of patients. Constipation and non-cyclic symptoms were improved in less than a third of patients.
Yela <i>et al.</i> , 2015 (13)	Prospective case series	16	Not specified	DNG 2 mg/day per os	6 months	Headache Acne	Dyschezia was assessed by 0-10 visual analog pain scale (0	Significant improvement of pain symptoms (dysm, dysp, CPP, and

Source	Study design	Patients enrolled (n)	Location of bowel endometriotic nodules	Study drug	Treatment period	Adverse effects (%)	Questionnaires adopted to evaluate bowel symptoms	Outcome
						Decreased libido Breast pain Hair loss Nausea/vomit Bloating Vaginal dryness	indicated the absence of the symptom; 10 indicated the highest severity of the symptom)	dyschezia). No significant changes in volume size of endometriotic nodules. No significant changes in QoL and sexual function.
Milochau <i>et al.</i> , 2016 (38)	Case report	1	Sigmoid colon	Cyproterone acetate 50 mg/day per os + Estradiol 0.5 mg/day percutaneous gel (first 2 years) Continuous medium dose OC (EE 30 µg + LNG 150 µg)/day (until the end of follow-up)	4 years	With cyproterone acetate: Mood changes	GIQLI (ref.40), KESS (ref.42)	With cyproterone acetate partial amelioration of gastrointestinal symptoms, with unchanged constipation and bloating. With OC worsening of gastrointestinal symptoms and enlargement of bowel nodule at MRI and CT-based virtual colonoscopy.

Source	Study design	Patients enrolled (n)	Location of bowel endometriotic nodules	Study drug	Treatment period	Adverse effects (%)	Questionnaires adopted to evaluate bowel symptoms	Outcome
Leonardo-Pinto <i>et al.</i> , 2017 (14)	Prospective case series	30	Not specified	DNG 2 mg/day per os	12 months	Headache (63) Breast pain (43) Decreased libido (43) Nausea/vomiting (23)	Intestinal pain was assessed by 0-10 visual analog pain scale (0 indicated the absence of the symptom; 10 indicated the highest severity of the symptom)	Significant improvement of pain symptoms (dysm, dysp, CPP, bowel pain) and QoL. No significant changes in volume size of endometriotic nodules.
Ng <i>et al.</i> , 2017 (39)	Case report	1	Proximal rectum and rectosigmoid junction	DNG 2 mg/day per os	6 months	Spotting	NR	Significant improvement of pain (dysm, dysp) and gastrointestinal symptoms.
Vercellini <i>et al.</i> , 2017 (29)	Retrospective cohort study	50 ^d	Proximal rectum, rectosigmoid junction, and sigmoid colon	Continuous low-dose monophasic OC (EE 15 µg + gestodene 60 µg)/day; NETA 2.5 mg/day per os; DNG 2 mg/day per os	40 [18-60] months	Weight gain (32), decreased libido (18), bloating (16), vaginal dryness (16), headache (10), and mood changes (4)	KESS; Intestinal symptoms were assessed by 0-10 numerical rating scale scale (0 indicated the absence of the symptom; 10 indicated the highest severity	At final follow-up, 14 patients were very satisfied, 22 satisfied, 5 neither satisfied nor dissatisfied, 7 dissatisfied, and 2 very dissatisfied. Significant improvements of bowel symptoms as assessed by both the

Source	Study design	Patients enrolled (<i>n</i>)	Location of bowel endometriotic nodules	Study drug	Treatment period	Adverse effects (%)	Questionnaires adopted to evaluate bowel symptoms	Outcome
							of the symptom)	KESS questionnaire and the numerical rating scale.

^aEgekvist *et al.*, 2017 (35) was not included in the table because the exact number of patients who used the different medical treatments (OC, LNG-intrauterine

device or oral progestins), the adverse effects associated with their use, and the different outcomes in terms of pain symptoms or gastrointestinal symptoms variation could not be extracted from the published report.

^bIn case of breakthrough bleeding the daily oral dose of NETA was doubled.

^cPatients with medium-low rectum nodules (*n* = 4) are excluded.

^dOnly patients who chose medical treatment are here reported.

BMD = bone mineral density; CPP = chronic pelvic pain; DNG = dienogest; dysm = dysmenorrhea; dysp = dyspareunia; EE = ethinyl-estradiol; GIQLI = Gastro Intestinal Quality of Life Index; IBS-D = diarrhea-predominant irritable bowel syndrome; KESS = Knowles-Eccersley-Scott-Symptom Questionnaire; LNG = levonorgestrel; MRI = magnetic resonance image; NETA = nor-ethisterone acetate; NA = not applicable; NR = not reported; OC = oral contraceptive.





