ADVANCES IN THE MEDICAL MANAGEMENT OF BOWEL ENDOMETRIOSIS

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ABSTRACT

Endometriosis infiltrating the bowel can be treated medically in accurately selected women not seeking conception and without overt obstructive symptomatology. When the rectosigmoid junction is involved, the probabilities of intestinal symptoms relief, undergoing surgery after treatment failure, and developing bowel obstruction during hormonal treatment are around 70%, 10%, and 1-2%, respectively. When the lesion infiltrates exclusively the mid-rectum, thus in cases of true rectovaginal endometriosis, the probabilities of intestinal symptoms relief and undergoing surgery are about 80% and 3%, respectively. Endometriotic obstructions of the rectal ampulla have not been reported. A recto-sigmoidoscopy or colonoscopy should be performed systematically before starting medical therapies, also to rule out malignant tumours arising from the intestinal mucosa. Progestogens are safe, generally effective, well tolerated, inexpensive, and should be considered as first-line medications for bowel endometriosis. Independently of symptom relief, intestinal lesions should be checked periodically to exclude nodule progression during hormonal treatment.

KEYWORDS

Endometriosis, bowel, pelvic pain, medical treatment, progestogens, GnRH agonists.

INTRODUCTION

The bowel is the extragenital site most frequently affected by endometriosis [1,2]. It is estimated that 1 in 10 women with endometriosis harbours deep bowel lesions infiltrating not only the serosa and the sub-serosal tissue but also the muscular layer of the bowel wall. [2–4].

Bowel endometriosis may cause functional, irritative-type symptoms (e.g., diarrhoea, intestinal cramping, hematochezia, passage of mucus) originating from the cyclic release of mediators of inflammation, and mechanical, obstructive-type symptoms (e.g., constipation and abdominal bloating), originating from enlarging nodules, intestinal angulation and strictures, and fibrotic tissue retraction. Moreover, some symptoms are associated with specific lesions (e.g., cyclic dyschezia and tenesmus are typical of rectal endometriosis) [5,6].

In patients with severe sub-occlusive symptoms, there is no alternative to surgery. However, in many women, bowel endometriosis does not cause overt obstruction to faecal transit. Thus, when conception is not an issue, medical treatment might constitute a therapeutic alternative, especially considering that resection of endometriotic lesions with opening of the intestinal lumen may be followed by complications such as suture leakage, rectovaginal fistula formation, anastomosis stenosis, atonic bladder, and de novo bowel dysfunction [7–10]. The magnitude of the risk is associated also with the distance between the endometriotic lesion and the anal verge and with the coexistence of multiple lesions requiring more than one excision or segmental resection of a long intestinal tract [11–14]. Thus, identifying the exact location and anatomic characteristics of endometriotic bowel lesions appears important to correctly inform women's decisions [3,15,16].

The objectives of this narrative review are to define the pathological and endocrine basis underpinning the hormonal therapy of bowel endometriosis, synthesize the published evidence on the effect of available drugs in women with rectosigmoid and rectovaginal endometriosis separately, and propose a three-tiered risk stratification system to be used in patients not seeking conception and without frankly obstructive lesions.

Ileocecal endometriosis and the rare, isolated nodules of the small bowel are not considered here because the high risk of intestinal obstruction associated with these types of lesions almost always mandates surgical resection [17,18].

We aimed at retrieving reports of studies including patients with a definite diagnosis of endometriosis infiltrating the muscular layer of the mid-rectum (rectovaginal endometriosis), and of the proximal rectum and rectosigmoid junction (colorectal or rectosigmoid endometriosis). Only articles written in English and published in peer-reviewed journals in the last two decades were included. Case reports were considered separately with the specific intent of identifying additional patients who experienced occlusive events during medical treatment and that were not included in the considered studies.

ANATOMICAL AND HISTOLOGICAL PREMISES

Probably due to local anatomical and physiological factors, endometriotic lesions of the left colon are much more frequent than those infiltrating the right colon [2]. Left lesions comprise those involving the rectosigmoid junction (proximal rectum plus distal sigmoid) and those above the rectosigmoid junction (nodules of the mid- and proximal sigmoid) [19,20]. Right infiltrating lesions generally involve the terminal ileum and the cecum. Endometriosis of the appendix is not considered in this review. Lesions infiltrating the mid-rectum, that is, below the rectosigmoid junction, are usually part of complex nodule or plaques of the deepest portion of the Douglas pouch, often infiltrating also the posterior vaginal fornix in addition to the anterior rectal wall [21]. Multiple lesions may coexist at different sites. With the exception of the terminal ileal loop, isolated small bowel nodules are very rare.

Endometriotic bowel lesions present three distinct histologic components, i) the usual ectopic endometrial-like mucosa; ii) smooth muscle fibres; iii) fibrous connective tissue [1]. The observation of a muscular component is not surprising whenever endometriosis infiltrates the wall of hollow viscera (e.g., bowel, bladder, ureter, vagina). The fibrotic component originates from

tissue injury and remodelling induced by local inflammation associated with ectopic endometrium metabolic activity and, possibly, repeated micro-haemorrhages [22].

According to the retrograde menstruation theory, for endometriotic lesions to develop, particular anatomic conditions favouring endometrial cells shelter and implantation are needed. In the case of bowel endometriosis, this anatomical niche can be constituted by a physiologic intestinal flexure in close proximity with the salpinges, such as the rectosigmoid and ileocolic junctions [2,17], or by the juxtaposition of the anterior rectal wall and the posterior vaginal wall [21]. The final result of this pathological healing process is the formation of a sort of desmoplastic nodule. Intestinal plication around an endometriotic nodule is possible when an abundant mesocolon is present, and angulation and stricture may result as a consequence of scar retraction. In rectovaginal lesions, the coalescence of the anterior rectal and posterior vaginal walls leads to the formation of a fibrotic plaque that abolishes the distal portion of the Douglas pouch, usually without causing strict bowel angulation [21].

RATIONALE FOR HORMONAL TREATMENT OF BOWEL ENDOMETRIOSIS

Progesterone receptors are expressed not only in the ectopic mucosa but also in the smooth muscle fibres of endometriotic nodules infiltrating the colon [23]. Accordingly, an effect should be expected on two out three components of these deep lesions. In addition, the anti-inflammatory properties of progestogens [24,25] might influence long-term fibrosis remodelling. However, a major impact of medical therapies on the often-predominant fibrotic component seems unlikely. Overall, nodules might undergo volume reduction over time, but fibrotic scarring, and thus angulation and stricture, may not subside.

More in general, two distinct therapeutic mechanisms can be hypothesized for the hormonal treatment of bowel endometriosis, one local, based on oestrogen and progesterone receptor expression of individual lesions, and one systemic, based on inhibition of the hypothalamic-pituitary-ovarian axis. Defining the respective importance of the two mechanisms would be

119 relevant. In fact, it is currently assumed that a large part of endometriotic lesions might be
120 refractory to the use of progestogens due to local progesterone resistance [26]. If this is true,
121 theoretically progestogens should not be used to treat deep bowel endometriosis. However, if the
122 systemic effect is more important, progestogens could be used not aiming at a direct local effect,
123 but rather with the intent of preventing ovulation and menstruation, thus reducing the metabolic and
124 proliferative activity of the ectopic mucosa through the induction of a stable hypo-oestrogenic
125 milieu. This *per se* would abate the intra- and perilesional inflammation. In this case, suppression of
126 the gonadal activity should attain partial lesion regression or temporary avoidance of progression
127 independently of receptor status [27].

128 Ferrero *et al*. [28] evaluated variation in rectovaginal endometriotic nodule volume in
129 women treated with progestogens as monotherapy (*n*=44) or combined with letrozole (*n*=8),
130 oestrogen-progestogen contraceptive pills (*n*=30), or triptorelin plus tibolone (n=10). At
131 ultrasonography assessment, nodule volume decreased by about 20% after 6 months of therapy, and
132 about 30% after 12 months, without significant differences between study drugs. Nodule volume
133 decreased in 74% of the participants but increased by around 20% in 12% of them.

134 Egekvist *et al*. [29] followed 80 women with rectosigmoid or rectovaginal nodules treated
135 for at least 12 months with a levonorgestrel-releasing intrauterine device (LNG-IUD; *n*=49), an oral
136 contraceptive (*n*=12), a progestogen (*n*=9), or a combination of therapies (*n*=10). The nodule length
137 and width increased in nine and six patients, respectively. During the study period, surgery was
138 required in 6% of the patients. Of note, the LNG-IUD does not inhibit ovulation except for a few
139 months after insertion [30], and acute rectosigmoid obstruction during LNG-IUD use has been
140 described [31].

141 Netter *et al*. [32] assessed rectosigmoid nodule measures variation in 43 women who
142 underwent two MRIs at least 12 months apart. Nodule progression or regression was defined as,
143 respectively, ≥20% increase or ≥20% decrease in length or in thickness. Any nodule with <20%
144 variation was defined as stable. Stability, progression or regression was observed in 60%, 28%, and

12% of the women, respectively. Moreover, progression was detected in more than one-third of women who never experienced amenorrhoea, but in no patient who experienced continuous amenorrhoea during therapy with GnRH agonists, progestogens, or combined oral contraceptives. The risk of progression was inversely related to the length of periods of amenorrhoea.

Barra *et al*. [33] treated 83 women with symptomatic rectosigmoid nodules with oral dienogest, 2 mg/day. Mean nodule volume, as assessed at transvaginal ultrasonography, decreased by 7.5% after 6 months of progestogen therapy, and by 22.5% after 12 months. Endometriotic nodules regressed in 53% of the participants, remained stable in 35%, and progressed (an increase of ≥10%) in 12%.

Nodule volume variation is not necessarily associated with symptom variation. As an example, Netter *et al*. [32] reported persistence of pain symptoms in the vast majority of women in whom the nodule regressed or remained stable. On the other hand, Egekvist *et al*. [29] observed that progression of nodule volume dimensions occurred without worsening of symptoms or health-related quality of life. Barra *et al*. [33] also confirmed that the increase in endometriotic nodule volume during dienogest therapy was not always associated with worsening of clinical symptoms.

ENDOMETRIOSIS OF THE MID-RECTUM (RECTOVAGINAL ENDOMETRIOSIS)

A total of 1232 patients were included in 23 studies published in the period January 2000-May 2020 (prospective cohort, *n*=11; patient preference trial, *n*=6; retrospective cohort, *n*=3; randomised controlled trial (RCT), *n*=2; before and after study, *n*=1; Table 1). The experimental study drug was a progestin in 11 studies, an oestrogen-progestogen combination (OPC) in 3, an aromatase inhibitor in 3, a GnRH agonist in 2, vaginal danazol in 2, an LNG-IUD in 1, and an etonogestrel-releasing implant in 1. The route of administration was mostly oral for progestogens and OPC, but also the vaginal, intramuscular, transdermal and intra-uterine route were assessed (Table 1).

The symptoms referred by recruited women were not always precisely described and accurately measured. Overall, the probability of partial or complete relief was 100% for rectal

tenesmus, feeling of incomplete evacuation and cyclic rectal bleeding, 92% for dyschezia, 64% for constipation, 58% for diarrhoea, 38% for passage of mucus, and 37% for abdominal bloating. In addition, dysmenorrhoea subsided in 78% of the considered women, deep dyspareunia in 77%, and non-cyclic pelvic pain in 73%.

A total of 38 women (3%) underwent surgery during the study period (persistence or worsening of pain symptoms, *n*=15; lesion size progression, *n*=3; indication not reported, *n*=20). No patient experienced bowel obstruction while using hormonal medications.

ENDOMETRIOSIS OF THE PROXIMAL RECTUM AND DISTAL SIGMOID (RECTOSIGMOID JUNCTION ENDOMETRIOSIS)

In the considered period, a total of 588 patients were included in 10 studies (prospective cohort, *n*=5; retrospective cohort, *n*=5; Table 2). However, 238 participants were enrolled in a single study [34]. The experimental study drug was a progestin in 3 studies, an OPC in 1, an aromatase inhibitor in 1, a GnRH agonist in 1, and multiple hormonal drugs in 4. The route of administration was always oral except for one study investigating the effect of a GnRH agonist injected intramuscularly in a depot formulation (Table 2).

Again, the description and assessment of symptoms sometimes were suboptimal. Overall, the probability of partial or complete relief was 100% for diarrhoea and passage of mucous, 98% for constipation, 90% for a feeling of incomplete evacuation and cyclic hematochezia, 82% for intestinal cramping, and 79% for abdominal bloating. In addition, dysmenorrhoea subsided in 80% of the considered women, deep dyspareunia in 78%, and non-cyclic pelvic pain in 67%.

A total of 123 women (21%) underwent surgery during the study period (persistence or worsening of pain symptoms, *n*=79; lesion size progression, *n*=26; intolerance of medical treatment, *n*=11; indication not reported, *n*=6; occlusive symptoms, *n*=1). Of note, 95 out of these 123 women were described in a single study [34]. Excluding this outlier, the probability of undergoing surgery

196 despite medical therapy was 8% (28/350; persistence or worsening of pain symptoms, *n*=11;
197 intolerance of medical treatment, *n*=11; indication not reported, *n*=6).
198
199 BOWEL OBSTRUCTION DURING MEDICAL TREATMENT
200 Complete intestinal obstruction caused by endometriotic stricture is rare, as it is estimated to occur
201 in < 1% of patients with bowel lesions [31,35]. However, for women considering medical treatment
202 as an alternative to surgery, it would be important to know not only the general risk of such
203 complication but the specific risk of this event while using suppressive therapies. In fact, the
204 volume of 5%-10% of endometriotic intestinal nodules increases during pharmacological treatment.
205 Only one case of sub-acute bowel obstruction in a woman with rectosigmoid junction endometriosis
206 was described in the 33 studies considered in this review [34]. The type of medication used was not
207 reported.
208 Among the case reports searched through PubMed, 15 additional cases of bowel obstruction
209 during medical treatment use (isolated sigmoid colon endometriosis, *n*=3; rectosigmoid junction
210 endometriosis, *n*=12) were identified. Ferrero *et al*. [36], Constantin *et al*. [37] and Millochau *et al*
211 [38] observed sub-acute [36,38] or acute [37] intestinal obstruction caused by an endometriotic
212 nodule infiltrating the sigmoid colon, in all cases after four years of cyclic [36,37] or continuous
213 [38] treatment with a combined oral contraceptive.
214 Navajas-Laboa *et al*. [39] reported a case of endometriotic rectosigmoid junction obstruction
215 occurred one month after discontinuation of an oral contraceptive used for more than 20 years.
216 Scioscia *et al*. [40] briefly described seven women who underwent laparoscopic colorectal resection
217 owing to progression of rectosigmoid stenosis after 9-16 months of daily oral therapy with
218 desogestrel 75 μg (*n*=3), dienogest 2 mg (*n*=2), or nor-ethisterone acetate 2.5 mg (*n*=2). All nodules
219 were larger than 4 cm. Whelton and Bhowmick reported a case of acute bowel obstruction due to
220 stenosis of the rectosigmoid junction in a woman wearing an LNG-IUD as a treatment for severe
221 deep endometriosis [31].

De Jong *et al*. described five patients who underwent emergency surgery because of an endometriotic stricture of the rectosigmoid junction. Three of these women used medical treatment, but it is unclear whether the bowel obstruction ensued during the use of respectively, a GnRH agonist, an LNG-IUD, and a progestogen, or if these drugs were used in the past for a limited time period. In fact, the authors only stated: "three patients were already treated with GnRH agonists or other hormone therapies" [35].

Of relevance, intestinal obstructions ensued during therapy for sigmoid or rectosigmoid lesions, but not for exclusively mid-rectal nodules. This supports the notion that the development of strict angulation of a bowel tract is a pre-requisite for occlusion to occur. An increase in endometriotic nodule dimension may further facilitate the process, as protrusion within a strictly angulated intestinal lumen may easily result in worsening of the stenosis to the point of impeding faecal transit. Importantly, for most of the reported cases, the baseline anatomic characteristics of bowel lesions were not described. Therefore, it is not possible to exclude that some of the women who experienced intestinal occlusion were not candidates to medical treatment according to currently agreed selection criteria.

MEDICAL THERAPY FOR BOWEL ENDOMETRIOSIS: WHEN AND HOW.

The quality of the available evidence on medical therapy for bowel endometriosis is suboptimal. Most studies were non-comparative. Several drugs were evaluated, often grouped in the same series, thus impeding definition of the effect of individual compounds and ascertainment of differences between therapies. Sometimes two different molecules were combined. Treatment periods were highly variable, ranging from a few months to years. It was not always possible to extract the precise location of bowel lesions, especially when the generic definition "colorectal endometriosis" was used. Thus, it may not be excluded that women at different prognosis were studied together, especially when patients with multiple lesions were included. Indeed, rectovaginal and recto-sigmoid junction lesions may coexist. Finally, when pain relief is considered,

248 discriminating the specific response to treatment of bowel endometriosis from that of other pelvic
249 lesions seems difficult.

250 As a consequence, only general conclusions can be drawn from the assessment of published
251 data. When the lesion is located above the mid-rectum, medical treatment should not be suggested if
252 the degree of lumen stenosis is ≥ 60%, or if the lesion infiltrates ≥ 50% of the bowel circumference,
253 or if the largest nodule diameter is >3 cm. In fact, the likelihood of substantial symptom
254 improvement and definitive avoidance of surgery seems strictly related to the above lesion
255 characteristics [3,4,41].

256 Moreover, medical therapy should never be suggested as an alternative to surgery for bowel
257 endometriosis in patients with i) severe sub-occlusive intestinal symptoms, ii) ureteral stenosis with
258 hydroureteronephrosis, iii) adnexal masses > 5 cm or with suspect ultrasonographic appearance, and
259 iv) current pregnancy desire. Women wishing to conceive in the future should also be carefully
260 counselled, not only because all the available hormonal medications interfere with ovulation, but
261 also because bowel obstruction and perforation during pregnancy and ovarian stimulation have been
262 reported [42–44]. In addition, intestinal procedures are more complex in the presence of a gravid
263 uterus and are associated with risk of harms to both the mother and the foetus [45].

264 In the absence of the above conditions, women should be informed in detail on the
265 advantages and disadvantages of medical and surgical options. Patients should know that hormonal
266 drugs might control, but not cure bowel endometriosis. Therefore, if medical treatment is chosen,
267 this means using medications for years, possibly until the physiologic menopause. On the other
268 hand, women should also know that excisional surgery as an isolated measure might not guarantee
269 complete and/or long-lasting symptom relief. To reduce the risk of symptom and lesion recurrence,
270 which is about 50% in 5 years [3,41,46,47], postoperative hormonal therapy may be needed anyway
271 for an indefinite period of time.

272 Women desiring to avoid surgery, willing to use medications for years, who are
273 psychologically tolerant of amenorrhoea and ready to deal with possible side effects of medications,

and without contraindications to available hormonal drugs, should then be informed about the absolute probability of i) experiencing pain and bowel symptoms relief, ii) undergoing surgery anyway for multiple reasons, iii) suffering episodes of frank bowel obstruction during medical treatment. This stage of the information process should be based on the precise location and characteristics of the lesion. In particular, patients should be aware that when the rectosigmoid junction is involved, the probability of intestinal symptoms relief is around 70%, and of undergoing surgery anyway around 10%. The risk of bowel obstruction is presumably between 1% and 2%. In most but not all cases, surgery can still be planned without the need for emergency procedures.

On the other hand, lesion dimension has little impact on the probability of success of medical therapy when the lesion infiltrates exclusively the mid-rectum as, to our knowledge, endometriotic obstructions of the rectal ampulla have not been reported. In case of true rectovaginal endometriosis, the probability of intestinal symptoms relief is around 80%, and that of undergoing surgery anyway for symptom persistence about 3%.

When multiple lesions are present, the shared decision process should focus on the lesion at worst prognosis. A recto-sigmoidoscopy or colonoscopy, in addition to transvaginal ultrasonography and MRI or other imaging techniques [15,16], should be suggested systematically before starting medical therapies, not only to verify the degree of lumen stenosis but also to rule out malignant tumours arising from the intestinal mucosa.

Women should also be aware that deciding between medical and surgical treatment is not necessarily an “either/or” decision but may be viewed as a stepwise approach. In a stepped care model, hormonal treatments should be tried first, resorting to surgery in women who do not respond to or do not tolerate medications [48]. However, when all the above selection criteria have been satisfied, generally no more than half of the patients with symptomatic bowel endometriosis actually remain available for a trial of medical therapy [20]. Obviously, the accurate selection of candidates for medical treatment on one hand reduces the number of potential users but, on the other hand, increases the likelihood of success and overall patient satisfaction with this choice.

Most of the evidence on medical treatment for bowel endometriosis concerns the use of progestogens or OPC. These compounds are safe, generally effective, well-tolerated, inexpensive, and may be used for years. For these reasons, progestogens and continuous, low-dose OPC should be considered as first-line medications also for bowel endometriosis. A difference in the magnitude of the effect of these two drugs has not been demonstrated. Moreover, intestinal sub-acute obstruction has been reported during treatment with both, progestogens [31,35,40] and OPC [36–39].

However, the pathogenic premise behind medical treatment for deep endometriosis is different from that for ovarian endometriomas. In the latter case, the objective is inhibiting ovulation independently of the oestrogen content of the medication used, whereas when dealing with infiltrating lesions the objective is achieving the maximum possible disease quiescence to avoid lesion progression [30,48].

Casper questioned the role of OPC in the management of endometriosis based on the hypothesis that owing to the supra-physiologic oestrogen content, these combinations may not adequately suppress lesions and relieve symptoms [24]. In addition, the results of a small RCT suggested a potentially detrimental role of even small amounts of a natural oestrogen [49]. The stimulating action of oestrogens on ectopic endometrium are generally effectively counteracted by progestogens when using OPC. Nevertheless, until this issue will be definitively disentangled, prescribing progestogen monotherapies to minimize the risk of lesion progression seems wiser when treating women with bowel endometriosis. Oral dienogest, 2 mg/day and nor-ethisterone acetate, 2.5 mg/day are similarly effective, although the former, costlier, compound seems better tolerated [50].

Progestogens are usually associated with several side effects in a large proportion of users. However, in most cases, untoward effects are not severe enough to cause drug discontinuation. An exception is irregular bleeding, as it may cause pelvic pain and bowel symptoms worsening, is scarcely tolerated, and may limit treatment adherence [30,48]. Women must be informed in

advanced that around one-third of women experiences repeated irregular bleeding and associated pelvic pain during progestogen treatment. Anticipating and describing these events may reduce anxiety, and providing information on tailored cycling may reduce the risk of drop out. Discontinuing progestogen assumption for one week generally allows successful management of breakthrough bleeding or prolonged spotting [30]. The frequency of these events generally decreases over time. Starting treatment with a GnRH agonist for a few months and then switching to an oral progestogen, may reduce the incidence of unexpected and painful bleeding episodes [51].

Bowel lesions, especially when infiltrating the sigmoid colon and the rectosigmoid junction, should be checked periodically with imaging techniques [15,16], with the aim of identifying nodule progression during progestogen treatment despite partial or complete symptom relief [33]. Moreover, kidneys and ureters should also be checked regularly to rule out silent progressive hydroureteronephrosis, especially in women with large rectovaginal plaques extending laterally toward the pelvic sidewall [14].

A LESION-BASED, THREE-TIERED RISK STRATIFICATION SYSTEM FOR BOWEL ENDOMETRIOSIS

The definition “bowel endometriosis” comprises different anatomical conditions associated with different clinical patterns. In particular, the likelihood of safely alleviating intestinal symptoms and avoiding surgery varies according to lesion location.

Bowel obstruction is probable when the lumen is intrinsically narrow, such as in cases of involvement of the last ileal loop and ileocecal valve [17,18]. Obstruction is possible when lesions infiltrate the wall of the sigmoid and the rectosigmoid junction, as the abundant mesocolon easily allows intestinal angulation around the nodule, which thus may act as a wedge impinging on a loop strictly fixed by fibrotic tissue. Conversely, the mid-rectum, which corresponds to the Douglas pouch, only has an anterior peritoneal covering. This, together with the large calibre and

distensibility of the rectal ampulla, renders sharp angulation and stenotic obstruction mechanically unlikely [14,20,48].

To define the therapeutic trade-offs that should inform patient choices, the potential harms of surgery for different bowel lesions should also be considered. Although lesion shaving is being fostered [8], actually nodulectomy (disk excision) and segmental resection are the procedures more frequently performed in case of bowel stenosis due to infiltrating endometriosis [3,4,10,13]. Proximal sigmoid nodule excision or segmental resection require standard surgically capabilities and are associated with a low risk of complications [9,12]. A temporary derivative ostomy is generally not necessary. Colorectal resection for rectosigmoid junction endometriosis may be technically demanding and is associated with a 5% risk of severe short- and medium-term complications [10,12]. The decision to confection an ostomy depends on local protocols, and variable percentages have been reported [4,12,13]. Patients requiring low-anterior rectal resection for rectovaginal endometriosis infiltrating the mid-rectum should be referred to centres of expertise where abdominal surgeons and gynaecologists specifically trained to manage complex pelvic endometriosis are available. The posterior vaginal fornix must be frequently excised at the same time, thus increasing the likelihood of rectovaginal fistula formation. For this reason, a protective ostomy is frequently performed. The risk of severe complication is around 10% [4,10,12,14,20].

Based on these considerations, a three-tiered risk stratification system could be envisaged when managing bowel endometriosis. As endometriosis of the proximal sigmoid is associated with a moderate risk of obstruction, an indefinite likelihood of improvement during medical treatment, and a low risk of surgical complications, excision should be preferred.

Endometriosis of the rectosigmoid junction is also associated with a moderate risk of obstruction, but sufficient evidence exists to anticipate a fairly good effect of medical therapy. The risk of surgical complications is also moderate. In this sort of therapeutic equipoise, the value of the two treatment options appears similar. Pharmacological therapy could be tried first, resorting to surgery in case of inefficacy of or intolerance to medications.

Rectovaginal endometriosis is not at risk of obstruction and usually responds well to hormonal compounds. Radical excision of this type of lesions carries a moderate-high risk of surgical complications [10,14]. Thus, medical treatment should be preferred.

Several other factors may influence the final decision, including the presence of multiple lesions, previous complex surgical procedures and overall surgical risk, age, and the long-term total expected costs of the different therapeutic options. In addition, the role of patients is here particularly important, as different women may be willing to accept different levels of surgical risks or may tolerate differently the same drug side effects. Whether to accept potential surgical morbidity or use medications for years is a very personal choice that should be based on complete, detailed, and unbiased information.

SUMMARY

The quality of the evidence on medical therapy for bowel endometriosis is suboptimal and only general conclusions can be drawn. Medical treatment should not be suggested to women wishing to conceive, and also when severe sub-occlusive symptoms are present, the degree of lumen stenosis is ≥ 60%, or the lesion infiltrates ≥ 50% of the bowel circumference, or the largest nodule diameter is >3 cm. Patients should be informed in detail about the advantages and disadvantages of medical and surgical options. Hormonal drugs might control, but not cure bowel endometriosis. This means using medications for long periods of time. However, excisional surgery as an isolated measure may not guarantee complete and/or long-lasting symptom relief, and postoperative hormonal therapy may be needed anyway. The information process should be based on the location and characteristics of the lesion. Approximately two-thirds of accurately selected patients with rectosigmoid endometriosis and three-fourths of those with rectovaginal lesions can be managed successfully with hormonal drugs. Progestogens are safe, effective, generally well-tolerated, inexpensive, may be used for years, and should be considered as first-line medications. Around one-third of women experiences repeated irregular bleeding with associated pelvic pain during continuous progestogen treatment, and instructions should be provided on how to manage these events. The risk of obstruction during therapy is low in women with rectosigmoid junction endometriosis, and virtually absent in those with rectovaginal disease. However, bowel lesions should be checked periodically with imaging techniques to identify possible nodule progression during medical treatment despite symptom relief.

CONFLICT OF INTEREST STATEMENT

None.

PRACTICE POINTS

- Medical treatment is a valuable therapeutic option that could be proposed in selected women with bowel endometriosis.

- About two-thirds of the patients with rectosigmoid endometriosis and three-fourths of those with rectovaginal lesions can be managed successfully with hormonal drugs, provided strict selection criteria are fulfilled.

- Endometriotic bowel lesions should be checked periodically with imaging techniques to identify possible nodule progression during medical treatment despite symptom relief.

RESEARCH AGENDA

- Comparative effectiveness research on medical treatment versus surgery for endometriosis of the proximal rectum and rectosigmoid junction (colorectal endometriosis)

- Comparative effectiveness research on medical treatment versus surgery for endometriosis of the mid-rectum (rectovaginal endometriosis)

- GnRH agonists followed by progestogens to reduce breakthrough bleeding.

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Table 1. Effect of aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRHa), oestrogen-progestins, and progestins as assessed in studies on the treatment of rectovaginal endometriosis (literature data, 2000-2020).

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
Fedele *et al*., 2000 [52]	Prospective	15	Leuprolide acetate 3.75 mg IM/28 day	6 months	NR	Improvement of pain symptoms during treatment. High rate of pain recurrence after drug discontinuation. Transient regression of nodule size during treatment with return to baseline volume during follow-up.
Fedele *et al*., 2001 [53]	Prospective	11	LNG-IUD	12 months	Headache (37) Breast tenderness (37) Weight gain >1 kg (37) Seborrhoea, oily hair, acne (27)	Significant improvement of dysm and CPP. Partial amelioration of deep dysp. Significant reduction of nodule size after 6 months of treatment. At the end of treatment period 9 patients were oligomenorrheic and 2 experienced amenorrhea.

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
Vercellini *et al.,* 2005 [54]	RCT	90	Continuous low-dose monophasic OC (EE 0.01 plus cyproterone acetate 3 mg)/day (*n* = 45) (VS NETA 2.5 mg/day per os) (*n* = 45)	12 months	Group OC: Weight gain (16) Headache (7) Nausea (7) Depression (4) Decreased libido (4) Acne (2) Bloating (2) Breast tenderness (2) Hypertriglyceridemia (2) Group NETA: Weight gain (27) Decreased libido (9) Bloating (9) Depression (7) Headache (4) Acne (4)	Similar pain relief and dropout rates. Higher satisfaction with treatment in NETA group.

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
					Erythematous cutaneous reaction (2)	
Hefler *et al.,* 2005 [55]	Prospective	10	Vaginal anastrozole 0.25 mg/day	6 months	No severe adverse events reported during study period	Significant improvement of dysm and QoL. CPP and dysp remained unchanged during treatment. No significant changes in BMD and nodule volume size during treatment.
Razzi *et al*., 2007 [56]	Prospective	21	Vaginal danazol 200 mg/day	12 months	Vaginal irritation (19)	Significant improvement of dysm, dysp, and CPP. Significant reduction of nodule size after 6-months of treatment. No significant change of serum metabolic and thrombophilic parameters.
Remorgida *et al*., 2007 [57]	Prospective	12	Letrozole 2.5 mg/day plus NETA 2.5/day per os	6 months	Weight gain (33) Mood swings (33) Weakness (25) Bone and joint pain (25)	Significant pain relief and QoL improvement during treatment. At 6-months' follow-up recurrence of pain symptoms and worsening of QoL

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
					Vaginal spotting (17) Muscle aches (17) Headache (17) Depression (17) Hot flushes (8) Nausea (8) Decreased libido (8)	scores in all patients. No BMD changes during treatment.
Ferrero *et al*., 2009 [58]	PPT	82	Letrozole 2.5 mg plus NETA 2.5 mg/day per os (n = 41) (VS NETA 2.5 mg/day per os) (n = 41)	6 months	Group Letrozole plus NETA: Weight gain (20) Joint pain (17) Myalgia (12) Spotting (10) Breakthrough bleeding (5) Migraine (5) Myalgia (2)	Greater pain relief with letrozole plus NETA, but fewer side effects and higher patient satisfaction rate with NETA only. Similar pain at follow-up. No BMD changes during treatment.

Source	Study design	Patients enrolled (*n*)	Study drug (comparator)	Treatment period	Adverse effects (%)	Outcome
					Depression (2) Hair loss (2) Decreased libido (2) Group NETA: Weight gain (17) Breakthrough bleeding (7) Spotting (7) Migraine (7) Depression (2)	
Vercellini *et al.,* 2010 [59]	PPT	59[a]	Vaginal ring (EE 15 μg plus etonogestrel 120 μg) (*n* = 38) (VS transdermal patch - EE 20 μg plus	12 months	Group vaginal ring: Bloating (10) Vaginal discomfort (7) Depression (6) Weight gain (6) Headache (6) Breast tenderness (5)	Greater pain relief and satisfaction with vaginal ring.

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
			norelgestromin 150 μg) (*n* = 21)		Decreased libido (4) Nausea (2) Group patch: Headache (18) Nausea (8) Breast tenderness (8) Weight gain (5) Depression (5) Decreased libido (5) Cutaneous reaction (5) Bloating (3) Vaginal dryness (2) Vomiting (2)	
Ferrero *et al*., 2011 [60]	Observational pilot study [b]	15	Vaginal danazol 100 mg/day	6 months	Seborrhea, oily hair, acne (27) Headache (20)	Significant improvement of dysm, dysp, CPP, and dyschezia and reduction of nodule size after 6 months of treatment. High

Source	Study design	Patients enrolled (*n*)	Study drug (comparator)	Treatment period	Adverse effects (%)	Outcome
					Weight gain >3 kg (13) Vaginal irritation (13)	satisfaction rate with the treatment (80% of women were satisfied or very satisfied).
Ferrero *et al.,* 2011 [61]	RCT	35	Letrozole 2.5 mg plus NETA 2.5 mg/day per os (*n* = 17) (VS letrozole 2.5 mg/day per os plus triptorelin 11.25 mg/3 months IM) (*n* = 18)	6 months	NETA group: Weight gain (12) Decreased libido (12) Spotting (12) Myalgia and arthralgia (12) Depression (6) Triptorelin group: Myalgia and arthralgia (56) Decreased libido (22) Depression (22) Hot flushes (22) Vaginal dryness (17)	Similar pain relief. Higher patient satisfaction with treatment in NETA group. Higher discontinuation rates in the triptorelin group. Greater nodule size reduction with triptorelin. Significant reduction of BMD in women treated with triptorelin.

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
					Insomnia (17) Hair loss (11) Headache (11) Weight gain (6)	
Mabrouk *et al.,* 2012 [62]	Retrospective	106	Cyclic low-dose monophasic OC (EE 20 µg plus drospirenone 3 mg)/day (*n* = 75) (VS no treatment) (*n* = 31)	5.8 (3.7) months [c]	NR	No significant variations in pain scores and nodule size in OC group. Significant worsening of dysm and deep dysp scores, and enlargement of nodule size in nonuser group. No significant changes in QoL scores during study period nor between groups.
Vercellini *et al*., 2012 [63]	PPT	59[a]	NETA 2.5 mg/day per os (*n* = 35)	12 months	Weight gain (34) Breakthrough bleeding (20) Decreased libido (19) Vaginal dryness (12)	At the end of follow-up comparable satisfaction and improvement of deep dysp.

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
			(VS second-line laparoscopic excision of endometriotic lesions) (*n* = 24)		Spotting (11) Breast tenderness (6) Bloating (5) Headache (4) Depression (4) Nausea (2)	
Leone Roberti Maggiore *et al*., 2014 [64]	PPT	143	DSG 75 µg/day per os (n = 60) (VS vaginal ring - EE 15 µg plus etonogestrel 120 µg) (n = 83)	12 months	Group DSG: Breakthrough bleeding (8) Metrorrhagia (2) Weight gain (2) Group vaginal ring: Weight gain (6) Spotting (2)	Higher patient satisfaction with treatment in DSG group. Similar reduction in the volume of rectovaginal nodules. Comparable discontinuation rates.
Morotti *et al*., 2014 [65]	PPT	144	DSG 75 µg/day per os (*n* = 62)	6 months	Group DSG: Bleeding (8)	Higher satisfaction with treatment in DSG group. Similar pain relief (dysp

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
			(VS cyclic low-dose monophasic OC - EE 20 µg plus DSG 150 µg/day) (*n* = 82)		Weight gain (2) Mood changes (2) Group OC: Increased migraine (11) Bleeding (6) Weight gain (2) Mood changes (1) Decreased libido (1) Acne (1) Peripheral edema (1)	and CPP). Lower rate of migraine attacks with DSG.
Morotti *et al*., 2014 [66]	Open-label prospective study[d]	25	DNG 2 mg/day per os (*n* = 25)	6 months	Headache (16) Nausea (8) Breast tenderness (4)	Improvement of pain symptoms, sexual function, QoL and satisfaction with DNG.
Roman *et al*., 2015 [67]	Prospective case series	70	Triptorelin acetate 11.25 mg IM depot injection	3.4 ± 1.8 months	--	Improvement of cyclic digestive complaints in more than half of patients. Constipation and non-cyclic

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
			plus percutaneous estradiol 0.1% /day			symptoms were improved in in less than a third of patients.
Yela *et al*., 2015 [68]	Prospective	16	DNG 2 mg/day per os	6 months	Headache Acne Decreased libido Breast pain Hair loss Nausea/vomit Bloating Vaginal dryness	Significant improvement of pain symptoms (dysm, dysp, CPP, and dyschezia). No significant changes in volume size of endometriotic nodules. No significant changes in QoL and sexual function.
Vercellini *et al*., 2016 [50]	Before-after study	60[a]	DNG 2 mg/day per os (*n* = 29) (VS NETA 2.5 mg/day per os) (*n* = 31)	6 months	Group DNG: Weight gain (16) Spotting (13) Decreased libido (9) Vaginal dryness (7) Bloating (6)	Similar satisfaction with treatment and pain relief.

Source	Study design	Patients enrolled (*n*)	Study drug (comparator)	Treatment period	Adverse effects (%)	Outcome
					Alopecia (5) Headache (3) Mood disorders (2) Breast tenderness (1) Nausea (1) Breakthrough bleeding (1) Group NETA: Weight gain (31) Spotting (22) Decreased libido (14) Vaginal dryness (13) Mood disorders (8) Breast tenderness (8) Bloating (5) Acne (4)	

Source	Study design	Patients enrolled (*n*)	Study drug (comparator)	Treatment period	Adverse effects (%)	Outcome
					Headache (3) Alopecia (1) Breakthrough bleeding (1)	
Leonardo-Pinto *et al*., 2017 [69]	Prospective	30	DNG 2 mg/day per os	12 months	Headache (63) Breast pain (43) Decreased libido (43) Nausea/vomit (23)	Significant improvement of pain symptoms (dysm, dysp, CPP, bowel pain) and QoL. No significant changes in volume size of endometriotic nodules. No relation between remission of pain symptoms and reduction of the volume of endometriotic nodules.
Morotti *et al*., 2017 [70]	Retrospective	103 (61 completed the 5 year follow-up)	NETA 2.5 mg/day per os [e]	5 years	Weight gain (30) Vaginal bleeding (23) Lipids alteration (12) Decreased libido (11)	Significant improvement of dysm, CPP, dyschezia and dysp. At the end of study period 69% of women were satisfied or very satisfied with the treatment, 40.8% of all patients in the

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
					Headache (9) Bloating (8) Depression (7) Acne (5) Erythematous cutaneous reaction (1)	intention to treat analysis (ITT). Significant reduction in the volume of the endometriotic nodules. At the end of study period, 11.9% of the patients displayed a volumetric increase of rectovaginal endometriosis.
Scala *et al.*, 2018 [71]	Patient preference study	100 (52 with rectovaginal endometriotic nodules)	NETA (2.5 mg/day) (VS Extended-cycle OC – LNG 150 mcg and EE 30 mcg for 84 days and EE 10 mcg for 7 days)	12 months	Unscheduled bleeding Spotting	No significant difference in the rate of satisfied patients at 12-month follow up between the two study groups. At 6-month and 12-month follow up, significant amelioration in the intensity of all pain symptoms compared with baseline in both groups. Significant within group reduction of rectovaginal endometriotic nodules

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
						volumes, without between groups differences.
Leonardo-Pinto *et al.,* 2018 [72]	Prospective	30	DNG 2mg/die	12 months	Headache (63) Decrease in desire (43) Nausea (23)	Significant improvement of dysm, CPP and dysp. Significant improvement in sexual function (assessed with FSFI), but no significant enhancement in desire, lubrication and satisfaction domains of FSFI. Sexual function was not completely restored.
Ferrero *et al.*, 2019 [73]	Retrospective	44	Etonogestrel-releasing implant	24 months	Headache (23) Dizziness (14) Acne (7)	Significant improvement of dysm, CPP, dyschezia and deep dysp. Significant improvement in all domains of the EHP-30

Source	Study design	Patients enrolled (*n*)	Study drug (comparator)	Treatment period	Adverse effects (%)	Outcome
						questionnaire. Significant reduction in endometriotic nodules volume.

[a] Only the sub-group of patients with rectovaginal endometriosis was considered.
[b] Only patients with symptomatic rectovaginal endometriosis who had pain persistence after insertion of a LNG-IUD were selected.
[c] Mean (SD).
[d] Only patients with symptomatic rectovaginal endometriosis who had pain persistence and were unsatisfied after 6-months of treatment with NETA were selected.
[e] In case of breakthrough bleeding the dose of NETA was increased from 2.5 to 5 mg/day.

BMD = bone mineral density; CPP = chronic pelvic pain; DNG = dienogest; DSG = desogestrel; dysm = dysmenorrhoea; dysp = dyspareunia; EE = ethinyl estradiol; EHP = endometriosis health profile; FSFI = female sexual function index; IUD = intrauterine device; IM = intramuscular; LNG = levonorgestrel; NETA = nor-ethisterone acetate; NR = not reported; OC= oral contraceptive; PPT = patient-preference trial; QoL = quality of life; RCT = randomized controlled trial; VAS = visual analogue scale.

Table 2. Effect of aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRHa), oestrogen-progestogens, and progestogens as assessed in studies on the treatment of proximal rectum and rectosigmoid junction endometriosis (literature data, 2000–2020) [a]

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
Ferrero *et al.*, 2010 [74]	Prospective case series	18	Triptorelin 11.25 mg/3 months IM plus tibolone 2.5 mg/day per os	12 months	Hot flushes (33) Vaginal bleeding (33) Sweating episodes 3(17) Vaginal dryness and superficial dyspareunia (11) Nervousness and irritability (11) Weight gain (11) Sleeplessness (6) Fatigue (6) Difficulty in concentration (6)	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 (11%) were uncertain, and 3 (17%) were dissatisfied.
Ferrero *et al*., 2010 [75]	Prospective case series	40	NETA 2.5 mg/day per os[b]	12 months	Worsening of constipation (7.5) Breakthrough bleeding (5)	Significant improvement of dysm, dysp, CPP, dyschezia and diarrhea. No significant improvement in

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
					Weight gain (5) Spotting (2.5) Depression (2.5) Migraine attacks (2.5)	patients with constipation, abdominal bloating and feeling of incomplete evacuation after bowel movements. 60% of patients were satisfied or very satisfied with the treatment.
Ferrero *et al*., 2010 [76]	Prospective case series	6	Letrozole 2.5 mg/day plus NETA 2.5 mg/day per os	6 months	Breakthrough bleeding (17) Weight gain (17) Joint pain (17) Decreased libido (17)	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 *et al.*, 2011 [77]	Retrospective case series	4	DNG 2 mg/day per os	12 months	Spotting (75) Hot Flushes (50) Gastralgia (25) Depression (25)	Significant improvement of pain symptoms and reduction in nodule size.

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
Ferrari *et al*., 2012 [78]	Prospective case series	26	Continuous low-dose monophasic OC (EE 15 μg plus gestodene 60 μg)/day	12 months	Breakthrough bleeding (38) Weight gain (23) Headache (12) Decreased libido (8)	Significant improvement of dysm, dysp, CPP, and dyschezia. Significant reduction of nodule size after 12 months of treatment. High satisfaction rate at the end of study period (69% of women were satisfied or very satisfied).
Vercellini *et al.*, 2018 [20]	Retrospective cohort study	50[c]	Continuous low-dose monophasic OC (EE 15 μg plus 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) Mood changes (4)	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 Knowles-Eccersley-Scott-Symptom Questionnaire (KESS) and the numerical rating scale.

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
Andres *et al.*, 2019 [34]	Retrospective cohort study	238	Oral progestogens, OCs, medroxyprogesterone acetate IM depot injection, LNG-IUD, GnRH analogues	6 months	Complications in the clinical group: intestinal partial obstruction requiring urgent surgery (0.6).	After 6 months, 60% patients reported improvement in pain symptoms, while 39.9% were referred for surgical treatment due to worsening or persistence of pain symptoms (28.6%), growth of endometriosis lesions (10.9%) or symptoms of bowel su-occlusion (0.4%). Significant reduction of dysm, dysp, CPP, dysuria and dyschezia in both medical and surgical treatment alike. Greater reduction in dyschezia and CPP in the medical group. Greater reduction of dyspareunia in the surgical group. Higher major

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
						complications rates in the surgical group.
Egekvist *et al.*, 2019 [29]	Prospective study	80	OCs, oral progestogens, LNG-IUD, GnRH analogues with oestrogen-progestogen add-back	12 months	NR	Significant improvement of dysmenorrhea. No significant improvement in CPP and dyschezia. Quality of life scores (SF-36 and EHP-30) were comparable to normative data for Danish women of similar age and did not change with time. No significant changes in volume of endometriotic nodules. No association between change in size of the rectosigmoid nodule and change in symptoms.
Netter *et al.,* 2019 [32]	Retrospective	43	Continuous OCs, oral progestogens and GnRH analogues	38.3 months (mean)	NR	About 60.5% of patients demonstrated stability of their colorectal lesions between the two

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug (comparator)**	**Treatment period**	**Adverse effects (%)**	**Outcome**
			(VS no amenorrhoea or pregnancy)			MRIs, 27.9% of patients ha a progression of lesions and 11.6% had a regression of lesions. Median duration of amenorrhoea was significantly lower in women with progression of lesions. Progression of rectosigmoid nodules was observed in 34% of patients without continuous amenorrhoea, in 39% who had never had amenorrhoea and in no patients with continuous amenorrhoea.
Barra *et al.,* 2020 [33]	Retrospective	83	DNG 2mg/die	6 - 36 months	Weight gain (30) Abnormal uterine bleeding (27) Headache (21) Depression (10)	Significant improvement of pain (dysm, dysp, CPP, dysuria and dyschezia) and intestinal symptoms. Progressive increase of the Endometriosis Health Profile-30

Source	Study design	Patients enrolled (*n*)	Study drug (comparator)	Treatment period	Adverse effects (%)	Outcome
					Decreased libido (4) Acne (2)	(EHP-30) and Gastrointestinal Quality of Life Index (GIQLI) scores was observed in the first two years of therapy. Significant reduction of endometriotic nodules volume.

[a] Egekvist *et al*. [29] was not included because the exact number of patients who used different medical treatments (oral oestrogen-progestogens, progestogens, or LNG-IUD), the adverse effects associated with their use, and the precise pain symptoms or gastrointestinal symptoms variation could not be extracted from the published report.
[b] In case of breakthrough bleeding the daily oral dose of NETA was doubled.
[c] Only 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; GnRH = gonadotropin-releasing hormone; IBS-D = diarrhoea-predominant irritable bowel syndrome; IM = intramuscular; IUD = intrauterine device; LNG = levonorgestrel; MRI = magnetic resonance imaging; NETA = nor-ethisterone acetate; NA = not applicable; NR = not reported; OC = oral contraceptive; SF-36 = Short Form 36.