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**Surgery versus hormonal therapy for deep endometriosis: is it a choice of the physician?**

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**Abstract**

Deep endometriosis, occurring approximately in 1% of women of reproductive age, represents the most severe form of endometriosis. It causes severe pain in the vast majority of affected women and it can affect the bowel and the urinary tract. Hormonal treatment of deep endometriosis with progestins, such as norethindrone acetate or dienogest, or estroprogestins is effective in relieving pain in more than 90% of women at one year follow up. Progestins and estroprogestins can be safely administered in the long-term, may be not expensive and are usually well tolerated. Therefore, they should represent the first-line treatment of deep endometriosis associated pain in women not seeking natural conception. However, hormonal treatment is ineffective or not tolerated in about 30% of women, the most common side effects being erratic bleeding, weight gain, decreased libido and headache. Surgical excision of deep endometriosis is mandatory in presence of symptomatic bowel stenosis, ureteral stenosis with secondary hydronephrosis, and when hormonal treatments fail. Surgical treatment is similarly effective as compared to hormonal treatment in relieving dysmenorrhea, dyspareunia and dyschezia at one year follow up in more than 90% of women with deep endometriosis. Surgical removal of the nodules may require resection of the bowel, ureter or bladder, with possible severe complications such as rectovaginal or ureterovaginal fistula and anastomotic leakage. A thorough counsel with the patient is necessary in order to pursue a therapeutic plan centered not on the endometriotic lesions, but on the patient's symptoms, priorities and expectations.

Keywords: deep endometriosis, pelvic pain, hormonal treatment, laparoscopic surgery

## Introduction

The endometriotic disease is differentiated in three different forms: ovarian cysts, superficial peritoneal lesions and deep infiltrating lesions. Deep infiltrating endometriosis, occurring approximately in 1% of women of reproductive age (1), represents the most severe form of the disease. Deep endometriotic lesions may involve the posterior compartment, affecting the uterosacral ligaments, the Douglas pouch, the anterior rectal wall and the posterior vaginal wall, with estimated prevalence of bowel involvement between 7% and 19% (2). Alternatively, or in concomitance with lesions of the posterior compartment, deep endometriosis may affect the ureter and the bladder. According to recent findings, the involvement of the urinary tract in women with deep endometriosis may be as high as 19% (3) or even 53% (4).

Deep infiltrating endometriosis is associated with severe pain in more than 95% of women (5).

Typically, women experience pain in the form of dysmenorrhea, deep dyspareunia or nonmenstrual pelvic pain. Symptoms and signs of infiltrative bowel lesions include severe constipation, dyschezia, menstrual diarrhea, menstrual hematochezia, and pain radiation to the perineum (6).

Bladder endometriosis is usually associated with catamenial mictalgia, frequency, urgency, or vesical tenesmus. Although women with ureteral endometriosis may present with colicky flank pain or gross hematuria, as many of 50% of them may be asymptomatic. Ureteral endometriosis represents therefore the most insidious form of the disease, because it may cause silent loss of renal function (5).

Treatment of deep endometriosis can be either surgical, aiming at restoring the normal anatomy by removing endometriotic lesions, or hormonal, aiming at inducing a hypo-estrogenic state, atrophy or quiescence of endometriotic lesions, and a reduction of the chronic peritoneal inflammatory status. In the present paper, we will describe the factors influencing the choice between a surgical or a hormonal treatment for deep endometriosis.

**Clinical assessment: anatomical characteristics of the disease**

Deep endometriosis has a typical multi-focal presentation (7). As a first diagnostic step, it is important to rely on a thorough physical examination. Performing a detailed exam allows the physician to map out the disease location and often assess severity and infiltrative status. In addition, in order to plan an appropriate surgical or medical treatment of this condition, ultrasonography and MRI are useful tools for assessing the number, size and anatomical localization of the endometriotic nodules (5,8). Although MRI is more accurate than transvaginal ultrasonography for lesions located on the upper level of the sigmoid, the two techniques are equally accurate for pelvic disease (9). Transvaginal and transrectal ultrasonography have the advantages over MRI of being less expensive, more easily repeatable and allowing pushing pelvic organs with the probe for the evaluation of mobility and elicited pain (10,11). Although the gold standard of diagnosing endometriosis, whether it be deep or superficial, remains surgical evaluation at laparoscopy, the preoperative mapping of endometriotic lesions provides the surgeon many important informations for each specific location of deep endometriosis.

*Bowel endometriosis.* Transrectal sonography can identify the normal rectal wall layers and detect rectal endometriosis as endometriotic infiltration of the muscularis layer; however, it is less accurate in assessing the involvement of the submucosal and mucosal layer (12, 13). Transrectal sonography can diagnose low rectal nodules as those below the level of the insertion of the uterosacral ligaments on the uterine cervix and can assess the lowest limit of the rectal nodule also by measuring its distance from the anus (14). This is important because low rectal nodules are associated with a higher rate of surgical complications as compared to upper rectal and sigmoid nodules. Colonoscopy is another useful tool for assessing the level of a rectal nodule by measuring the distance from the dentate line; moreover colonoscopy allows obtaining tissue biopsies for histologic diagnosis of endometriosis and for the assessment of the depth of rectal wall involvement. A double-contrast enema is particularly useful for the evaluation of the degree and length of bowel occlusion in case of lesions higher than the rectum, i.e. endometriotic nodules of

the high rectosigmoid or sigmoid colon (5). Computerized tomography colonography (CTC), or otherwise virtual colonoscopy represents a new modality for imaging endometriosis of the bowel. In a recent study comparing CTC with rectal-water contrast transvaginal ultrasonography (RWC-TVUS), the two techniques showed a similar accuracy of 90% and 94%, respectively, in the diagnosis of rectosigmoid endometriosis and similar precision in estimating the size of the nodules. CTC was more precise than RWC-TVUS in estimating the distance between the nodules and the anal verge (15).

*Ureteral endometriosis.* At transvaginal ultrasound, the ureteral course can be directly evaluated for possible endometriotic infiltration from the renal pelvis down to the anterior parametrium. The ultrasonographic evaluation of possible ureteral involvement is particularly important in presence of deep nodules of the posterior compartment greater than 3cm or deep nodules extending laterally in the parametrium, because these nodules are more likely to affect the ureter and to cause urinary retention after surgery (5, 16). When ureteral involvement is suspected, hydronephrosis must be ruled out by means of renal ultrasound. In presence of ureteral stenosis associated with hydronephrosis, a preoperative ureteral stent is required, when feasible, and the surgical procedure is planned accordingly with the intraoperative availability of an expert urologist (17).

*Bladder endometriosis.* The accuracy of transvaginal ultrasound with a partially replete bladder for the detection of bladder endometriosis has been reported as high as 97% (9). When an endometriotic nodule of the bladder is suspected, a cystoscopy is performed in order to rule out a transitional epithelium carcinoma and to measure the distance between the endometriotic lesion and the ureteral meatus. The removal of nodules affecting or being closer than 2 cm to the ureteral meatus is more difficult, is associated with a higher rate of complications, and may require ureteroneocystostomy.

### **Surgical treatment: outcome and complications**

The outcome and complications of surgical treatment for deep endometriosis are difficult to assess, because they are influenced by numerous variables including severity of the disease, number and

location of endometriotic nodules, degree of infiltration of the bowel or the urinary tract and overall experience of the surgical team.

*Bowel endometriosis.* The techniques for removing an endometriotic nodule from the rectum or rectosigmoid include the shaving of the nodule, i.e. without entering the bowel mucosa, the discoid resection or the segmental resection. The choice of the surgical procedure must be tailored basing on the anatomical extension of the disease and the patient symptoms, avoiding unnecessary procedures. It has been suggested that women with a bowel occlusion of >50% or longer than 2–3 cm should be scheduled for elective bowel resection, whereas all other women should undergo excision of the nodule (5). It is important to bear in mind that the lower the level of bowel resection, the more difficult is to obtain a tension-free, well vascularized anastomosis. Therefore, low and ultra-low rectal resection, with a distance from the anal verge of  $\leq 6$  cm or  $\leq 4$  cm respectively, are associated with a higher risk of complications. Overall, a protective colostomy is required in 10%–14% of women undergoing bowel surgery for deep endometriotic lesions (14).

According to a systematic review evaluating 34 articles describing 1889 procedures, segmental bowel resection is effective in reducing dismenorrhea, dyspareunia and dyschezia at one year follow up in more than 90% of women. Pain relief after surgery was consistent with 71.4–93.6% of women being pain free after 1 year of follow-up (table 1). In this series, treatment of deep endometriosis with bowel resection was associated with a 22% overall risk of complications, with an incidence of major complications of 11%, including anastomotic leakage, rectovaginal fistula and severe bowel obstruction (Table 2). A repeat procedure within 5 years from primary surgery because of recurrence of pain was reported in about one in five women (19%) who underwent bowel resection (18). In comparison, in a series of 500 patients who underwent removal of a rectovaginal nodule by the shaving technique in a single institution, a lower rate of complications was reported: rectal perforation in 1.4%, immediately repaired without sequelae in all cases; ureteral injury in 0.8%; transient urinary retention in 0.8%; and blood loss > 300 ml in 0.2% (19).

*Ureteral endometriosis.* Ureterolysis is adequate for treating ureteral endometriosis in many patients (17); however, a ureteral resection is necessary in case of hydroureteronephrosis with intrinsic localization of the disease (20). According to a review evaluating 243 women surgically treated for ureteral endometriosis by means of ureterolysis (176 women), ureteral anastomosis (28 women) and ureteroneocystostomy (39 women), the overall rate of major complications was 9%, including ureteral or uretero-vaginal fistula and stenosis persistence/recurrence (table 2) (21).

*Bladder endometriosis.* Segmental bladder resection represents the standard treatment for vesical endometriosis. In a series of 69 patients (21 with partial cystectomy, 24 with nodule resection without bladder invasion and 24 with bladder nodule coagulation and ablation) 92.7 % of the women were asymptomatic or reported improvement in symptoms at a median follow up of 60 months, and no intraoperative complications were noted (22).

### **Hormonal treatment: rationale and available drugs**

In the last decade, the substantial progress of diagnostic imaging has allowed a reliable noninvasive diagnosis of deep endometriosis, i.e. without the need for surgical and histological confirmation, thus opening the possibility to shift first-line treatment of endometriosis from surgery to medical therapy. Hypo-estrogenizing drugs induce atrophy of the ectopic endometrium and possibly allow control of pain symptoms by reducing the intra- and peri-lesional inflammation of endometriotic nodules, with diminished production of prostaglandins and cytokines and thus less stimulation of pain fibers. However, since the discontinuation of hormonal medications for endometriosis is associated with the recovery of endometrial function under the influence of ovarian steroids and thus with the recurrence of pain symptoms, such medications need to be administered for long periods (23). Therefore, provided that the efficacy in the control of pain is comparable between all the available hormonal compounds (24, 25), the choice of treatment is primarily based on safety in the long-term, side effects and costs. Basing upon such principles, progestogens and estroprogestins represent the first choice for the medical treatment of endometriosis (26, 27). A detailed description



of second-line medications for rectovaginal endometriosis (including GnRH-a plus add back therapy, vaginal danazol and aromatase inhibitors) is beyond the scopes of the present paper. A recent paper has reviewed the available evidence on this topic (2).

### **Progestins and estroprogestins: efficacy and side effects**

Norethindrone acetate (NETA) and dienogest are the progestins that have been more extensively evaluated for the treatment of endometriosis. Both of them are 19-nortestosterone derivative progestins and the pharmacological differences between the two compounds are limited: NETA has “strongly effective” progestogenic activity and androgenic activity, whereas dienogest has “effective” progestogenic activity and antiandrogenic activity (28, 29).

The only randomized controlled trial available, evaluating the medical treatment of rectovaginal endometriosis, has compared oral NETA 2.5 mg daily with an oral contraceptive pill containing ethinyl estradiol 0.01 mg and cyproterone 3 mg (30). In the NETA group, women who were free of symptom at 12-month follow up ranged between 74% for dyspareunia and 92% for dysmenorrhea (table 3). Comparable results were observed in the estrogen-progestin combination group.

Another study showed that after 12 month of treatment with NETA, 40 women with rectosigmoid endometriosis, who were still symptomatic following non-radical surgery, experienced significant improvements in diarrhea, intestinal cramping, passage of mucus with stool, and cyclic rectal bleeding (31).

In 2014, a 24-week open-label prospective study suggested that treatment with dienogest might improve pain symptoms in women with rectovaginal endometriosis who had pain persistence after 6-months of NETA therapy (32).

A recent study has shown that dienogest is as effective as NETA in improving pain symptoms in women with rectovaginal endometriosis. Because the two molecules are similar and because all hormonal therapies for endometriosis have proven effective without significant differences among different drugs (24, 25), this outcome was expected. However, this study has thoroughly evaluated

the tolerability of the two drugs. No major adverse events were recorded. Side effects were experienced by 55% of women in the NETA group and 41% of women in the dienogest group, the most frequent being weight gain, spotting and decreased libido (Table 4). Overall tolerability was significantly better in women using dienogest than in those using norethindrone acetate. However, the overall effectiveness was higher with NETA, owing to limited compliance with dienogest therapy resulting from the high cost of this drug (33).

Other studies have demonstrated that women with rectovaginal endometriosis- associated pain benefit from treatment with non-oral contraceptives such as the contraceptive vaginal ring and the contraceptive patch (34), a desogestrel-only pill (35) and the levonorgestrel-releasing intrauterine device (36). Continuous combined oral contraceptives (37) and dienogest (38) proved effective in improving urinary symptoms associated with bladder endometriosis.

### **Counselling the patient: surgical or medical treatment?**

Available data suggest that surgical excision and medical treatment are similarly effective in improving pain symptoms associated with deep endometriosis. Accordingly, a study that have formally compared surgery with daily administration of NETA 2.5 mg, found no significant between-group difference in the severity of dyspareunia at 12-month follow up in women with rectovaginal endometriosis (39). Women in the surgery group experienced a marked and rapid short-term relief followed by partial recurrence of pain, whereas women in the NETA group reported a gradual and progressive improvement of dyspareunia throughout the study period. Progestogens or estroprogestins are effective in relieving deep endometriosis related pain and their long-term administration is safe (40) and may not be expensive. Basing upon current knowledge, these hormones represent the first-line medical treatment for deep endometriosis related pain. Although untoward effects are common, occurring in more than 50 % of women, they are usually

well tolerated by the majority of women (33). Moreover, when side effects are poorly tolerated, it is possible to switch to a different available formulation that may be accepted.

Surgical excision of deep endometriotic nodules is necessary when they cause bowel stenosis associated with subocclusive symptoms or ureteral stenosis causing hydronefrosis. In addition, surgery is necessary in the approximately one woman out of three in whom hormonal treatments fail (39). The reasons for hormonal treatment failure include: ineffectiveness in relieving pain; the onset of unbearable side effects, more frequently represented by erratic bleeding, weight gain, decreased libido and headache; the presence of contraindications to hormonal treatment such as hypertension, migraine with aura, previous venous thrombosis or depression (40); the woman refusing to take chronic medications.

Eventually, in the vast majority of cases, the choice of surgical versus medical treatment of deep endometriosis must be shared between the physician and the woman, after she has been adequately informed of the risks and benefits associated with both options. Each individual woman must have clear in mind that endometriotic deep lesions are benign and usually not progressive (41) and therefore, the choice of treatment should focus on her symptoms and expectations rather than the eradication of the disease. The information about the likelihood of pain relief after surgery or medical therapy should be as detailed as possible and the rates of both international and institutional surgical complications should be provided (42).

Finally, the desire of pregnancy and the woman's age are two important variables influencing the therapeutic plan. In women seeking pregnancy, IVF should be considered because currently available hormonal treatments are all contraceptive. In case of repeated IVF failures, surgery is indicated (43). However, it has been pointed out that medical therapy may play a role also in women seeking pregnancy. In fact, a prolonged medical therapy that is temporarily discontinued to allow IVF attempts may be associated with an acceptable quality of life and it may even increase the IVF-associated pregnancy rate (44-46). As for the role of age, a more radical treatment seems to be justified in younger patients for the possible more aggressive nature of the disease and the higher

recurrence rates (47), whereas a more conservative management may be pursued among women approaching the menopause (43).

### **Conclusions**

Symptomatic deep endometriosis is a complex clinical condition, usually associated with chronic pelvic pain, which can adversely affect women's quality of life, sexual satisfaction and the possibility to conceive. In addition, deep endometriotic lesions can undermine the anatomical and functional integrity of vital organs such as bowel, ureter and bladder. The treatment of this condition may require chronic hormonal medications, complex surgical procedures, assisted reproduction techniques and psychological support. The role of the physician is to guide the woman across all therapeutic possibility in order to resolve or minimize the impact of the disease and possibly helping her to fulfil her expectations.

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**Table 1. Women free of symptoms after segmental bowel resection for deep endometriosis evaluated at 1-year postoperative follow-up** (modified from reference 18).

Type of pain	Women free of symptoms
	n (%)
Overall pain (n=135)	111 (82)
Dysmenorrhoea (n=82)	45 (55)
Deep dyspareunia (n=100)	62 (62)
Chronic pain (n=16)	5 (31)
Dyschezia (n=41)	19 (46)

48.

**Table 2. Complication rates for surgical excision of deep endometriosis of the bowel and the ureter.**

<i>Major complications of bowel surgery (n=1717) *</i>	
Anastomotic leakage	1.9%
Rectovaginal fistula	1.8%;
Severe bowel obstruction	2.7%,
Haemorrhage	2.5%
Infections	1%
Other major complications	1.1%
Total	11%
<i>Minor complications of bowel surgery (n=1717) *</i>	
Bladder dysfunction	8.1%
Temporary bowel dysfunction	3.6%
Total	11.7%
<i>Major complications of ureteral surgery (n=243) **</i>	
Ureteral or uretero-vaginal fistula	1.6%
hemoperitoneum	0.4%
Stenosis persistence/recurrence requiring reoperation	7.4%
Total	9.4%

\*Data from reference 18

\*\* Data from reference 21

**Table 3. Women free of symptom after treatment with norethindrone acetate 2.5 mg /die for deep endometriosis evaluated at 1-year follow-up (modified from reference 30).**

<b>Type of pain</b>	<b>Women free of symptoms</b>
Dysmenorrhoea	37/40 (92%)
Deep dyspareunia	30/40 (74%)
Nonmenstrual pain	32/40 (80%)
Dyschezia	34/40 (85%)

49.

**Table 4. Side effects reported during the first 6 months of treatment with norethindrone acetate or dienogest (modified from reference 33).**

Side effects	Dienogest (n = 85)	NETA (n = 89)	P value
<i>Absence of side effects</i>	<b>50 (59)</b>	<b>40 (45)</b>	
<i>Type of side effect</i>			
Weight gain a	14 (16)	28 (31)	.02
Spotting	11 (13)	20 (22)	.07
Decreased libido	8 (9)	13 (14)	.35
Vaginal dryness	6 (7)	12 (13)	.21
Mood disorders	2 (2)	7 (8)	.16
Breast tenderness	1 (1)	7 (8)	.06
Bloating or swelling	5 (6)	4 (5)	.74
Acne	0 (0)	4 (4)	.12
Headache	3 (3)	3 (3)	1.00
Alopecia	4 (5)	1 (1)	.20
Breakthrough bleeding	1 (1)	1 (1)	1.00
Nausea	1 (1)	0 (0)	1.00
Total			.07

**Note: Some women reported more than one side effect. Values are number (percentage).**

**NETA = norethindrone acetate;**