SUPPLEMENTAL FIGURE 2
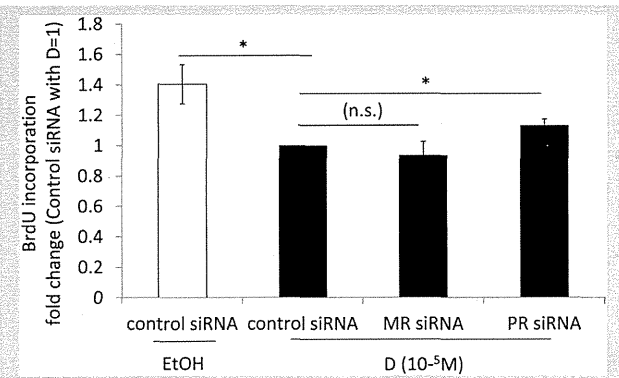

The effect of silencing of mineralocorticoid receptor (MR) or P receptor (PR) on the drospirenone-reduced DNA synthesis in EcSC. EcSC were transfected with negative control siRNA, MR siRNA, or PR siRNA for 7 hours. After the transfection, EcSC were treated with drospirenone (10^{-5} mol/L) for 24 hours. Values are the mean ($\pm$SEM) of the aggregated data from three independent experiments using different EcSC preparations. *$P<.05$ versus EcSC transfected with negative control siRNA and treated with drospirenone.

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Prevention of the recurrence of symptom and lesions after conservative surgery for endometriosis

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Although surgical excision of endometriosis both improves pain and enhances fertility, recurrence can further exacerbate pain and reduce fertility, which in turn impacts the quality of life and increases personal as well as social costs. Therefore, it is crucial to prevent the recurrence of symptoms and lesions after conservative surgery. This article reviews evidence regarding the prevention of postoperative recurrence of endometriosis reported since the 1990s. Over the past 5 years, many new studies have been conducted and have demonstrated that long-term postoperative medication markedly reduces the recurrence. Most of these studies used oral contraceptives (OC), with either the cyclic or continuous regimen, while some used oral or intrauterine progestin. Continuous OC is more efficacious than cyclic OC, especially for dysmenorrhea. The levonorgestrel-releasing intrauterine system is also shown to prevent recurrence of dysmenorrhea and possibly endometriosis lesions. Dienogest, a new progestin, is shown to reduce the recurrence of endometrioma. Similar to the case of ovarian endometriosis, long-term postoperative medication after conservative surgery for deep infiltrating or extragenital endometriosis seems important, although data are limited. Regardless of the lesion and the medication type, patients who discontinued medication experienced a higher incidence of recurrence, indicating that the protective effect of these medications seems to vanish rapidly after the discontinuation. On the basis of these facts, together with the pathogenesis of recurrence (retrograde menstruation and ovulation), regular and prolonged medication until the patient wishes to conceive is highly recommended to prevent the postoperative recurrence of endometriosis. (Fertil Steril® 2015;104:793–801. ©2015 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, recurrence, prevention, oral contraceptives, progestin

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S urgery is frequently selected for the treatment of endometriosis since medical treatment alone is often inadequate. Surgical excision of lesions (conservative surgery) has been shown to both improve pain and enhance fertility (1), and conservative surgery is preferred over radical surgery because most women with endometriosis are of reproductive age. Until the

early 1990s, it was believed that the nature of endometriosis was "static" and that postoperative recurrence was relatively rare (2). However, a recent systematic review of the literature estimated the recurrence rate of endometriosis to be 21.5% at 2 years and 40%–50% at 5 years (3), which is much more frequent than previously believed. Although surgical excision

of endometriosis both improves pain and enhances fertility, recurrence and repeated surgery can further exacerbate pain and reduce fertility (4), which in turn impacts quality of life and increases personal as well as social costs. Therefore, it is crucial to prevent the recurrence of symptoms and lesions after conservative surgery to maintain the improvement in pain and enhancement in fertility for as long as possible (5–8).

The purpose of this article is to review the evidence regarding the prevention of postoperative recurrence of endometriosis reported since the 1990s. We conducted a search of the MEDLINE database (http://www.nlm.nih.gov/medlineplus/) using

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combinations of the following key words: "endometriosis," "endometrioma," "endometrial cyst," "recurrence," and "prevention." The search was limited to peer-reviewed, full-text articles in the English language published between January 1990 and July 2015. Randomized controlled trials (RCTs) with prospective and retrospective cohorts investigating the efficacy of postoperative medications prescribed for more than 6 months are described in the tables, although studies with shorter medication periods are discussed in the text. A manual search of review articles and cross-references completed the search.

Pathogenesis of Recurrences

There are two possible pathogeneses leading to the recurrence of endometrial lesions: regrowth of residual lesions and de novo lesion formation. Vignali et al. (9) found that the recurrence of deep endometriosis observed in a second operation often occurred in the same area of the pelvis that was involved in the first operation. With regard to endometrioma, the majority of recurrent cases (88.7%) involved the formerly treated ovary (3). It is also possible that regrowth can occur from a satellite lesion in areas with multiple endometriotic foci that are independent of the primary lesion (10). Surgery, especially conservative, is sometimes insufficient to completely remove these lesions; therefore, lesions frequently redevelop postoperatively.

Other studies suggested that recurrence may originate from de novo endometriosis lesions through retrograde menstruation (3). Bulletti et al. (11) reported that laparoscopy plus ablation of the endometrium effectively eliminated recurrence. This finding supports a role of eutopic endometrium in recurrence, although this evidence is challenged by the case of endometriosis recurrence after hysterectomy (12). In this context, it is interesting to introduce the notion that not only the retrograde endometrium but also ovulation may cause endometriosis, which is supported by the observation that ovarian endometrioma develops from a growing follicle (13) or the corpus luteum (14).

In comparison with endometriosis lesions, the pathogenesis of the recurrence of endometriosis-associated symptoms seems more complicated. A correlation has been demonstrated between the lesion site and pain (15); for instance, deep dyspareunia is associated with a deep lesion infiltrating the uterosacral and cardinal ligaments, the pouch of Douglas, the posterior vaginal fornix, or the anterior rectal wall (16). However, the recurrence of pain does not necessarily mean that a lesion recurred at that site.

Prevention of Symptom Recurrence

Regarding the recurrence of symptoms, studies conducted to evaluate the effect of postoperative medications on endometriosis-associated symptoms (i.e., dysmenorrhea, chronic pelvic pain, and dyspareunia) found that short-term therapy of 6 months of oral contraceptives (OCs) did not reduce the incidence of pain recurrence (9.1% vs. 17.1% for control at the 22-month follow-up) (17), suggesting that women experienced recurrence after OC cessa-tion. An RCT comparing the efficacy between two OC regimens (cyclic and continuous administration) found no difference in the recurrence of pain (32% vs. 17%; $P=.23$) (18). However, the time frame (6 months) of this study was possibly too short to discern a difference, if any.

In contrast to short-term medical treatment, long-term (>6 months) administration of postoperative medications seems to prevent recurrence of symptoms (Table 1).

Dysmenorrhea, the most frequent symptom associated with endometriosis, can be successfully controlled by postoperative OCs (19–21) when used for >24 months, as demonstrated by the rate of lesion recurrence, which will be discussed later. Vercellini et al. (22) demonstrated that continuous use of monophasic OCs can control endometriosis-associated recurrent dysmenorrhea that does not respond to cyclic OC use (the mean visual analogue scale [VAS] score was 75 at baseline and 31 at the 2-year follow-up; $P<.01$). An RCT that compared the efficacy of 24-month cyclic OC, continuous OC, and surgery alone demonstrated that the frequency of recurrent dysmenorrhea was significantly lower in the cyclic (31%) or continuous (4%) OC group than in the surgery alone group (40%) and that the benefits of OC appeared earlier in the continuous group than in the cyclic group (6 vs. 18 months) (19). A similar trend for a preferable outcome in continuous OC users was also observed in a recent cohort study (9.4% vs. 20.9% for cyclic group; $P<.05$) (20). It is possible that the capacity of continuous OC to prevent or reduce the recurrence of dysmenorrhea could be due to inhibition of menses per se rather than to actual interference with pain mechanisms (23). It is also interesting to note that the benefit of continuous OC over cyclic OC regarding the prevention of lesion recurrence seems not as obvious as the prevention of symptom recurrence (24), suggesting that the effect of continuous OC in reducing symptom recurrence may not necessarily be a consequence of the effect on lesion recurrence.

In addition to OC, the levonorgestrel-releasing intrauterine system (LNG-IUS) reduces the recurrence of postoperative dysmenorrhea (25–27). A pilot cohort study confirmed that the use of LNG-IUS postoperatively prevented recurrence of moderate-to-severe dysmenorrhea compared with the surgery-only group (10% vs. 45%) (25). The effectiveness of postoperative LNG-IUS for relieving pain was also demonstrated in a double-blind RCT, which found that at 12 months, women in the LNG-IUS group achieved a greater reduction in dysmenorrhea than controls (reduction in dysmenorrhea VAS of -81.0 vs. -50.0 mm; $P<.001$) (27). On the other hand, two cohort studies compared the efficacy of LNG-IUS with that of other medications. Morelli et al. (21) revealed that in comparison with LNG-IUS use, OC use was markedly more effective in reducing the extent of pelvic pain (VAS of 29.0 vs. 19.1 mm; $P<.05$) and also disease recurrence (but not significantly), although patient satisfaction was markedly greater in the LNG-IUS group. Wong et al. (26) demonstrated that both LNG-IUS and depot medroxyprogesterone acetate (MPA) administered for 3 years after laparoscopy can inhibit dysmenorrhea and chronic pelvic pain recurrence, but LNG-IUS showed slightly higher pain reduction and better compliance.

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TABLE 1

List of studies that reported the efficacy of postoperative medications administrated for more than 6 months on pain recurrence.

Author	Reference	Year	Study design	Interventions	No. of patients	Follow-up period, mo	Outcome measured	Methods of measurement	Definition of recurrence	Results (recurrence rate)	P value
Vercellini et al.	22	2003	Cohort	Continuous OC	50	24	Dysmenorrhea	VAS, VRS	Not specified	mean VAS 75→31, mean VRS 2.4→0.7	NS
Vercellini et al.	25	2003	RCT	LNG-IUS/EM	20/20	12	(a) Dysmenorrhea	VAS	VAS ≥ 51	LNG-IUS (10%)/EM (45%)	<.05
				LNG-IUS/EM	5/7	12	(b) Chronic pelvic pain	VAS	Not specified	Median VAS reduction 17/10	NS
				LNG-IUS/EM	9/8	12	(c) Dyspareunia	VAS	Not specified	Median VAS reduction 31/15	NS
Seracchioli et al.	19	2010	RCT	Cyclic OC/ continuous OC/EM	92/95/87	24	(a) Dysmenorrhea	VAS	VAS ≥ 40	Cyclic OC (31%)/ continuous OC (4%)/EM (40%)	<.001
				Cyclic OC/ continuous OC/EM	92/95/87	24	(b) Chronic pelvic pain	VAS	VAS ≥ 40	Cyclic OC (29%)/ continuous OC (27%)/EM (40%)	NS
				Cyclic OC/ continuous OC/EM	92/95/87	24	(c) Dyspareunia	VAS	VAS ≥ 40	Cyclic OC (35%)/ continuous OC (29%)/EM (35%)	NS
Wong et al.	26	2010	RCT	LNG-IUS/MPA depot	15/15	36	(a) Pain score[a]	VRS	Not specified	Lower pain score with LNG-IUS only at 36M	<.05
				LNG-IUS/MPA depot	15/15	36	(b) Dyspareunia	VRS	Not specified	No significant difference	NS
				LNG-IUS/MPA depot	15/15	36	(c) Urinary/bowel symptoms	VRS	Not specified	No significant difference	NS
Tanmahasamut et al.	27	2012	RCT	LNG-IUS/EM	28/26	12	(a) Dysmenorrhea	VAS	Not specified	Lower VAS scores with LNG-IUS	<.001
				LNG-IUS/EM	28/26	12	(b) Chronic pelvic pain	VAS	Not specified	Lower VAS scores with LNG-IUS	<.05
				LNG-IUS/EM	28/26	12	(c) Dyspareunia	VAS	Not specified	LNG-IUS did not influence score	NS
Morelli et al.	21	2013	Cohort	LNG-IUS/OC	44/48	24	Pain	VAS	Not specified	LNG-IUS (VAS 29.0)/OC (VAS 19.1)	<.05
Vlahos et al.	20	2013	Cohort	Cyclic OC/ continuous OC	167/85	21/23	(a) Dysmenorrhea	Questionnaire[b]	Not specified	Cyclic OC (20.9%)/ continuous OC (9.4%)	<.05
				Cyclic OC/ continuous OC	167/85	21/23	(b) Chronic pelvic pain	Questionnaire[b]	Not specified	Cyclic OC (23.9%)/ continuous OC (9.4%)	<.01
				Cyclic OC/ continuous OC	167/85	21/23	(c) Dyspareunia	Questionnaire[b]	Not specified	Cyclic OC (17.3%)/ continuous OC (10.5%)	NS

Note: VRS = verbal rating score; EM = expectant management; NA = not available; NS = not significant.
[a] Dysmenorrhea plus chronic pelvic pain.
[b] Self-administered questionnaire (www.endometriosisfoundation.org/WERF-WHSSQuestionnaire-English.pdf).

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In contrast to dysmenorrhea, control of postoperative recurrence of chronic pelvic pain (or nonmenstrual pain, noncyclic pain) and dyspareunia remains challenging. Regarding chronic pelvic pain, the above-mentioned RCT comparing the efficacy of postoperative cyclic OC, continuous OC, and surgery alone found no differences in chronic pelvic pain recurrence between patients treated with OC and those treated with surgery alone (19). In contrast, the other above-mentioned recent cohort study found that the 2-year recurrence rate of nonmenstrual pelvic pain was lower in the continuous OC group than in the cyclic OC group (9.4% vs. 23.9%; $P<.01$) (20), although no comparison was available between OC users and nonusers in this study. The lower impact of OC administration on noncyclic pain in comparison with dysmenorrhea can be explained by the fact that dysmenorrhea is correlated with endometrial bleeding, which can be decreased or suppressed by OC use, while chronic pelvic pain is caused by different physiopathological mechanisms (23). The effect of postoperative LNG-IUS on noncyclic pain also seemed to be limited in the above-mentioned pilot cohort study (25). In contrast, the above-mentioned double-blind RCT found that LNG-IUS achieved a greater reduction in noncyclic pain than in the control group (VAS of -48.5 vs. -22.0 mm; $P<.05$) (27); however, this reduction was less than that observed in dysmenorrhea. Collectively, as observed by the use of OCs, LNG-IUS also appears to be less beneficial in reducing the extent of noncyclic pain than the prevalence of dysmenorrhea, possibly because LNG-IUS does not suppress ovulation, which may be the main cause of noncyclic pain (28).

Regarding dyspareunia, there is no evidence of a positive effect of postoperative medical treatment, as neither cyclic or continuous OC regimens reduced the prevalence of symptoms (19, 20), as was also the case with LNG-IUS (27). Furthermore, a 6-month study of placebo-controlled hormone therapy demonstrated that the placebo seemed to be more effective than hormone therapy for relief of dyspareunia (29). The authors explained that this finding might be influenced by psychological factors that are dependent on personality, marital, and psychosexual issues (29).

Prevention of Ovarian Endometriosis (Endometrioma) Recurrence

Table 2 provides a list of studies that reported the efficacy of postoperative medications prescribed for more than 6 months on endometrioma recurrence.

OCs. The initial report of postoperative OC use for 6 months versus a control group demonstrated a significant difference in recurrence of both symptoms and endometrioma development between the two groups (6.2% vs. 10.2%; $P=.041$), whereas no significant differences were detected at 24 (9.4% vs. 13.6%) or 36 months (12.1% vs. 17.4%), suggesting that the use of OCs for 6 months can delay, but not prevent, long-term recurrence (17). In contrast, all studies of postoperative OC use for 2 years or more demonstrated significant protective effects against recurrence of ovarian endometrioma (30). A study of 277 patients showed that the 36-month cumulative proportion of subjects free from endometrioma

recurrence was significantly greater than that of patients who used OC for the entire follow-up period (94% vs. 51%; $P<.001$) (30). A cohort study of 73 patients demonstrated that the recurrence rate in those who used OC for 2 years was significantly lower than that for non-OC users or for patients who discontinued OC (2.9% vs. 35.8%; $P<.001$) (31). Interestingly, recurrence is frequently observed in patients who discontinued OC. The same study reported recurrence in two of 14 (14.3%) women who discontinued OC use (31). Likewise, a cohort study with a mean follow-up period of 38 months found a significant difference in ovarian endometrioma recurrence between always OC users (OC use during the entire follow-up period) and ever OC users (OC discontinued during the follow-up period; 0% vs. 55.5%; $P<.05$) (32). In addition, women who used OC for shorter periods were at a higher risk for recurrence than those who used OC for longer periods. The 36-month cumulative proportion of subjects free from endometrioma recurrence was significantly greater among those who used OCs for 12 months or more than among those who used these agents for <12 months (78% vs. 51%; $P<.001$) (30). Collectively, these findings demonstrate that postoperative OC conveys a protective effect against recurrence of ovarian endometrioma, but the effect seems to vanish rapidly after discontinuation.

Cyclic or continuous?. An RCT of 6-month administration of OCs found similar reductions in the recurrence of lesions in both cyclic and continuous regimens (1 of 28, 3.6% vs. 0 of 29; 0.0%) (18), although this time frame may have been too short to discern any difference, as also demonstrated by symptom recurrence. Another RCT of 24-month administration of OCs revealed that the crude recurrence rate within 24 months was significantly lower in the cyclic and continuous OC groups as than in nonusers (14.7% and 8.2% vs. 29%); however, no significant differences were detected between the cyclic and continuous OC groups ($P=.21$) (24). These investigators commented that although there was no statistically significant difference, there was a positive trend in size and growth of recurrent endometrioma among patients receiving continuous therapy (24). A recent cohort study of 356 patients demonstrated a lower recurrence rate of endometrioma among women receiving continuous OC than among those receiving cyclic OC (16.6% vs. 9.2%; $P<.005$) (20). These investigators suggested that continuous OC appears to offer significant advantages over cyclic OC (33).

Type of progestin in OC: does it make a difference?. To determine whether the type of progestin used in OCs influences the protective efficacy of lesion recurrence, Cucinella et al. (34) recently compared the efficacy of three OC regimens with different progestins (i.e., desogestrel, gestodene, and dienogest) in an RCT but found no significant difference in the recurrence rate between these agents (26.5%, 31.8%, and 20.5%), although the recurrence rate in nonusers (74.7%) was significantly higher than that in all OC groups ($P<.005$).

Progestins. Dienogest is an estrane, a 19-nortestosterone derivative, with a very strong progestogenic effect in the endometrium but with anti-androgenic activity (35). A 24-week multicenter, randomized, open-label study demonstrated that dienogest was as effective as leuprolide acetate for

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TABLE 2

List of studies that reported the efficacy of postoperative medications administrated for more than 6 months on endometrioma recurrence.

Author	Reference	Year	Study design	Interventions (when no duration is indicated, the duration is not limited)	No. of patients	Follow-up period, months	Outcome measured	Methods of measurement	Definition of recurrence	Results (recurrence rate)	P value
Park et al.	40	2008	Cohort	GnRHa 6 months + OC (<24/24–48/ 48< months)	22/19/10	41 (19–94)	Endometrioma	TV US	>20 mm	OC <24 (4.5%)/24–48 (0%)/48< months (0%)	NA
Vercellini et al.	30	2008	Cohort	OC (always)/OC (ever)/EM	102/129/46	28 (median)	Endometrioma	TV US	>20 mm	OC (always) (6%)/EP (49%)	<.001
Takamura et al.	31	2009	Cohort	OC for 24 months/EM	34/39	24	Endometrioma	TV US	>20 mm	OC (2.9%)/EM (43.5%)	<.001
Lee et al.	41	2010	Cohort	GnRHa 3 or 6 months + OC/GnRHa 3 or 6 months alone	175/187	35 (12–114)	Endometrioma	TV US	>20 mm	GnRHa + OC (7.4%)/ GnRHa alone (28.9%)	<.001
Seracchioli et al.	24	2010	RCT	Cyclic OC/ continuous OC/EM	75/73/69	24	Endometrioma	TV US	>15 mm	Cyclic OC (14.7%)/ continuous OC (8.2%)/EM (29%)	<.005
Wong et al.	26	2010	RCT	LNG-IUS/MPA depot	15/15	36	Endometrioma	TV US	>30 mm	No recurrence were detected in both groups	NS
Morelli et al.	21	2013	Cohort	LNG-IUS/OC	44/48	24	Disease recurrence	CA125, TV US, pelvic exam	CA125 elevation and/or positive findings	LNG-IUS (20.5%)/OC (12.5%)	NS
Vlahos et al.	20	2013	Cohort	Cyclic OC/ continuous OC at least 6 months	167/85	21/23	Endometrioma	TV US	Not specified	Cyclic OC (16.6%)/ continuous OC (9.2%)	<.05
Cucinella et al.	34	2013	RCT	OC with desogestrel/ OC with gestodene/OC with dienogest/ EM	43/44/43/38	24	Endometrioma	TV US	Not specified	Desogestrel (26.5%)/ Gestodene (31.8%)/ Dienogest (20.5%)/ EM (74.7%)	<.005 (all OC vs. EM)
Cho et al.	39	2014	Cohort	GnRHa 3 months followed by LNG-IUS/ followed by OC	42/57	17	Endometrioma	TV US	>20 mm	LNG-IUS (4.8%)/OC (10.5%)	NS
Ouchi et al.	32	2014	Cohort	OC (always)/OC (ever)/Dienogest/ GnRHa 6 months/EM	25/9/7/16/110	38.3	Endometrioma	TV US	>20 mm	OC (always) (0%)/ OC (ever) (56%)/ Dienogest (0%)/ GnRHa (25%)/EM (23%)	<.05 (OC always vs OC ever)
Ota et al.	38	2015	Cohort	Dienogest/EM	151/417	60	Endometrioma	TV US	>20 mm	Dienogest (4%)/ EM 69%)	<.0001

Note: TV US = transvaginal ultrasonography; EM = expectant management; NA = not available; NS = not significant.

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relieving endometriosis-associated pain and was associated with a favorable safety profile and, therefore, can be considered an effective and well-tolerated treatment for endometriosis (36). Dienogest was approved for the treatment of endometriosis in October 2007 in Japan and is also currently available in the European Union and Australia (37). Ouchi et al. (33) reported no recurrence in seven patients who used postoperative dienogest over a mean follow-up period of 13.28 months. Very recently, Ota et al. (38) demonstrated that the cumulative recurrence rate at postoperative year 5 was significantly less in the 2-mg dienogest group than in the no postoperative medication group (69% vs. 4%; odds ratio = 0.09; 95% confidence interval = 0.03–0.26; $P<.0001$). The investigators suggested that although care should be taken to avoid development of metrorrhagia and decrease in bone mineral density, dienogest presents an alternative agent for a long-term postoperative management of endometriosis (38).

Wong et al. (26) demonstrated that both LNG-IUS and depot MPA administered for 3 years after laparoscopy can inhibit lesion recurrence (recurrence was not detected in any patient in either group). In this study, the authors also found that LNG-IUS was associated with better compliance (reduced vaginal bleeding) and greater safety (reduced bone mineral density loss) than MPA (26).

Two cohort studies compared the efficacy of OC to that of LNG-IUS. Morelli et al. (21) observed that OC use seemed more effective for the control of disease recurrence than LNG-IUS, but the difference was not significant (recurrence rate at 24 months, 12.5% vs. 20.5%; $P=.30$), although patient satisfaction was significantly greater in the LNG-IUS group (satisfaction rate at 24 months: 83.3% vs. 97.7%; $P<.05$). Cho et al. (39) reported that the recurrence rate during a median follow-up period of 17 months in women receiving LNG-IUS was comparable to that in women receiving OC after 3-month administration of a GnRH analogue (GnRHa; 4.8% vs. 10.5%) and concluded that postoperative use of a LNG-IUS seems to be as effective as the use of OC for the prevention of endometrioma recurrence.

Combinations of short-term GnRHa and OCs. Two studies (40, 41) compared the use of GnRHa alone and GnRHa followed by long-term OC use and found that the incidence of endometrioma recurrence was significantly lower in the OC plus GnRHa group than in the GnRHa alone group. However, the impact of initial GnRHa administration was unclear. Given the inefficiency of short-term GnRHa use and the lack of a difference between administration of GnRHa for 3 or 6 months on the recurrence rate of subsequent OC use ($P=.148$) (41), it is questionable whether GnRHa administration before long-term OC use further reduced the risk of recurrence (5, 8).

Prevention of Deep Lesion Recurrence

Risk of postoperative recurrence and its prevention have also been reported in deep infiltrating endometriosis, although data are sparse (42). According to a recent review, the recurrence rate after surgery observed in several studies varied between 5% and 25%, with most of the studies reporting 10%

when considering a follow-up period of >2 years (43). The recurrence rate appeared to be lower in the bowel resection anastomosis group than in the mixed study groups (full-thickness disc excision, bowel resection anastomosis, and shave/superficial excision; total recurrence rate and the visually and/or histologically proven recurrence rates were 5.8% and 2.5% in the bowel resection anastomosis group and 17.6% and 5.7% in the mixed study groups, respectively) (44). A prospective study of 500 women managed for deep infiltrating rectovaginal endometriosis by shave excision demonstrated a low rate of recurrence (7.8%) within a follow-up period of 2–6 years (45). In this prospective study, the rate of recurrence was very low among women who received continuous postoperative progestin (1%) and in those who had interrupted the medical treatment and rapidly conceived (2%), when compared with women who had abandoned treatment but did not become pregnant (20%); this suggests the importance of postoperative medical treatment among women who do not wish to conceive. A review article by Roman et al. (46) stated that continuous medical treatment can prevent recurrence of deep infiltrating endometriosis after surgical management and that instead of choosing either medical or surgical management, the two therapies should be combined to optimize effectiveness.

Prevention of Extragenital Lesion Recurrence

Endometriosis also involves extragenital or extrapelvic organs, such as the diaphragm, abdominal wall, umbilicus (47), sciatic nerve (48), pleura, and lungs. Although surgical removal of symptomatic disease is recommended (49) and is commonly selected for management of extragenital endometriosis (50, 51), evidence of postoperative recurrence is extremely limited and discussed generally only in case reports. In addition, most case reports did not describe a long-term prognosis of more than 6 months and postoperative medication, if administrated, consisted of short-term (approximately 6 months) GnRHa administration (52, 53). However, many cases experienced recurrence during the interval or after cessation of medical therapy (54–56), suggesting that long-term, constant, hormonal control is also important to prevent recurrence in extragenital endometriosis.

DISCUSSION
Summary of Evidence

Over the past 5 years, several studies have demonstrated that long-term postoperative medication markedly reduces the recurrence rates of endometriosis. Most of these studies used OC, with either the cyclic or continuous regimen, while some used oral or intrauterine progestin. Continuous OC is more efficacious than cyclic OC (20, 24), especially for dysmenorrhea (19), probably owing to inhibition of menses. Therefore, continuous OC is worth recommending to patients who have a higher risk of recurrence of dysmenorrhea. The LNG-IUS is also shown to prevent recurrence of dysmenorrhea (27) and possibly endometriosis lesion (26). Given the fewer side effects and greater satisfaction (21),

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LNG-IUS presents an alternative option for patients who have a contraindication for, or poor compliance with, OC use. Dienogest, a new progestin, is shown to reduce the recurrence rate of endometrioma and is another alternative agent for long-term management (32, 38), although further comparisons should be made between the efficacy and long-term safety of the use of this agent and OCs. Regardless of the medication type, patients who discontinued medication experienced recurrence at a higher rate (30–32), indicating that the protective effect of these medications seems to vanish rapidly after discontinuation. Therefore, the medication should be continued until the patient wishes to conceive. Regarding the prevention of the recurrence of chronic pelvic pain and dyspareunia, evidence is very limited and further studies are needed. Postoperative long-term medical treatment is also encouraged after conservative surgery for deep infiltrating endometriosis (45, 46). In comparison with ovarian endometriosis, evidence is very limited regarding extragenital endometriosis; however, many cases experienced recurrence during the interval or after cessation of medical therapy (54–56), suggesting that long-term, constant, hormonal control is also important to prevent recurrence in these cases of endometriosis.

A Paradigm Shift from "Short-term Treatment with Strong Drugs" to "Long-term Treatment with Drugs with Fewer Adverse Effects and Higher Compliance" is Recommended for Prevention of Recurrence

Most observational studies conducted up to the early 2000s have failed to find any evidence of the efficacy of postoperative medication for prevention of recurrence (57–60). Prospective studies using 3-month administration of GnRHa (61, 62), 6-month of danazol (63), and OC (17) have shown unsatisfactory results. Based on these studies, the online 2007 version of the European Society of Human Reproduction and Embryology (ESHRE) guidelines (http://guidelines.endometriosis.org/concise-pain.html) state that "post-operative hormonal treatment does not produce a significant reduction in pain recurrence at 12 or 24 months, and has no effect on disease recurrence."

In contrast, the studies conducted after the mid-2000s that are reviewed in this article evaluated long-term medical treatment of >6 months and selected OC or progestin, because these drugs are associated with fewer adverse effects and higher compliance and are therefore suitable for long-term use. On the basis of these results and those of a review article (8), the latest ESHRE guidelines were markedly revised in 2013, particularly the description of postoperative therapies (49), including recommendations such as, "After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe combined hormonal contraceptives for the secondary prevention of endometrioma" and "[i]n women operated on for endometriosis, clinicians are recommended to prescribe post-operative use of a LNG-IUS or a combined hormonal contraceptive for at least 18–24 months, as one of the options for these secondary prevention of endometriosis-associated

dysmenorrhea, but not for non-menstrual pelvic pain or dyspareunia."

The term "secondary prevention" used in this description seems somewhat confusing because in preventative medicine, the term "secondary prevention" is defined as methods to detect and address an existing disease before the appearance of symptoms, while methods to reduce the negative impact of symptomatic disease are termed "tertiary prevention" (64). Therefore, the prevention of postoperative recurrence should have been termed "tertiary prevention" rather than "secondary prevention."

This recommendation should be acknowledged by all gynecologists outside of Europe as well as by nongynecological physicians, including surgeons, dermatologists, and orthopedists, who may also have opportunities to treat cases of extragenital endometriosis.

Mechanism by Which Long-term, but Not Short-term, Medication Prevents Recurrence

As described above, recurrence in endometriosis is a consequence of not only regrowth of residual lesions but also of the formation of de novo lesions (3), and as retrograde endometrium and ovulation (13, 14) cause de novo lesions, recurrence may occur as long as the patient continues to menstruate. Therefore, achieving a hypoestrogenic or hyperprogestogenic hormonal state using short-term GnRHa or progestin is ineffective because the menstrual cycles recover after the cessation of medication. Instead, medication that stops ovulation (i.e., OCs and systemic progestin), reduces menstrual bleeding (i.e., LNG-IUS and OCs), or stops menstruation (i.e., systemic progestin), which is associated with fewer adverse effects and higher compliance, can prevent recurrence if used over a long term.

Suggestions on Future Studies

Despite recent progress, additional comparisons should be made between the efficacy and long-term safety of the use of OCs and progestins and among the same drug types. Until what age should long-term management be recommended should also be determined. Moreover, although the use of postoperative medications was found to be effective to reduce the risk of recurrence, it is questionable whether such medications are beneficial to all patients. Therefore, further studies are necessary to develop novel markers to identify patients at high risk of recurrence who will truly benefit from such medications. A comprehensive survey is needed for cases with deep lesions and extragenital endometriosis to clarify whether the nature of endometriosis varies according to the organ involved. Efforts to improve current knowledge of endometriosis among nongynecological physicians, such as surgeons, dermatologists, and orthopedists, who may have opportunities to treat cases of extragenital disease, should be made. Furthermore, now that minimally invasive surgery combined with medical treatment is preferred over radical surgery, it would be of interest to compare surgery plus medical treatment versus medical treatment alone. With regard to medications, all of the present options for the prevention or

treatment of endometriosis recurrence inhibit ovulation; therefore, these agents cannot be prescribed to patients who currently wish to conceive. Hence, great efforts should be made to develop novel drugs that do not affect ovulation. Finally, although long-term use of OCs has been shown to provide protection against ovarian cancer among women with endometriosis (65), whether or not preventing recurrence after conservative surgery can prevent the development of endometriosis-associated cancer remains unknown, thus ultra-long-term follow-up studies are warranted.

Conclusion

In summary, regular and prolonged medications should be recommended after conservative surgery to prevent recurrence of endometriosis symptoms and lesions. Medications should be used until the patient wishes to conceive. As stated in the American Society for Reproductive Medicine committee opinion, endometriosis should be viewed as a chronic disease that requires lifelong management (66). Hence, short-sighted, temporary solutions should be avoided and lifelong management aimed to prevent recurrence should be emphasized.

REFERENCES

1. Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C, Garry R, et al. Laparoscopic surgery for endometriosis. Cochrane Database Syst Rev 2014: CD011031.
2. Redwine DB. Conservative laparoscopic excision of endometriosis by sharp dissection: life table analysis of reoperation and persistent or recurrent disease. Fertil Steril 1991;56:628–34.
3. Guo SW. Recurrence of endometriosis and its control. Hum Reprod Update 2009;15:441–61.
4. Vercellini P, Somigliana E, Vigano P, De Matteis S, Barbara G, Fedele L. The effect of second-line surgery on reproductive performance of women with recurrent endometriosis: a systematic review. Acta Obstet Gynecol Scand 2009;88:1074–82.
5. Koga K, Osuga Y, Takemura Y, Takamura M, Taketani Y. Recurrence of endometrioma after laparoscopic excision and its prevention by medical management. Front Biosci (Elite Ed) 2013;5:676–83.
6. Somigliana E, Vercellini P, Vigano P, Benaglia L, Busnelli A, Fedele L. Postoperative medical therapy after surgical treatment of endometriosis: from adjuvant therapy to tertiary prevention. J Minim Invasive Gynecol 2014;21: 328–34.
7. Vercellini P, Matteis DE, Somigliana E, Buggio L, Frattaruolo MP, Fedele L. Long-term adjuvant therapy for the prevention of postoperative endometrioma recurrence: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2013;92:8–16.
8. Vercellini P, Somigliana E, Vigano P, De Matteis S, Barbara G, Fedele L. Postoperative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiological and clinical evidence. Reprod Biomed Online 2010;21:259–65.
9. Vignali M, Bianchi S, Candiani M, Spadaccini G, Oggioni G, Busacca M. Surgical treatment of deep endometriosis and risk of recurrence. J Minim Invasive Gynecol 2005;12:508–13.
10. Jinushi M, Arakawa A, Matsumoto T, Kumakiri J, Kitade M, Kikuchi I, et al. Histopathologic analysis of intestinal endometriosis after laparoscopic low anterior resection. J Minim Invasive Gynecol 2011;18:48–53.
11. Bulletti C, DeZiegler D, Stefanetti M, Cicinelli E, Pelosi E, Flamigni C. Endometriosis: absence of recurrence in patients after endometrial ablation. Hum Reprod 2001;16:2676–9.
12. Goumenou AG, Chow C, Taylor A, Magos A. Endometriosis arising during estrogen and testosterone treatment 17 years after abdominal hysterectomy: a case report. Maturitas 2003;46:239–41.
13. Jain S, Dalton ME. Chocolate cysts from ovarian follicles. Fertil Steril 1999; 72:852–6.
14. Vercellini P, Somigliana E, Vigano P, Abbiati A, Barbara G, Fedele L. "Blood On The Tracks" from corpora lutea to endometriomas. Br J Obstet Gynecol 2009;116:366–71.
15. Fauconnier A, Chapron C, Dubuisson JB, Vieira M, Dousset B, Breart G. Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. Fertil Steril 2002;78:719–26.
16. Vercellini P, Vigano P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 2014;10:261–75.
17. Muzii L, Marana R, Caruana P, Catalano GF, Margutti F, Panici PB. Postoperative administration of monophasic combined oral contraceptives after laparoscopic treatment of ovarian endometriomas: a prospective, randomized trial. Am J Obstet Gynecol 2000;183:588–92.
18. Muzii L, Maneschi F, Marana R, Porpora MG, Zupi E, Bellati F, et al. Oral estroprogestins after laparoscopic surgery to excise endometriomas: continuous or cyclic administration? Results of a multicenter randomized study. J Minim Invasive Gynecol 2011;18:173–8.
19. Seracchioli R, Mabrouk M, Frasca C, Manuzzi L, Savelli L, Venturoli S. Long-term oral contraceptive pills and postoperative pain management after laparoscopic excision of ovarian endometrioma: a randomized controlled trial. Fertil Steril 2010;94:464–71.
20. Vlahos N, Vlachos A, Triantafyllidou O, Vitoratos N, Creatsas G. Continuous versus cyclic use of oral contraceptives after surgery for symptomatic endometriosis: a prospective cohort study. Fertil Steril 2013;100:1337–42.
21. Morelli M, Sacchinelli A, Venturella R, Mocciaro R, Zullo F. Postoperative administration of dienogest plus estradiol valerate versus levonorgestrel-releasing intrauterine device for prevention of pain relapse and disease recurrence in endometriosis patients. J Obstet Gynaecol Res 2013;39: 985–90.
22. Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. Fertil Steril 2003;80:560–3.
23. Seracchioli R, Mabrouk M, Manuzzi L, Vicenzi C, Frasca C, Elmakky A, et al. Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis. Hum Reprod 2009;24:2729–35.
24. Seracchioli R, Mabrouk M, Frasca C, Manuzzi L, Montanari G, Keramyda A, et al. Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. Fertil Steril 2010; 93:52–6.
25. Vercellini P, Frontino G, De Giorgi O, Aimi G, Zaina B, Crosignani PG. Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. Fertil Steril 2003;80:305–9.
26. Wong AY, Tang LC, Chin RK. Levonorgestrel-releasing intrauterine system (Mirena) and Depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: a randomised controlled trial. Aust N Z J Obstet Gynaecol 2010;50: 273–9.
27. Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Indhavivadhana S, Leerasiri P. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain: a randomized controlled trial. Obstet Gynecol 2012;119:519–26.
28. Vercellini P. Endometriosis: what a pain it is. Semin Reprod Endocrinol 1997; 15:251–61.
29. Sesti F, Capozzolo T, Pietropolli A, Marziali M, Bollea MR, Piccione E. Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo. Eur J Obstet Gynecol Reprod Biol 2009; 147:72–7.
30. Vercellini P, Somigliana E, Daguati R, Vigano P, Meroni F, Crosignani PG. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. Am J Obstet Gynecol 2008;198:504.e1–5.
31. Takamura M, Koga K, Osuga Y, Takemura Y, Hamasaki K, Hirota Y, et al. Post-operative oral contraceptive use reduces the risk of ovarian

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endometrioma recurrence after laparoscopic excision. Hum Reprod 2009; 24:3042–8.

32. Ouchi N, Akira S, Mine K, Ichikawa M, Takeshita T. Recurrence of ovarian endometrioma after laparoscopic excision: risk factors and prevention. J Obstet Gynaecol Res 2014;40:230–6.

33. Zorbas KA, Economopoulos KP, Vlahos NF. Continuous versus cyclic oral contraceptives for the treatment of endometriosis: a systematic review. Arch Gynecol Obstet 2015;292:37–43.

34. Cucinella G, Granese R, Calagna G, Svelato A, Saitta S, Tonni G, et al. Oral contraceptives in the prevention of endometrioma recurrence: does the different progestins used make a difference? Arch Gynecol Obstet 2013; 288:821–7.

35. Ruan X, Seeger H, Mueck AO. The pharmacology of dienogest. Maturitas 2012;71:337–44.

36. Strowitzki T, Marr J, Gerlinger C, Faustmann T, Seitz C. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial. Hum Reprod 2010; 25:633–41.

37. Angioni S, Cofelice V, Pontis A, Tinelli R, Socolov R. New trends of progestins treatment of endometriosis. Gynecol Endocrinol 2014;30:769–73.

38. Ota Y, Andou M, Yanai S, Nakajima S, Fukuda M, Takano M, et al. Long-term administration of dienogest reduces recurrence after excision of endometrioma. J Endomet Pelv Pain Disord 2015;7:63–7.

39. Cho S, Jung JA, Lee Y, Kim HY, Seo SK, Choi YS, et al. Postoperative levonorgestrel-releasing intrauterine system versus oral contraceptives after gonadotropin-releasing hormone agonist treatment for preventing endometrioma recurrence. Acta Obstet Gynecol Scand 2014;93: 38–44.

40. Park HJ, Koo YA, Yoon BK, Choi D. Postoperative long-term maintenance therapy with oral contraceptives after gonadotropin-releasing hormone analog treatment in women with ovarian endometrioma. J Minim Invasive Gynecol 2009;16:34–9.

41. Lee DY, Bae DS, Yoon BK, Choi D. Post-operative cyclic oral contraceptive use after gonadotrophin-releasing hormone agonist treatment effectively prevents endometrioma recurrence. Hum Reprod 2010;25:3050–4.

42. Abrao MS, Petraglia F, Falcone T, Keckstein J, Osuga Y, Chapron C. Deep endometriosis infiltrating the recto-sigmoid: critical factors to consider before management. Hum Reprod Update 2015;21:329–39.

43. Meuleman C, Tomassetti C, D'Hoore A, Van Cleynenbreugel B, Penninckx F, Vergote I, et al. Surgical treatment of deeply infiltrating endometriosis with colorectal involvement. Hum Reprod Update 2011;17:311–26.

44. Kavallaris A, Kohler C, Kuhne-Heid R, Schneider A. Histopathological extent of rectal invasion by rectovaginal endometriosis. Hum Reprod 2003;18: 1323–7.

45. Donnez J, Squifflet J. Complications, pregnancy and recurrence in a prospective series of 500 patients operated on by the shaving technique for deep rectovaginal endometriotic nodules. Hum Reprod 2010;25:1949–58.

46. Roman H, Vassilieff M, Gourcerol G, Savoye G, Leroi AM, Marpeau L, et al. Surgical management of deep infiltrating endometriosis of the rectum: pleading for a symptom-guided approach. Hum Reprod 2011; 26:274–81.

47. Saito A, Koga K, Osuga Y, Harada M, Takemura Y, Yoshimura K, et al. Individualized management of umbilical endometriosis: a report of seven cases. J Obstet Gynaecol Res 2014;40:40–5.

48. Koga K, Osuga Y, Harada M, Hirota Y, Yamada H, Akahane M, et al. Sciatic endometriosis diagnosed by computerized tomography-guided biopsy and CD10 immunohistochemical staining. Fertil Steril 2005;84:1508.

49. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400–12.

50. Song JY, Borncamp E, Mehaffey P, Rotman C. Large abdominal wall endometrioma following laparoscopic hysterectomy. J Soc Laparendosc Surg 2011;15:261–3.

51. Nezhat C, Hajhosseini B, King LP. Robotic-assisted laparoscopic treatment of bowel, bladder, and ureteral endometriosis. J Soc Laparendosc Surg 2011; 15:387–92.

52. Ding Y, Zhu J. A retrospective review of abdominal wall endometriosis in Shanghai, China. Int J Gynecol Obstet 2013;121:41–4.

53. Floyd JR 2nd, Keeler ER, Euscher ED, McCutcheon IE. Cyclic sciatica from extrapelvic endometriosis affecting the sciatic nerve. J Neurosurg Spine 2011; 14:281–9.

54. Leong AC, Coonar AS, Lang-Lazdunski L. Catamenial pneumothorax: surgical repair of the diaphragm and hormone treatment. Ann R Coll Surg Engl 2006;88:547–9.

55. Visouli AN, Darwiche K, Mpakas A, Zarogoulidis P, Papagiannis A, Tsakiridis K, et al. Catamenial pneumothorax: a rare entity? Report of 5 cases and review of the literature. J Thorac Dis 2012;4(Suppl 1):17–31.

56. Ichiki Y, Nagashima A, Yasuda M, Takenoyama M, Toyoshima S. Surgical treatment of catamenial pneumothorax: report of three cases. Asian J Surg 2015;38:180–5.

57. Koga K, Takemura Y, Osuga Y, Yoshino O, Hirota Y, Hirata T, et al. Recurrence of ovarian endometrioma after laparoscopic excision. Hum Reprod 2006;21:2171–4.

58. Kikuchi I, Takeuchi H, Kitade M, Shimanuki H, Kumakiri J, Kinoshita K. Recurrence rate of endometriomas following a laparoscopic cystectomy. Acta Obstet Gynecol Scand 2006;85:1120–4.

59. Liu X, Yuan L, Shen F, Zhu Z, Jiang H, Guo SW. Patterns of and risk factors for recurrence in women with ovarian endometriomas. Obstet Gynecol 2007; 109:1411–20.

60. Busacca M, Chiaffarino F, Candiani M, Vignali M, Bertulessi C, Oggioni G, et al. Determinants of long-term clinically detected recurrence rates of deep, ovarian, and pelvic endometriosis. Am J Obstet Gynecol 2006;195: 426–32.

61. Busacca M, Somigliana E, Bianchi S, De Marinis S, Calia C, Candiani M, et al. Post-operative GnRH analogue treatment after conservative surgery for symptomatic endometriosis stage III-IV: a randomized controlled trial. Hum Reprod 2001;16:2399–402.

62. Loverro G, Carriero C, Rossi AC, Putignano G, Nicolardi V, Selvaggi L. A randomized study comparing triptorelin or expectant management following conservative laparoscopic surgery for symptomatic stage III-IV endometriosis. Eur J Obstet Gynecol Reprod Biol 2008;136:194–8.

63. Bianchi S, Busacca M, Agnoli B, Candiani M, Calia C, Vignali M. Effects of 3 month therapy with danazol after laparoscopic surgery for stage III/IV endometriosis: a randomized study. Hum Reprod 1999;14:1335–7.

64. Katz DL, Ali A. Preventive medicine, integrative medicine, and the health of the public. Commissioned IOM Summit Integr Med Health Public 2009:1–45.

65. Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. Am J Obstet Gynecol 2004;191:733–40.

66. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril 2014;101:927–35.

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Deep endometriosis infiltrating the recto-sigmoid: critical factors to consider before management

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BACKGROUND: Deep endometriosis invading the bowel constitutes a major challenge for the gynecologist. In addition to the greater impact on pain, the high incidence of surgical morbidity involved with bowel endometriosis poses a therapeutic dilemma for the surgeon. Intestinal involvement by deep endometriotic nodules has been estimated to occur in 8–12% of women with endometriosis. Individual and clinical factors, pre-operative morphologic characteristics from imaging, surgical considerations and impact on quality of life are critical variables that should be considered in determining the best therapeutic strategy for a patient with deep endometriosis involving the sigmoid and/or the rectum. Pre-operative planning is fundamental for defining the optimal therapeutic strategy; patient counseling of treatment options, and when surgery is indicated, involvement of a multidisciplinary surgical team is required.

METHODS: The PubMed and Cochrane database were searched for all original and review articles published in English, French and Italian, until June 2014. Search terms included 'deep endometriosis', 'surgical and clinical approach', 'bowel disease', 'quality of life', 'management of deep endometriosis'. Special attention was paid to articles comparing features of discoid and segmental resection.

RESULTS: The rationale for the best therapeutic options for patients with deep endometriosis has been shown and an evidence-based treatment algorithm for determining when and which surgical intervention may be required is proposed. In deciding the best treatment option for patients with deep endometriosis involving the sigmoid and rectum, it is important to understand how the different clinical factors and pre-operative morphologic imaging affect the algorithm. Surgery is not indicated in all patients with deep endometriosis, but, when surgery is chosen, a complete resection by the most appropriate surgical team is required in order to achieve the best patient outcome.

CONCLUSION: In women with deep endometriosis, surgery is the therapy of choice for symptomatic patients when deep lesions do not improve with a medical treatment.

Key words: deep endometriosis / ultrasound / MRI / minimally invasive surgery / recurrence

Introduction

Deep endometriosis (DE) invading the bowel constitutes a major challenge for the gynecologist. In addition to the greater impact on pain (Fauconnier and Chapron, 2005; Jacobson et al., 2009), the high incidence of surgical morbidity involved with bowel (Vercellini et al., 2009a; Roman et al., 2011; Ruffo et al., 2012) poses a therapeutic dilemma for the surgeon (Chapron et al., 2004; Abrao et al., 2007). Intestinal involvement by deep endometriotic nodules has been estimated to occur in 8–12% of women with endometriosis (Seracchioli et al., 2007; Wills et al., 2008), and colorectal disease represents almost 90% of these cases (Coronado et al., 1990; Bailey et al., 1994; Tran et al., 1996; Jerby et al., 1999; Remorgida et al., 2007; De Cicco et al., 2011).

Deep endometriosis is defined as endometriosis involving the bowel only if the muscularis layer is affected (Chapron et al., 2010) (Fig. 1). Lesions with dense adhesions and/or endometriotic infiltration up to the bowel serosa are not considered DE, because these lesions usually are <5 mm in depth. To determine the best therapeutic options for patients with DE involving the sigmoid and/or rectum, it is important to understand the roles of clinical factors, pre-operative morphologic characteristics from imaging, surgical considerations, recurrence rate and impact on quality of life. The analysis of all these parameters may contribute to restraining the current trend toward excessive use of laparoscopic colorectal resections (Acién et al., 2013).

The present review produces an overview of the main critical factors that should be considered in determining the best therapeutic options for patients with DE and proposes an evidence-based treatment algorithm in determining when may be required and which surgical intervention should be chosen.

Methods

This review is based upon a literature search in PubMed and Cochrane database focusing on original and review articles published in English, French and Italian, until June 2014. Search terms included 'deep endometriosis', 'surgical and clinical approach', 'bowel disease'. Special attention was paid to articles comparing features of discoid and segmental resection. Reference lists from all relevant original articles and review articles were consulted in order to identify additional studies. This preliminary search resulted in 291 articles. To ensure the relevance of the publications retrieved, additional inclusion criteria were applied which contained an explanation of the surgical technique used as well as an adequate follow-up phase describing data on at least one of

the following terms: post-operative complications, evaluation of pain (dysmenorrhea, dyspareunia, chronic non-menstrual pelvic pain) and management of deep endometriosis. This second screening resulted in 167 citations. Additionally, the terms: quality of life (pre-operative versus post-operative), fertility and recurrence rate were also considered, resulting in 35 articles. The citations whose content did not address the specific proposed objectives in this study were excluded. Finally, a total of 122 articles were retained for analysis.

Clinical symptoms and co-morbidities

Compared with peritoneal and ovarian endometriosis, DE is associated more frequently with dysmenorrhea, dyspareunia, noncyclic pelvic pain and infertility (Ruffo et al., 2010; Chapron et al., 2012), as well as specific bowel symptoms, including cyclic bowel alterations, dyschezia and rectal bleeding (Remorgida et al., 2007). The bowel disease affects patient quality of life as it can increase the number of evacuations or cause progressive constipation leading to bowel obstruction (Bailey et al., 1994; Garry et al., 2000; Redwine and Wright 2001; Darai et al., 2007a; Dousset et al., 2010; Fourquet et al., 2011). A prospective study performed by Roman et al. (2012) demonstrated that women presenting with rectal endometriosis were more likely to present a high prevalence of digestive complaints, such as cyclic defecation pain and cyclic constipation, although these complaints were also frequent in women with deep endometriosis without digestive involvement. Rectal stenosis was observed in 26.4% of women with rectal endometriosis, suggesting that various digestive complaints may be unrelated to rectal infiltration by the deep endometriotic nodules. Symptoms can be similar to irritable bowel syndrome and may even mimic colonic adenocarcinoma (Haggag et al., 2011). The degree of symptoms may not be correspondent to the size of the lesions and painful symptoms are not indicative of surgical intervention. Some patients with extensive rectosigmoid endometriosis can be almost asymptomatic (Chapron et al., 2010), while others with small lesions can present severe symptoms. This makes it more difficult to indicate an intervention, especially with radical surgery (Daraï et al., 2007b).

In several patients, the presence of deep endometriosis coincides with other forms of endometriosis. When only rectosigmoid lesions patients were evaluated, 48 and 84% had ovarian endometriosis and retrocervical lesions, respectively (Goncalves et al., 2010). These findings are relevant
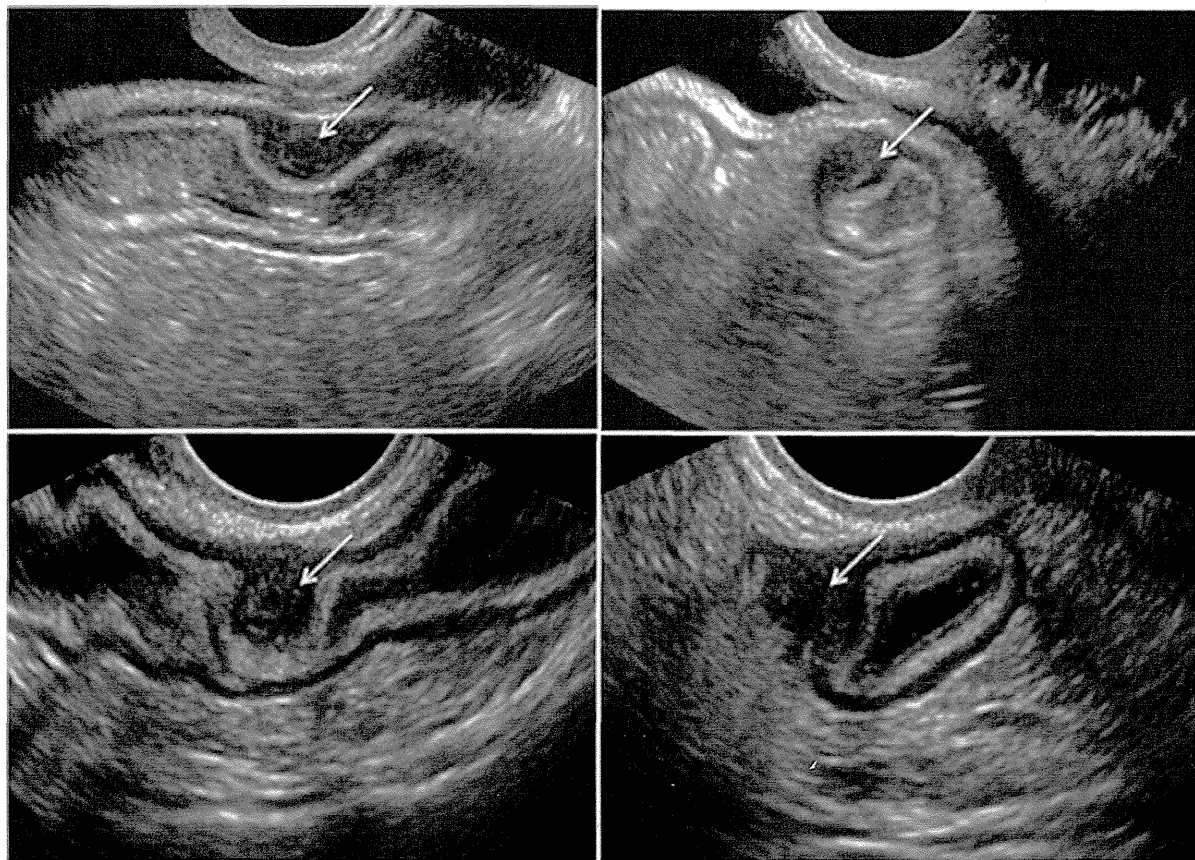
Figure 1 Transvaginal ultrasound showing a hypoechoic lesion suggesting endometriosis compromising the muscularis layer of the rectum.

considering the other possible sites whenever the disease is present in the bowel (Chapron et al., 2003). Both superficial peritoneal and ovarian endometrioma may be found in association with DE in variable percentages, thus contributing to the intensity of painful stimuli as well as to the infertility status (Chapron et al., 2012), and also contributing to the question of whether DE is an independent form of the disease or represents the most severe clinical representation (Acién and Velasco, 2013). Indeed, some cases of DE are described at a second surgery for endometriosis, and the history of a previous surgery is a marker for severity of the disease (Sibiude et al., 2014). In a series of recent studies, it has been shown that DE is associated in >70% of cases with adenomyosis (Lazzeri et al. 2014), raising the question of common pathogenic mechanisms underlying such pathologies (Ferrero et al., 2009a, b; Di Donato and Seracchioli, 2014). Other concurrent chronic inflammatory diseases have also been found in association with DE, such as inflammatory bowel disease (Jess et al., 2012).

The relationship between DE and infertility is controversial (van Dijk et al., 2011). There are no studies showing that bowel endometriosis causes more infertility than other locations of the disease, and in most cases of bowel disease, the other sites are also compromised (Somigliana et al., 2007; Chapron et al., 2009). So it is difficult to determine the specific contribution of each affected sites. Individual (age, hormonal status, desire for fertility) and clinical factors (intensity of pain, pre-operative

findings) should be considered in the treatment algorithm of patients with DE. Surgery should be indicated only in the following situations: (i) patients who present with significant pain such as dyspareunia and dyschezia (VAS > 7) (Anaf et al., 2000; Chapron et al., 2012) that results in major impairment of quality of life; (ii) patients who present with signs of bowel obstruction; and (iii) patients who have failed previous in vitro fertilization (IVF) cycles (Littman et al., 2005). Symptomatic patients approaching menopause may be treated more conservatively, in comparison to younger patients with advanced disease and severe symptoms.

Asymptomatic patients whose lesions were diagnosed on clinical exam and/or radiologic findings do not systematically warrant surgery. However, a large lesion that compromises the lumen of the recto-sigmoid, a severe hemorrhage, or a progressive disease, can be an indication for surgery (Bachmann et al., 2014).

The best treatment approach for infertile patients with asymptomatic bowel lesion is still controversial. There is only one prospective study showing that surgery improved IVF for patients with bowel endometriosis. This study was limited however by its lack of proper randomization (Bianchi et al., 2009). Only after two IVF failures should bowel surgery be considered due to the lack of Level I evidence that surgery may improve pregnancy rates. In cases of infertility associated with pain, both options of surgery and ART have been shown to result in a satisfactory chance of

pregnancy (De Ziegler et al., 2010). When surgery is indicated, there are two options concerning the surgical modalities. Firstly, the pregnancy rate after minimally invasive procedures (shaving and discoid excision) seemed to be higher in a preliminary study, when compared with segmental resection (Mohr et al., 2005). Secondly, some studies have demonstrated high pregnancy rates after laparoscopic bowel resection, for symptomatic women: from 41.6 to 45.5% of women wishing to conceive after surgery (Daraï et al., 2008; Ferrero et al., 2009a, b; Minelli et al., 2009; Meuleman et al., 2014). If the pain is not severe and the desire for pregnancy is the priority, proceeding to ART is the best approach. On the other hand, in cases with debilitating pain, in patients with moderate (stage III) or severe (stage IV) endometriosis (intestinal and/or other sites of disease), surgery is indicated first and ART is proposed when no pregnancy occurs, resulting in a delay of >6 months (Pagidas et al., 1996).

In a prospective, multicenter study performed by Ballester et al. (2012), ICSI–IVF offered a high cumulative pregnancy (CPR) rate in patients without prior surgery for deep infiltrating endometriosis. A progressive increase in the CPR was observed after one, two and three ICSI–IVF cycles/patient, 29.3, 52.9 and 68.6%, respectively. However, determinant factors of the CPR should be considered, such as the presence of adenomyosis, anti-Mullerian hormone levels and the patient age. In patients with colorectal endometriosis, the presence of adenomyosis appears to be a negative determinant factor of fertility outcome in ICSI–IVF.

A review evaluating the effect of conservative surgery for rectovaginal and rectosigmoid endometriosis on reproductive performance demonstrated that the mean pregnancy rate after surgery in all patients who wanted to become pregnant, independently of pre-operative fertility status and IVF performance, was 39%, but in patients who conceived spontaneously, the pregnancy rate was only 24% (Vercellini et al., 2012).

When the patient's priority is to conceive, there is no clear consensus (first surgery or first ICSI–IVF), which determines the fertility outcome. Within this same reasoning, the results of Cohen et al. (2014) suggested a potential benefit of combining surgery and medically assisted reproduction (in vitro fertilization and intrauterine insemination) on fertility outcomes in patients with bowel endometriosis, whereas in patients with DE without bowel involvement, a high spontaneous pregnancy rate was reported.

Recently, in preliminary results related to women with colorectal endometriosis, the overall pregnancy rate after primary surgery, followed or not by IVF, reached up to 66% (ENDORE – WCE Sao Paolo, 2014).

For asymptomatic patients and when the pelvic pain is not a deleterious symptom to the patient, assisted reproductive technology must be the first-line option for the treatment of infertility.

Modalities for pre-operative diagnosis of deep endometriosis

Deep endometriotic nodules involving the retrocervical region, uterosacral ligaments, vagina and recto-sigmoid must be accurately detected pre-operatively, so, the adequate use of complementary diagnostic methods is very important. The use of the ENZIAN-score (Tuttlies et al., 2005) can also be helpful for planning the surgical procedure.

In multiple published studies, transvaginal ultrasound (TVUS) with bowel preparation has shown a superior sensitivity (75–98%) for

detecting DE compared with magnetic resonance imaging, transrectal ultrasonography, computer tomography and clinical examination (Abrao et al., 2007; Pronio et al., 2007). When endometriosis involves the recto-sigmoid, TVUS with bowel preparation is able to define not only the size and number of lesions, but also the depth of invasion into the bowel wall and the distance from the anal verge (Guerriero et al., 2008; Hudelist et al., 2009; Goncalves et al., 2010). For these patients, pre-operative TVUS must be the first-line imaging modality (Piketty et al., 2009; Goncalves et al., 2010). Recently, a well-defined protocol for performing an accurate TVUS evaluation in cases of DE has been proposed and may represent a valid pre-surgical approach (Exacoustos et al. 2014). Some authors recommend that the pre-operative work-up should also include a colonoscopy and magnetic resonance imaging (MRI) (Zanardi et al., 2003). Meuleman et al. (2011) described that, in 59% of the studies analyzed, the pre-operative assessment of bowel endometriosis included barium enema (26%), computerized tomography (31%) and/or MRI (28%). After diagnosis, pre-operative planning along with patient counseling is fundamental for defining the optimal therapeutic strategy and, when surgery is indicated, involvement of a multidisciplinary surgical team is required.

Anatomical and histological characteristics

According to the Sampson's theory concerning endometriosis pathogenesis (Sampson, 1927), endometriotic lesions affect the recto-sigmoid starting from the serosa, invade towards the lumen of the bowel and finally infiltrate the rectal wall. The fibrotic component represents around 80% of the lesions in cases of intestinal endometriosis and therefore, surgical management is more difficult (Thomassin et al., 2004). In this context, it is important to evaluate the surgical treatment carefully, considering the risk of complications associated with these complex procedures (Abrao et al., 2006; Benbara et al., 2008). With this understanding, it is important to precisely define the parameters that are crucial to determine the best surgical approach. These parameters are described below.

Number of intestinal DE lesions

Multifocality is one of the main characteristics of DE, especially when the intestinal tract is involved (Chapron et al., 2003). When deep endometriosis affects the recto-sigmoid, multifocal bowel lesions are observed in 40% or more patients (Remorgida et al., 2005; Chapron et al., 2006). Kavallaris et al. (2003) reported that for rectal endometriosis, multifocal involvement (defined as presence of deep lesions within 2 cm area of the main lesions) and multicentric involvement (defined as a satellite deep nodule found >2 cm from the main lesions) were observed respectively in 62 and 38% of the cases. These histopathological observations were in accordance with the observations of Anaf et al. (2004) who demonstrated that deep endometriotic lesions infiltrate the large bowel wall preferentially along the nerves, even at a distance from the palpated nodule, while the mucosa is rarely and only focally involved.

Size of the intestinal DE lesion(s)

Lesions larger than 3 cm in diameter require a segmental resection in order to avoid significant distortion of the bowel axis and subsequent stricture (Abrao et al., 2008; Moawad et al., 2011). Alternatively, an

original technique using combined laparoscopic and transanal approaches, including deep rectal shaving, followed by transanal full-thickness disc excision was performed in a 30-year-old nullipara. Rectal stenosis was due to a large endometriotic nodule infiltration measured over 30 mm in diameter. The authors support that this conservative technique is feasible in large low rectal endometriosis and can prevent complications inherent to low colorectal resection (Roman et al., 2014; Roman and Tuech, 2014a, b). Fibrotic tissue must be considered part of the lesions, as evidence suggests that estrogen and progestogen receptors are present not only in glands and stroma but also in the smooth muscle and fibrosis surrounding the lesions of bowel endometriosis (Noël et al., 2010). We recommend complete excision of the surrounding fibrotic tissue during surgery in order to prevent disease recurrence. A discoid resection could be considered only for nodules smaller than 3 cm (Remorgida et al., 2005; de Almeida et al., 2014).

Extent of bowel circumference involvement

The extent of the bowel circumference compromised is positively correlated with the depth of the endometriotic nodule invasion into the bowel wall (Abrao et al., 2008). In this study, it was demonstrated that when the DE involves the rectum and/or sigmoid deeper than the submucosal layer, the circumference of the bowel affected by the disease is higher than 40% (Abrao et al., 2003). For these situations, removing a disk that compromises >40% of the circumference of the rectum could put the patient at risk for bowel stenosis.

Depth of lesions

It is also important to consider how deeply the bowel wall is infiltrated by endometriotic lesions. The lesions of the serosa without infiltration of the muscularis are superficial, and may not justify any specific surgical bowel procedure (Chapron et al., 2003). In a literature review, Meuleman et al. (2011) reported that 95% of the patients undergoing bowel resection anastomosis had bowel serosa involvement; 95% had lesions infiltrating the muscularis while 38% had lesions infiltrating the submucosa and 6% had lesions infiltrating the mucosa.

Distance to the anal verge

The distance of the inferior border of the lowest bowel lesion to the anal verge should be evaluated pre-operatively. The surgical treatment of low rectal lesions (defined as <5–8 cm from the anal verge) is associated with a higher risk of post-operative anastomotic leaks (Ruffo et al., 2010) and transient neurogenic bladder dysfunction (Dousset et al., 2010). However an innovative technique combining a laparoscopic and transanal approach can be applied to remove the full thickness of the infiltrating endometrial nodules of the lower and middle rectum. This technique avoids post-operative complaints, especially rectal stenosis and denervation and its related symptoms (Bridoux et al., 2012; Roman and Tuech, 2014b). It is therefore critical to obtain this information prior to surgery (Pronio et al., 2007; Goncalves et al., 2010).

Histological pattern classification

Histologic patterns associated with endometriosis may be well-differentiated glandular, pure stromal, glandular or mixed differentiation, or pure undifferentiated glandular (Abrao et al., 2003). Deep infiltrative lesions are significantly associated with the undifferentiated glandular pattern (Abrao et al., 2003; Kamergorodsky et al., 2009) and with

disease stages III and IV (Abrao et al., 2003). This finding suggests that undifferentiated endometriotic lesions (when the epithelium is flattened or low cuboidal, with no correspondence with eutopic endometrium) possibly the result from the tissue's inability to respond to suppressor effects of the peritoneal fluid, allowing these endometrial foci to infiltrate more deeply (Kamergorodsky et al., 2009).

Lymphatic dissemination

After segmental bowel resection for deep endometriosis, lymph node involvement is observed between 26 and 42% of the cases and is correlated with the severity of the disease (Abrao et al., 2006; Noël et al., 2008; Mechsner et al., 2010). Lymph node involvement is correlated with the size of the bowel lesion (Abrao et al., 2006; Noël et al., 2008; Mechsner et al., 2010), the percentage of the intestinal wall affected by the deep nodule (Abrao et al., 2006) and the presence of lymphovascular invasion which can contribute to post-operative recurrence (Noël et al., 2008).

Parameters to be considered for surgery

The size of the lesions, depth of infiltration, percentage of the intestinal wall circumference infiltrated and lymph node involvement are all correlated and are not independent parameters. Because of these findings, complete resection of large size nodules with lymphovascular involvement is important in order to avoid residual disease. The rate of recurrence has been correlated with the completeness of surgical excision (Sibiude et al., 2014). Similar conclusions were obtained by Nirgianakis et al. (2014), when clinical and histological characteristics were examined as possible predictive factors for bowel endometriosis recurrence after laparoscopic segmental bowel resection. Three independent predictor factors, positive bowel resection margins, age <31 years and body mass index ≥23 kg/m², were also significantly associated with recurrence which was observed in 16% of patients. Additionally as the surgeon's skills increase, the surgery becomes more complete and the recurrence rate significantly decreases (Carmona et al., 2009).

To summarize, the complete exeresis of bowel endometriotic lesions could be most effective for avoiding recurrence of the disease, but this depends upon the parameters described above: the number, size and depth of intestinal nodules, associated fibrosis, rectal circumference involvement, lymph node involvement and distance to the anal verge.

Surgery, complications and recurrences

The complete excision of all endometriotic lesions is the main objective of both laparoscopic and laparotomic surgeries which require a multidisciplinary approach (Possover et al., 2000; Keckstein and Wiesinger, 2005) and highly skilled surgeons.

Laparoscopic excision of deep infiltrating bowel endometriosis has become a frequently used treatment modality, and segmental bowel resection has been performed in many cases, despite the relatively high rate of morbidity. However, in most of the studies (Ford et al., 2004; Campagnacci et al., 2005; Mohr et al., 2005; Brouwer and Woods, 2007; Pereira et al., 2009), the indication of segmental resection instead of more conservative surgery methods is often not documented, and there are few studies comparing the results of different surgical techniques. Three studies have provided results related to the comparison of different surgical approaches (nodule excision, shaving and segmental

resection) for the management of women presenting colorectal endometriosis and its impact on digestive symptoms (Roman et al., 2010, 2011, 2013). Most of the authors also do not compare the quality of life for women after radical surgery with others who have not undergone bowel resection. In these conditions, it is difficult to determine whether a greater or similar health improvement can be achieved with less aggressive surgery (Acién et al., 2013). However according to Roman et al. (2013), post-operative digestive symptoms may be associated with different surgical philosophies regarding radical and conservative approached (colorectal resection and shaving/rectal nodule excision, respectively). For women managed for rectal endometriosis, better functional outcomes were observed in those who underwent conservative surgical approaches aiming at rectal conservation instead of routine radical rectal excision.

The three options in the surgical treatment of endometriosis of the rectosigmoid include: (i) the shaving technique (Donnez and Squifflet, 2010; Mabrouk et al., 2011; Roman et al., 2011; Moawad and Caplin, 2013); (ii) resection of the endometriotic nodule (nodular resection) (Reich, 1997; Fanfani et al., 2010; Oliveira et al., 2014); and (iii) segmental resection with end-to-end anastomosis (Panebianco et al., 1994; Duepree et al., 2002; Abrao et al., 2008; Dousset et al., 2010; Roman et al., 2011). Figures 2 and 3 represent nodular and segmental bowel resection of endometriotic lesions respectively.
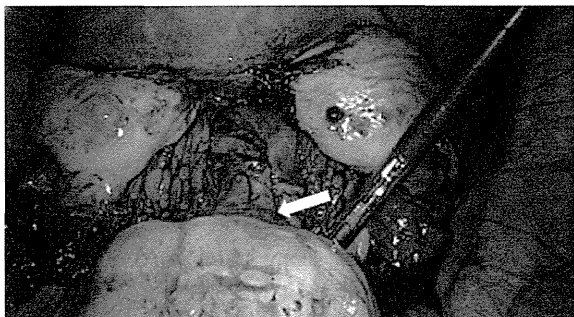
Figure 2 Endometriosis lesion with <3 cm of longitudinal diameter being resected with a circular stapler (disc resection).
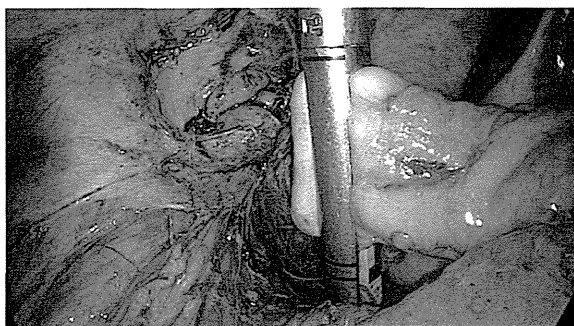
Figure 3 Segmental resection of the rectum for a multifocal endometriosis.

For advanced endometriosis with bowel extension, different nerve sparing techniques used in surgeries for pelvic malignant disease are successful in reducing functional problems (urine retention, constipation, sexual dysfunction) related to pelvic denervation after surgery (Maas et al., 1999; Possover et al., 2005; Landi et al., 2006).

Both major and minor surgical complications have been reported after surgical excision of deep endometriosis involving the bowel. These include: fistula (0–14%) (Duepree et al., 2002; Keckstein and Wiesinger, 2005; Ruffo et al., 2010), hemorrhage (1–11%) (Darai et al., 2007a; Seracchioli et al., 2007), infections (1–3%) (Meuleman et al., 2009; Ruffo et al., 2010), laparoconversion (up to 12%) (Dubernard et al., 2006; Darai et al., 2007a), and bladder (1–71%) and bowel (1–15%) dysfunction (Mangler et al., 2008; Ruffo et al., 2010) such as post-operative severe constipation (Armengol-Debeir et al., 2011). Considering the major complications, there are three frequently observed risk factors: opening of the vagina at the time of the bowel surgical procedure (Meuleman et al., 2011); excessive use of electrocoagulation that may increase the risk of rectovaginal fistulae and abscesses, as it can lead to necrosis of the posterior vaginal cuff (Dubernard et al., 2006); and surgical treatment of low rectal lesions (<5–8 cm from the anal verge) which increases the risk of anastomotic leaks (Ruffo et al., 2010; Trencheva et al., 2013).

It is difficult to interpret the relevance of the complications because the morphologic aspects of the disease, such as the location, size and diameter of nodule(s), are not always specifically reported (De Cicco et al., 2011). Nonetheless, it is important to note that the overall quality of life of patients with bowel endometriosis submitted to bowel surgery is significantly improved (Dousset et al., 2010; Bassi et al., 2011; Moawad et al., 2011).

Brouwer and Woods (2007) described in their review that the type of surgical approach does not change the rate of complications. However many factors are affected by the surgeon's learning curve, such as the rate of conversion, operating time, complication rate and surgical effectiveness (Carmona et al., 2009). Despite this, complications can occur even among experienced surgeons (Haggag et al., 2011).

Data regarding recurrence rates after surgical treatment of DE are scarce, since most studies available have analyzed recurrence of ovarian endometriomas (Fedele et al., 2004; Li et al., 2005; Vercellini et al., 2006). According to Meuleman et al. (2011), when considering a follow-up period >2 years, in general, the recurrence rate after surgery observed in several studies varied between 4 and 25%. When comparing bowel resection anastomosis groups and mixed study groups (full-thickness disc excision, bowel resection anastomosis, shave/superficial excision), the recurrence rates were 5.8 and 17.6%, respectively.

In a recent review, the surgical treatment of DE provides excellent results, with >85% of women showing complete improvement of symptoms and recurrence rates lower than 5% (Koninckx et al., 2012). Recurrence of deep endometriosis can be invariably considered a result of incomplete surgery (Vignali et al., 2005; Koninckx et al., 2012). The indication of a second surgery must be based on a meticulous evaluation of risks and benefits, since it has been demonstrated that repeat conservative surgery for DE has the same efficacy and limitations as primary surgery (Vercellini et al., 2009a; Berlanda et al., 2010). When a second surgical approach is intended, definitive surgery (hysterectomy and bilateral oophorectomy) promotes the best results and must be considered, particularly in women over 40 years old and who do not

wish to conceive (Vercellini et al., 2009b). Alternatively, it has been shown that hormonal and non-hormonal medical treatments may provide a good efficacy for the treatment of pain in women presenting recurrent DE (Razzi et al., 2007; Rocha et al., 2012; Borghese et al., 2014). When dealing with recurrence of DE, it is important to distinguish between pain control and fertility as the main goal of treatment. For patients in whom fertility is the aim, there is clear evidence that assisted reproductive technology leads to better results compared with a second operation (The Practice Committee of the ASRM, 2006; Vercellini et al., 2009c; Berlanda et al., 2013).

The modern management of bowel endometriosis and quality of life

The treatment algorithm for deep endometriosis compromising the bowel must be individualized (Fig. 4). Critical clinical factors such as the age of the patient, intensity of pain (VAS > 7), risk of bowel obstruction and desire for pregnancy should be considered. Asymptomatic patients with deep intestinal nodule do not require surgery and must be followed clinically (for pain symptoms) and perhaps sonographically

(for enlargement of lesion that may compromise bowel lumen) (Abrao et al., 2007; Hudelist et al., 2009; Goncalves et al., 2010).

For asymptomatic patients, the indications for surgery are limited to the risk of bowel obstruction and, possibly, the aim for fertility after IVF failures. For patients who are not interested in pregnancy, medical treatment should be the first option (Vercellini et al., 2010). Surgery is then indicated when patients with pelvic pain do not respond to medical treatment. When surgery is chosen, complete resection of endometriosis should be performed in order to reduce the risk of residual disease (Carmona et al., 2009; Sibiude et al., 2014). Bowel resection with end-to-end anastomosis is preferred to nodule resections in cases of multiple intestinal nodules (to avoid multiple risky sites for dehiscence in the bowel), nodules located in the sigmoid, lesions >3 cm in size, and deep intestinal lesions involving the submucosa and/or mucosa.

Oxidized regenerated cellulose can be considered after laparoscopic surgery for endometriosis in the prevention of adhesions (Ahmad et al., 2008). In a similar context, the safety and effectiveness of Seprafilm adhesion barrier, in relation to abdominal or pelvic abscess and pulmonary embolism, when administered to patients undergoing abdominopelvic surgery has been confirmed. However, when Seprafilm was used for fresh bowel anastomosis, anastomotic leaks, fistula, peritonitis, abscess or sepsis, occurred more frequently in a subpopulation of patients (Beck et al., 2003).
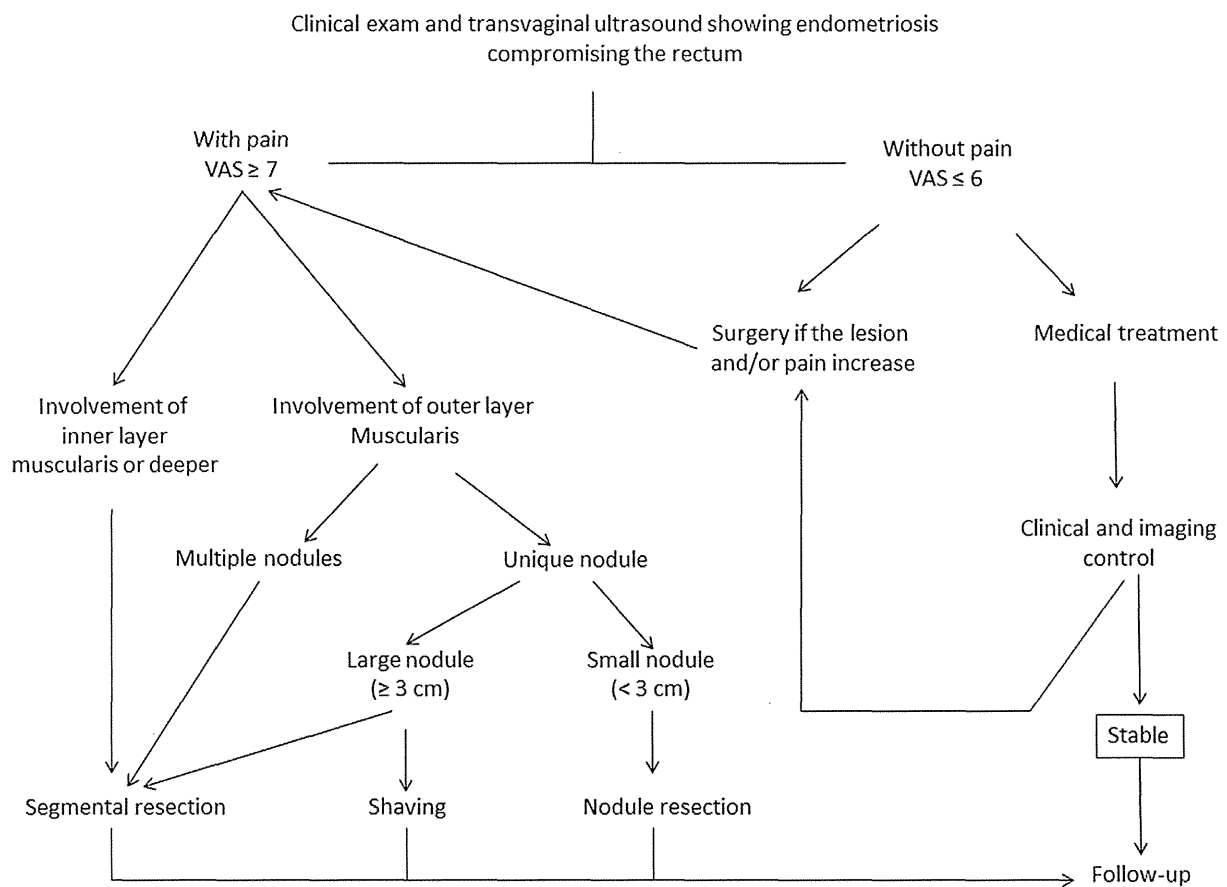
Figure 4 Treatment algorithm for deep endometriosis compromising the bowel. VAS: visual analogic scale.

Imaging technology and adequate training in techniques have made it possible to identify the precise characteristics of deep endometriotic nodules pre-operatively (Chapron et al., 1998; Abrao et al., 2007). The detailed imaging findings allow us to define and plan the optimal procedure prior to surgery. This permits proper patient counseling and selection of an appropriate multidisciplinary surgical team to achieve the best patient outcome (De Ziegler et al., 2011).

Although there are no specific data focused on DE post-operative management, post-operative prescription of hormonal treatment after cystectomy for endometrioma is effective for secondary prevention of recurrence (Vercellini et al., 2010) and pelvic pain (Seracchioli et al., 2009). Furthermore, recurrence of disease must be differentiated from persistence that results from incomplete excision (Sibiude et al., 2014). When a sizable deep nodule that compromises a large circumference of the bowel is detected pre-operatively, the patient should be counseled regarding the greater risk of persistence of residual disease when complete excision is not accomplished.

Intestinal endometriosis significantly impacts the quality of life (QoL) of the patients due to its association with chronic pelvic pain, dysmenorrhea, deep dyspareunia and cyclic bowel alterations (Garry et al., 2000; Redwine and Wright, 2001; Dubernard et al., 2006, 2008). The main objective of any treatment for intestinal endometriosis is to offer the best possible relief from these symptoms, thus improving the quality of life of these women. Medical treatment is only suppressive and does not cure the deep endometriosis probably because of the fibrotic component which represents around 80% of the lesions in cases of intestinal endometriosis (Thomassin et al., 2004; Darai et al., 2005). This reinforces the importance of the indication of surgical treatment (Benbara et al., 2008; English et al., 2014; Laas et al., 2014). However, medical treatment is effective for symptom relief (Ferrero et al., 2010) in numerous patients who consequently do not need surgery.

Bassi et al. (2011) used the SF-36 to evaluate the QoL of patients with bowel disease submitted to a segmental resection of the rectum. A significant increase was found after surgery in the mean scores for all the domains in this questionnaire as well as total scores, confirming the beneficial role of this surgical treatment in relieving the symptoms of rectosigmoid endometriosis and consequently in improving the QoL of these patients.

Preliminary results of an evaluation of post-operative gastrointestinal symptoms related to radical and conservative surgery for rectal endometriosis have also been reported by Roman et al. (2013). Significant improvement in Qol was achieved for women who underwent conservative surgical approach, based on the results obtained from gastrointestinal standardized questionnaires (Knowles-Eccersley-Scott Symptom Questionnaire, Gastrointestinal Quality of Life Index, and depression/self-perception Fecal Incontinence Quality of Life Score).

Conclusions

In deciding the best treatment option for patients with deep endometriosis involving the sigmoid and rectum, it is important to understand how different clinical and pre-operative morphologic factors from clinical assessment and imaging affects the algorithm. Although surgery is not indicated in all patients with deep endometriosis, when surgery is chosen, a complete resection of the endometriosis by the most appropriate surgical team should be provided with the goal to achieve the best patient outcome.

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Authors' roles

M.S.A. and C.C. developed the original design and wrote the first draft of the manuscript; M.S.A., C.C., F.P., T.F., J.K., Y.O. revised critically the manuscript for important intellectual content. All authors contributed to the writing of the final manuscript and approved it to be published.

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Conflict of interest

The authors certify that they have no conflicts of interest.

References

Abrao MS, Neme RM, Carvalho FM, Aldrighi JM, Pinotti JA. Histological classification of endometriosis as a predictor of response to treatment. Int J Gynaecol Obstet 2003; **82**:31–40.

Abrao MS, Podgaec S, Dias JA Jr, Averbach M, Garry R, Ferraz Silva LF, Carvalho FM. Deeply infiltrating endometriosis affecting the rectum and lymph nodes. Fertil Steril 2006;**86**:543–547.

Abrao MS, Gonçalves MO, Dias JA Jr, Podgaec S, Chamie LP, Blasbalg R. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. Hum Reprod 2007;**22**:3092–3097.

Abrao MS, Podgaec S, Dias JA Jr, Averbach M, Silva LF, Marino de Carvalho F. Endometriosis lesions that compromise the rectum deeper than the inner muscularis layer have more than 40% of the circumference of the rectum affected by the disease. J Minim Invasive Gynecol 2008;**15**:280–285.

Acién P, Velasco I. Endometriosis: a disease that remains enigmatic. ISRN Obstet Gynecol 2013;**17**:2013:242149.

Acién P, Núñez C, Quereda F, Velasco I, Valiente M, Vidal V. Is a bowel resection necessary for deep endometriosis with rectovaginal or colorectal involvement? Int J Womens Health 2013;**5**:449–455.

Ahmad G, Duffy JMN, Farquhar C, Vail A, Vanderkerchose P, Watson A, Wiseman D. Barrier agents for adhesion prevention after gynaecological surgery. Cochrane Database Syst Rev 2008; Issue 2. Art. No.:CD 000475.

Anaf V, Simon P, El Nakadi I, Fayt I, Buxant F, Simonart T, Peny MO, Noel JC. Relationship between endometriotic foci and nerves in rectovaginal endometriotic nodules. Hum Reprod 2000;**15**:1744–1750.

Anaf V, El Nakadi I, Simon P, Van de Stadt J, Fayt I, Simonart T, Noel JC. Preferential infiltration of large bowel endometriosis along the nerves of the colon. Hum Reprod 2004;**19**:996–1002.

Armengol-Debeir L, Savoye G, Leroi AM, Gourcerol G, Savoye-Collet C, Tuech JJ, Vassilieff M, Roman H. Pathophysiological approach to bowel dysfunction after segmental colorectal resection for deep endometriosis infiltrating the rectum: a preliminary study. Hum Reprod 2011;**26**:2330–2335.

Bachmann R, Bachmann C, Lange J, Krämer B, Brucker SY, Wallwiener D, Königsrainer A, Zdichavsky M. Surgical outcome of deep infiltrating colorectal endometriosis in a multidisciplinary setting. Arch Gynecol Obstet 2014;**290**:919–924.

Bailey HR, Ott MT, Hartendorp P. Aggressive surgical management for advanced colorectal endometriosis. Dis Colon Rectum 1994;**37**:747–753.

Ballester M, d'Argent EM, Morcel K, Belaisch-Allart J, Nisolle M, Daraï E. Cumulative pregnancy rate after ICSI-IVF in patients with colorectal endometriosis: results of a multicentre study. Hum Reprod 2012;**27**:1043–1049.

Bassi MA, Podgaec S, Dias JA Jr, D'Amico Filho N, Petta CA, Abrao MS. Quality of life after segmental resection of the rectosigmoid by laparoscopy in patients with deep

infiltrating endometriosis with bowel involvement. *J Minim Invasive Gynecol* 2011; 18:730–733.

Beck DE, Cohen Z, Fleshman JW, Kaufman HS, van Goor H, Wolff BG; Adhesion Study Group Steering Committee. A prospective, randomized, multicenter, controlled study of the safety of Seprafilm adhesion barrier in abdominopelvic surgery of the intestine. *Dis Colon Rectum* 2003;46:1310–1309.

Benbara A, Fortin A, Martin B, Palazzo L, Le Tohic A, Madelenat P, Yazbeck C. Surgical and functional results of rectosigmoidal resection for severe endometriosis. *Gynecol Obstet Fertil* 2008;36:1191–1201.

Berlanda N, Vercellini P, Fedele L. The outcomes of repeat surgery for recurrent symptomatic endometriosis. *Curr Opin Obstet Gynecol* 2010;22:320–325.

Berlanda N, Vercellini P, Somigliana E, Frattaruolo MP, Buggio L, Gattei U. Role of surgery in endometriosis-associated subfertility. *Semin Reprod Med* 2013;31:133–143.

Bianchi PH, Pereira RM, Zanatta A, Alegretti JR, Motta EL, Serafini PC. Extensive excision of deep infiltrative endometriosis before *in vitro* fertilization significantly improves pregnancy rates. *J Minim Invasive Gynecol* 2009;16:174–180.

Borghese B, Santulli P, Streuli I, Lafay-Pillet MC, de Ziegler D, Chapron C. Recurrence of pain after surgery for deeply infiltrating endometriosis: how does it happen? How to manage? *J Gynecol Obstet Biol Reprod (Paris)* 2014;43:12–18.

Bridoux V, Roman H, Kianifard B, Vassilieff M, Marpeau L, Michot F, Tuech JJ. Combined transanal and laparoscopic approach for the treatment of deep endometriosis infiltrating the rectum. *Hum Reprod* 2012;27:418–426.

Brouwer R, Woods RJ. Rectal endometriosis: results of radical excision and review of published work. *ANZ J Surg* 2007;77:562–571.

Campagnacci R, Perretta S, Guerrieri M, Paganini AM, De Sanctis A, Ciavattini A, Lezoche E. Laparoscopic colorectal resection for endometriosis. *Surg Endosc* 2005;19:662–664.

Carmona F, Martínez-Zamora A, González X, Ginés A, Buñesch L, Balasch J. Does the learning curve of conservative laparoscopic surgery in women with rectovaginal endometriosis impair the recurrence rate? *Fertil Steril* 2009; 92:868–875.

Chapron C, Dumontier I, Dousset B, Fritel X, Tardif D, Roseau G, Chaussade S, Couturier D, Dubuisson JB. Results and role of rectal endoscopic ultrasonography for patients with deep pelvic endometriosis. *Hum Reprod* 1998;13:2266–2270.

Chapron C, Fauconnier A, Vieira M, Barakat H, Dousset B, Pansini V, Vacher-Lavenu MC, Dubuisson JB. Anatomical distribution of deeply infiltrating endometriosis: surgical implications and proposition for a classification. *Hum Reprod* 2003;18:157–161.

Chapron C, Chopin N, Borghese B, Malartic C, Decuypere F, Foulot H. Surgical management of deeply infiltrating endometriosis: an update. *Ann N Y Acad Sci* 2004;1034:326–337. Review.

Chapron C, Chopin N, Borghese B, Foulot H, Dousset B, Vacher-Lavenu MC, Vieira M, Hasan W, Bricou A. Deeply infiltrating endometriosis: pathogenetic implications of the anatomical distribution. *Hum Reprod* 2006;21:1839–1845.

Chapron C, Pietin-Vialle C, Borghese B, Davy C, Foulot H, Chopin N. Associated ovarian endometrioma is a marker for greater severity of deeply infiltrating endometriosis. *Fertil Steril* 2009;92:453–457.

Chapron C, Bourret A, Chopin N, Dousset B, Leconte M, Amsellem-Ouazana D, de Ziegler D, Borghese B. Surgery for bladder endometriosis: long-term results and concomitant management of associated posterior deep lesions. *Hum Reprod* 2010;25:884–889.

Chapron C, Santulli P, de Ziegler D, Noel JC, Anaf V, Streuli I, Foulot H, Souza C, Borghese B. Ovarian endometrioma: severe pelvic pain is associated with deeply infiltrating endometriosis. *Hum Reprod* 2012;27:702–711.

Cohen J, Thomin A, Mathieu d'Argent E, Laas E, Canlorbe G, Zilberman S, Belghiti J, Thomassin-Naggara I, Bazot M, Ballester M et al. Fertility before and after surgery for deep infiltrating endometriosis with and without bowel involvement: a literature review. *Minerva Ginecol* 2014;66:575–587.

Coronado C, Franklin RR, Lotze EC, Bailey HR, Valdés CT. Surgical treatment of symptomatic colorectal endometriosis. *Fertil Steril* 1990;53:411–446.

Darai E, Thomassin I, Barranger E, Detchev R, Cortez A, Houry S, Bazot M. Feasibility and clinical outcome of laparoscopic colorectal resection for endometriosis. *Am J Obstet Gynecol* 2005;192:394–400.

Darai E, Ackerman G, Bazot M, Rouzier R, Dubernard G. Laparoscopic segmental colorectal resection for endometriosis: limits and complications. *Surg Endosc* 2007a;21:1572–1577.

Daraï E, Bazot M, Rouzier R, Houry S, Dubernard G. Outcome of laparoscopic colorectal resection for endometriosis. *Curr Opin Obstet Gynecol* 2007b;19:308–313. Review.

Daraï E, Bazot M, Rouzier R, Coutant C, Ballester M. Colorectal endometriosis and fertility. *Gynecol Obstet Fertil* 2008;36:1214–1247. Review.

de Almeida A, Fernandes LF, Averbach M, Abrão MS. Disc resection is the first option in the management of rectal endometriosis for unifocal lesions with less than 3 centimeters of longitudinal diameter. *Surg Technol Int* 2014;24:243–248.

De Cicco C, Corona R, Schonman R, Mailova K, Ussia A, Koninckx P. Bowel resection for deep endometriosis: a systematic review. *BJOG* 2011;118:285–291.

De Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. *Lancet* 2010;376:730–738.

De Ziegler D, Streuli MI, Borghese B, Bajouh O, Abrao M, Chapron C. Infertility and endometriosis: a need for global management that optimizes the indications for surgery and ART. *Minerva Ginecol* 2011;63:365–373.

Di Donato N, Seracchioli R. How to evaluate adenomyosis in patients affected by endometriosis? *Minim Invasive Surg* 2014;2014:507230.

Donnez J, Squifflet J. Complications, pregnancy and recurrence in a prospective series of 500 patients operated on by the shaving technique for deep rectovaginal endometriotic nodules. *Hum Reprod* 2010;25:1949–1958.

Dousset B, Leconte M, Borghese B, Millischer AE, Roseau G, Arkwright S, Chapron C. Complete surgery for low rectal endometriosis: long-term results of a 100-case prospective study. *Ann Surg* 2010;251:887–895.

Dubernard G, Piketty M, Rouzier R, Houry S, Bazot M, Darai E. Quality of life after laparoscopic colorectal resection for endometriosis. *Hum Reprod* 2006; 21:1243–1247.

Dubernard G, Rouzier R, David-Montefiori E, Bazot M, Darai E. Use of the SF-36 questionnaire to predict quality-of-life improvement after laparoscopic colorectal resection for endometriosis. *Hum Reprod* 2008;23:846–851.

Duepree HJ, Senagore AJ, Delaney CP, Marcello PW, Brady KM, Falcone T. Laparoscopic resection of deep pelvic endometriosis with rectosigmoid involvement. *J Am Coll Surg* 2002;195:754–748.

ENDORE – WCE Sao Paolo 2014. Functional Outcomes of Surgical Management of Deep Endometriosis Infiltrating the Rectum: http://clinicaltrials.gov/ct2/show/NCT01291576?term=NCT01291576&rank=1.

English J, Sajid MS, Lo J, Hudelist G, Baig MK, Miles WA. Limited segmental rectal resection in the treatment of deeply infiltrating rectal endometriosis: 10 years' experience from a tertiary referral unit. *Gastroenterol Rep (Oxf)* 2014;2:288–294.

Exacoustos C, Malzoni M, Di Giovanni A, Lazzeri L, Tosti C, Petraglia F, Zupi E. Ultrasound mapping system for the surgical management of deep infiltrating endometriosis. *Fertil Steril* 2014;102:143–150.e2.

Fanfani F, Fagotti A, Gagliardi ML, Ruffo G, Ceccaroni M, Scambia G, Minelli L. Discoid or segmental rectosigmoid resection for deep infiltrating endometriosis: a case-control study. *Fertil Steril* 2010;94:444–449.

Fauconnier A, Chapron C. Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications. *Hum Reprod Update* 2005;11:595–606.

Fedele L, Bianchi S, Zanconato G, Bettoni G, Gotsch F. Long-term follow-up after conservative surgery for rectovaginal endometriosis. *Am J Obstet Gynecol* 2004; 190:1020–1024.

Ferrero S, Anserini P, Abbamonte LH, Ragni N, Camerini G, Remorgida V. Fertility after bowel resection for endometriosis. *Fertil Steril* 2009a;92:41–46.

Ferrero S, Camerini G, Menada MV, Biscaldi E, Ragni N, Remorgida V. Uterine adenomyosis in persistence of dysmenorrhea after surgical excision of pelvic endometriosis and colorectal resection. *J Reprod Med* 2009b;54:366–372.

Ferrero S, Camerini G, Ragni N, Venturini PL, Biscaldi E, Remorgida V. Norethisterone acetate in the treatment of colorectal endometriosis: a pilot study. *Hum Reprod* 2010; 25:94–100.

Ford J, English J, Miles WA, Giannopoulos T. Pain, quality of life and complications following the radical resection of rectovaginal endometriosis. *BJOG* 2004;111:353–356.

Fourquet J, Báez L, Figueroa M, Iriarte RI, Flores I. Quantification of the impact of endometriosis symptoms on health-related quality of life and work productivity. *Fertil Steril* 2011;96:107–112.

Garry R, Clayton R, Hawe J. The effect of endometriosis and its radical laparoscopic excision on quality of life indicators. *BJOG* 2000;107:44–54.

Goncalves MO, Podgaec S, Dias JA Jr, Gonzalez M, Abrao MS. Transvaginal ultrasonography with bowel preparation is able to predict the number of lesions and rectosigmoid layers affected in cases of deep endometriosis, defining surgical strategy. *Hum Reprod* 2010;25:665–671.

Guerriero S, Ajossa S, Gerada M, Virgilio B, Angioni S, Melis GB. Diagnostic value of transvaginal 'tenderness-guided' ultrasonography for the prediction of location of deep endometriosis. *Hum Reprod* 2008;23:2452–2457.

Haggag H, Solomayer E, Juhasz-Böss I. The treatment of rectal endometriosis and the role of laparoscopic surgery. Curr Opin Obstet Gynecol 2011;**23**:278–282.

Hudelist G, Tuttlies F, Rauter G, Pucher S, Keckstein J. Can transvaginal sonography predict infiltration depth in patients with deep infiltrating endometriosis of the rectum? Hum Reprod 2009;**24**:1012–1017.

Jacobson TZ, Duffy JM, Barlow D, Koninckx PR, Garry R. Laparoscopic surgery for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 2009:CD001300.

Jerby BL, Kessler H, Falcone T, Milson JW. Laparoscopic management of colorectal endometriosis. Surg Endosc 1999;**13**:1125–1158.

Jess T, Frisch M, Jørgensen KT, Pedersen BV, Nielsen NM. Increased risk of inflammatory bowel disease in women with endometriosis: a nationwide Danish cohort study. Gut 2012;**61**:1279–1283.

Kamergorodsky G, Ribeiro PA, Galvão MA, Abrão MS, Donadio N, Lemos NL, Aoki T. Histologic classification of specimens from women affected by superficial endometriosis, deeply infiltrating endometriosis, and ovarian endometriomas. Fertil Steril 2009;**92**:2074–2077.

Kavallaris A, Köhler C, Kühne-Heid R, Schneider A. Histopathological extent of rectal invasion by rectovaginal endometriosis. Hum Reprod 2003;**18**:1323–1327.

Keckstein J, Wiesinger H. Deep endometriosis, including intestinal involvement—the interdisciplinary approach. Minim Invasive Ther Allied Technol 2005;**14**:160–166.

Koninckx PR, Ussia A, Adamyan L, Wattiez A, Donnez J. Deep endometriosis: definition, diagnosis, and treatment. Fertil Steril 2012;**98**:564–571.

Laas E, Zacharopoulou C, Montanari G, Seracchioli R, Abrão MS, Bassi MA, Ballester M, Daraï E. External validation of the SF-36 quality-of-life questionnaire in Italian and Brazilian populations to select patients with colorectal endometriosis for surgery. J Minim Invasive Gynecol 2014;**46:50**:308–302.

Landi S, Ceccaroni M, Perutelli A, Allodi C, Barbieri F, Fiaccavento A, Ruffo G, McVeigh E, Zanolla L, Minelli L. Laparoscopic nerve-sparing complete excision of deep endometriosis: is it feasible? Hum Reprod 2006;**21**:774–781.

Lazzeri L, Di Giovanni A, Exacoustos C, Tosti C, Pinzauti S, Malzoni M, Petraglia F, Zupi E. Preoperative and postoperative clinical and transvaginal ultrasound findings of adenomyosis in patients with deep infiltrating endometriosis. Reprod Sci 2014;**21**:1027–1033.

Li HJ, Leng JH, Lang JH, Wang HL, Liu ZF, Sun DW, Zhu L, Ding XM. Correlative factors analysis of recurrence of endometriosis after conservative surgery. Zhonghua Fu Chan Ke Za Zhi 2005;**40**:13–16.

Littman E, Giudice L, Lathi R, Berker B, Milki A, Nezhat C. Role of laparoscopic treatment of endometriosis in patients with failed in vitro fertilization cycles. Fertil Steril 2005;**84**:1574–1578.

Maas K, Moriya Y, Kenter G, Trimbos B, van de Velde C. A plea for preservation of the pelvic autonomic nerves. Lancet 1999;**354**:772–773.

Mabrouk M, Montanari G, Guerrini M, Villa G, Solfrini S, Vicenzi C, Mignemi G, Zannoni L, Frasca C, Di Donato N et al. Does laparoscopic management of deep infiltrating endometriosis improve quality of life? A prospective study. Health Qual Life Outcomes 2011;**9**:98.

Mangler M, Loddenkemper C, Lanowska M, Bartley J, Schneider A, Köhler C. Histopathology-based combined surgical approach to rectovaginal endometriosis. Int J Gynaecol Obstet 2008;**103**:59–64.

Mechsner S, Weichbrodt M, Riedlinger WF, Kaufmann AM, Schneider A, Köhler C. Immunohistochemical evaluation of endometriotic lesions and disseminated endometriosis-like cells in incidental lymph nodes of patients with endometriosis. Fertil Steril 2010;**94**:457–463.

Meuleman C, d'Hoore A, Van Cleynenbreugel B, Beks N, d'Hooghe T. Outcome after multidisciplinary CO2 laser laparoscopic excision of deep infiltrating colorectal endometriosis. Reprod Biomed Online 2009;**18**:282–289.

Meuleman C, Tomassetti C, D'Hoore A, Van Cleynenbreugel B, Penninckx F, Vergote I, D'Hooghe T. Surgical treatment of deeply infiltrating endometriosis with colorectal involvement. Hum Reprod Update 2011;**17**:311–326.

Meuleman C, Tomassetti C, Wolthuis A, Van Cleynenbreugel B, Laenen A, Penninckx F, Vergote I, D'Hoore A, D'Hooghe T. Clinical outcome after radical excision of moderate-severe endometriosis with or without bowel resection and reanastomosis: a prospective cohort study. Ann Surg 2014;**259**:522–531.

Minelli L, Fanfani F, Fagotti A, Ruffo G, Ceccaroni M, Mereu L, Landi S, Pomini P, Scambia G. Laparoscopic colorectal resection for bowel endometriosis: feasibility, complications, and clinical outcome. Arch Surg 2009;**144**:234–239.

Moawad NS, Caplin A. Diagnosis, management, and long-term outcomes of rectovaginal endometriosis. Int J Womens Health 2013;**5**:753–763. Review.

Moawad NS, Guido R, Ramanathan R, Mansuria S, Lee T. Comparison of laparoscopic anterior discoid resection and laparoscopic low anterior resection of deep infiltrating rectosigmoid endometriosis. JSLS 2011;**15**:331–338.

Mohr C, Nezhat FR, Nezhat CH, Seidman DS, Nezhat CR. Fertility consideration in laparoscopic treatment of infiltrative bowel endometriosis. J Soc Laparosc Surg 2005;**9**:16–24.

Nirgianakis K, McKinnon B, Imboden S, Knabben L, Gloor B, Mueller MD. Laparoscopic management of bowel endometriosis: resection margins as a predictor of recurrence. Acta Obstet Gynecol Scand 2014;**93**:1262–1267.

Noël JC, Chapron C, Fayt I, Anaf V. Lymph node involvement and lymphovascular invasion in deep infiltrating rectosigmoid endometriosis. Fertil Steril 2008;**89**:1069–1072.

Noël JC, Chapron C, Bucella D, Buxant F, Peny MO, Fayt I, Borghese B, Anaf V. Estrogen and progesterone receptors in smooth muscle component of deep infiltrating endometriosis. Fertil Steril 2010;**93**:1774–1747.

Oliveira MA, Crispi CP, Oliveira FM, Junior PS, Raymundo TS, Pereira TD. Double circular stapler technique for bowel resection in rectosigmoid endometriosis. J Minim Invasive Gynecol 2014;**21**:136–141.

Pagidas K, Falcone T, Hemmings R, Miron P. Comparison of reoperation for moderate (stage III) and severe (stage IV) endometriosis-related infertility with in vitro fertilization-embryo transfer. Fertil Steril 1996;**65**:791–795.

Panebianco V, Poli A, Blandino R, Pistritto A, Puzzo L, Grasso A, Petino AG. Low anterior resection of the rectum using mechanical anastomosis in intestinal endometriosis. Minerva Chir 1994;**49**:215–217.

Pereira RM, Zanatta A, Preti CD, de Paula FJ, da Motta EL, Serafini PC. Should the gynecologist perform laparoscopic bowel resection to treat endometriosis? Results over 7 years in 168 patients. J Minim Invasive Gynecol 2009;**16**:472–479.

Piketty M, Chopin N, Dousset B, Millischer-Bellaische AE, Roseau G, Leconte M, Borghese B, Chapron C. Preoperative work-up for patients with deeply infiltrating endometriosis: transvaginal ultrasonography must definitely be the first-line imaging examination. Hum Reprod 2009;**24**:602–607.

Possover M, Diebolder H, Plaul K, Schneider A. Laparoscopically assisted vaginal resection of rectovaginal endometriosis. Obstet Gynecol 2000;**96**:304–307.

Possover M, Quakernack J, Chiantera V. The LANN technique to reduce postoperative functional morbidity in laparoscopic radical pelvic surgery. J Am Coll Surg 2005; **201**:913–917.

Pronio A, Di Filippo A, Narilli P, Mancini B, Caporilli D, Piroli S, Vestri A, Montesani C. Anastomotic dehiscence in colorectal surgery. Analysis of 1290 patients. Chir Ital 2007;**59**:599–609.

Razzi S, Luisi S, Calonaci F, Altomare A, Bocchi C, Petraglia F. Efficacy of vaginal danazol treatment in women with recurrent deeply infiltrating endometriosis. Fertil Steril 2007;**88**:789–794.

Redwine DB, Wright JT. Laparoscopic treatment of complete obliteration of the cul-de-sac associated with endometriosis: long-term follow-up of en bloc resection. Fertil Steril 2001;**76**:358–365.

Reich H. Laparoscopic surgery for bowel endometriosis. Surg Technol Int 1997; **6**:199–206.

Remorgida V, Ragni N, Ferrero S, Anserini P, Torelli P, Fulcheri E. How complete is full thickness disc resection of bowel endometriotic lesions? A prospective surgical and histological study. Hum Reprod 2005;**20**:2317–2320.

Remorgida V, Ferrero S, Fulcheri E, Ragni N, Martin DC. Bowel endometriosis: presentation, diagnosis, and treatment. Obstet Gynecol Surv 2007;**62**:461–470. Review.

Rocha AL, Reis FM, Petraglia F. New trends for the medical treatment of endometriosis. Expert Opin Investig Drugs 2012;**21**:905–919.

Roman H, Loisel C, Resch B, Tuech JJ, Hochain P, Leroi AM, Marpeau L. Delayed functional outcomes associated with surgical management of deep rectovaginal endometriosis with rectal involvement: giving patients an informed choice. Hum Reprod 2010;**25**:890–899.

Roman H, Tuech JJ. Laparoscopic and transanal excision of large lower- and mid-rectal deep endometriotic nodules: the Rouen technique. Fertil Steril 2014a;**102**:e7.

Roman H, Tuech JJ. New disc excision procedure for low and mid rectal endometriosis nodules using combined transanal and laparoscopic approach. Colorectal Dis 2014b; **16**:O253–256.

Roman H, Vassilieff M, Gourcerol G, Savoye G, Leroi AM, Marpeau L, Michot F, Tuech JJ. Surgical management of deep infiltrating endometriosis of the rectum: pleading for a symptom-guided approach. Hum Reprod 2011;**26**:274–281.

Roman H, Ness J, Suciu N, Bridoux V, Gourcerol G, Leroi AM, Tuech JJ, Ducrotté P, Savoye-Collet C, Savoye G. Are digestive symptoms in women presenting with