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REVIEW *Gynaecology*

Medical treatment for rectovaginal endometriosis: what is the evidence?

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BACKGROUND: Rectovaginal endometriosis usually causes distressing pain. Surgical treatment may be effective but is associated with a high risk of morbidity and major complications. Information on the effect of medical alternatives for pain relief in this condition is scarce.

METHODS: A comprehensive literature search was conducted to identify all the English language published observational and randomized studies evaluating the efficacy of medical treatments on pain associated with rectovaginal endometriosis. A combination of keywords was used to identify relevant citations in PubMed, MEDLINE and EMBASE.

RESULTS: A total of 217 cases of medically treated rectovaginal endometriosis were found; 68 in five observational, non-comparative studies, 59 in one patient preference cohort study, and 90 in a randomized controlled trial. An aromatase inhibitor was used in two of the non-comparative studies, vaginal danazol in one, a GnRH agonist in one, and an intrauterine progestin in one. Two estrogen–progestin combinations used transvaginally or transdermally were evaluated in the patient preference study, whereas an oral progestin and an estrogen–progestin combination were compared in the randomized controlled trial. With the exception of an aromatase inhibitor used alone, the antalgic effect of the considered medical therapies was high for the entire treatment period (from 6 to 12 months), with 60–90% of patients reporting considerable reduction or complete relief from pain symptoms.

CONCLUSIONS: Despite problems in interpretation of data, the effect of medical treatment in terms of pain relief in women with rectovaginal endometriosis appear substantial.

Key words: rectovaginal endometriosis / chronic pelvic pain / dysmenorrhoea / dyspareunia / medical treatment

Introduction

Endometriosis is definitely the most frequent cause of pelvic pain in women of reproductive age (Vercellini, 1997a) and may cause prolonged suffering and disability, negatively affecting health-related quality of life (Gao *et al*., 2006; Bianconi *et al*., 2007). In particular, endometriosis infiltrating the posterior vaginal and anterior rectal walls usually causes symptoms such as disabling dysmenorrhea, deep dyspareunia limiting sexual activity and severe dyschezia (Vercellini *et al*., 1996). Several conservative surgical techniques have been proposed to deal with this technically demanding condition (Vercellini *et al*., 2009b). Incomplete lesion resection generally does not achieve pain relief, whereas radical interventions carry the risk of major complications, and ureteral and rectal injuries with associated sequelae are not uncommon (Fedele *et al*., 2004a; Koninckx *et al*., 1996; Vercellini *et al*., 2004, 2009b, 2009d).

Current practice erroneously takes for granted that medical treatments are not effective for rectovaginal endometriosis (Ford *et al*., 2004; Vercellini *et al*., 2004). This unchallenged belief, based on a reportedly different receptor pattern from eutopic endometrium (Ford *et al*., 2004), leads to the biased conclusion that surgery is the only reasonable therapeutic choice, and thus exposes women to potentially severe morbidity, especially if procedures are performed by gynaecologists not specifically trained in this difficult and technically demanding field (Carter, 2003). This clinical approach should be challenged, as good results are also obtainable with drugs for these patients, provided bowel and ureteral stenosis or adnexal masses with doubtful characteristics are ruled out, because estrogen and progesterone receptors are indeed normally expressed in deeply infiltrating endometriotic lesions (Noël *et al*., 2009).

Along this line, the Practice Committee of the American Society for Reproductive Medicine (2008) has recently stated that 'endometriosis

should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures'.

Because information on pharmacological therapy for symptomatic rectovaginal endometriosis is scarce, we considered it of interest to search for and analyse data on this issue that had been published in scientific literature over the last 20 years in order to obtain an overall estimate of its efficacy. The main purpose of the present systematic review was to assess the effect of different drugs with diverse action mechanisms on pelvic pain symptoms associated specifically with this deeply infiltrating disease form.

Materials and Methods

The present literature overview was conducted according to a protocol based on the MOOSE guidelines for systematic reviews of observational studies (Stroup *et al*., 2000). Since published, de-identified data were used, the present study was exempt from Institutional Review Board approval.

Sources

An electronic database search (EMBASE, MEDLINE, PubMed) was performed with the objective of identifying all observational studies and randomized controlled trial (RCTs) published in the English language between January 1989 and March 2009 on the effect of medical treatments on pain associated with rectovaginal endometriosis. Combinations of medical subject heading terms including 'deep endometriosis', 'deeply infiltrating endometriosis', 'rectovaginal endometriosis', 'pelvic pain', 'medical therapy/treatment', 'danazol', 'gestrinone', 'GnRH agonists', 'progestins', 'oral contraceptives' and 'aromatase inhibitors' were used. All pertinent articles were retrieved and the relative reference lists were systematically reviewed in order to identify further reports that could be included in the overview. Moreover, review articles, books and monographs published on endometriosis were consulted and their reference lists were searched for any potential additional studies. No attempt was made to identify unpublished studies.

Study selection

Two authors (N.B. and G.B.) performed an initial screening of the title and abstract of all articles to exclude citations deemed irrelevant by both observers (e.g. if only women without rectovaginal endometriotic lesions were evaluated). Studies were excluded if *ad interim* results were reported in advance of an available later full report. Abstracts and proceedings of scientific meetings were not included (e.g. Igarashi *et al*., 1997). Articles were selected according to the following inclusion criteria: diagnosis of rectovaginal endometriosis (either as a primary or recurrent lesion) based on, as a minimum, vaginal and rectal examination, transvaginal and/or transrectal ultrasonography, and biopsy with histologic confirmation; treatment with drugs only without concomitant surgical procedures except biopsy; definition of type of symptoms at baseline as well as measurement of pain variation during the study period by means of visual analogue (VAS) or verbal rating (VRS) scales. Studies on combination of surgical and immediate post-operative adjuvant treatment were not included, whereas we considered reports on medical therapy also when persistent or recurrent rectovaginal endometriosis was diagnosed after previous failed attempts at surgical removal.

Data extraction

Reports were categorized based on research design into observational studies and RCTs. The year of publication, location, setting, study design, number and clinical characteristics of recruited subjects, modality of diagnosis, and type and schedule of medical treatment were recorded. The numbers of patients with pain at baseline and at the end of follow-up, as well as symptom variations during the study period were obtained from individual studies. Methodological quality of the considered studies was classified as limited, moderate or adequate based on design and internal validity. The two observers independently evaluated all articles and abstracted data into standardized forms. A final abstraction form was compiled from the two evaluation forms, with correction or resolution of any discrepancies between reviewers by consensus reached after discussion or arbitration by a third reviewer (P.V.).

Results

Figure 1 shows the flow diagram of the literature search results. The EMBASE, MEDLINE and PubMed search identified 189 articles of which 16 abstracts reported findings on medical treatments for rectovaginal endometriosis; these articles were retrieved for detailed assessment. After reviewing the reference lists, another study was identified. No other studies were found from search of reference list of books and monographs. Of the 17 studies found, three were excluded because no original data were described (Vercellini *et al*., 2004; Emmanuel and Davis, 2005; Ferrero *et al*., 2008), two were excluded because no subjects with deeply infiltrating lesions were included (Coutinho and Azadian-Boulanger, 1988; Mizutani *et al*., 1995), one was excluded because figures on pain variation were not

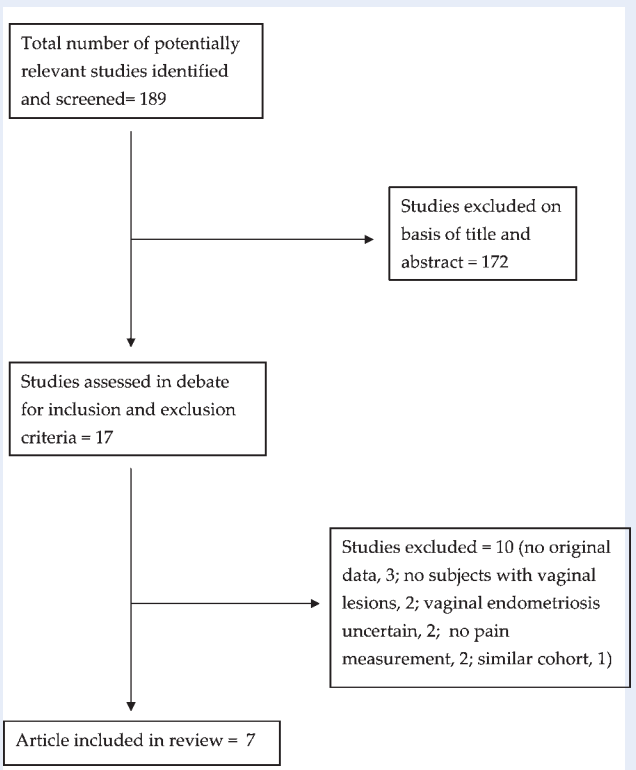

Figure 1 Study selection flow chart.

presented (Mizutani *et al.*, 1999), and another was excluded because it reported preliminary analyses on a similar cohort in advance of a later report (Igarashi, 1990).

Complete reviewer agreement regarding inclusion and exclusion of studies was achieved with the exception of the reports by Koskimies *et al.* (1984), Igarashi *et al.* (1998) and Matsuzaki *et al.* (2007). In the first study (Koskimies *et al.*, 1984) oral danazol 600 mg/day was prescribed to six patients with vaginal endometriosis for 6 months, with an objectively determined reduction of the endometriotic lesions. This article was excluded because the main outcome was likelihood of conception after drug withdrawal and no data were reported on pain assessment and variation. In the second study (Igarashi *et al.*, 1998) a vaginal ring delivering danazol locally was used in 42 patients with deeply infiltrating endometriosis. This article was excluded because the diagnosis of rectovaginal endometriosis was undefined and no instrument for pain measurement was adopted. In the third study (Matsuzaki *et al.*, 2007) a GnRH agonist ($n = 8$) and an oral progestin/progesterone ($n = 8$) were used preoperatively for >4 months in symptomatic patients with deeply infiltrating endometriosis. Although pain was measured at baseline and during treatment by means of a visual analog scale, neither the type nor the dose of the GnRH agonist and of the progestin was indicated. In addition, it was unclear if progesterone or a progestin was used. Finally, it was uncertain if women with definite vaginal lesions were recruited. This article was eventually excluded after discussion and arbitration by the third reviewer.

Data on the effect of medical treatment of pain associated with rectovaginal endometriosis were extracted from the remaining seven articles, all published in full in peer-review journals between 2000 and 2009. Five were observational, non-comparative studies (Fedele *et al.*, 2000, 2001; Hefler *et al.*, 2005; Razzi *et al.*, 2007; Remorgida *et al.*, 2007b), one was a patient preference cohort study in which part of the recruited subjects had vaginal lesions (Vercellini *et al.*, 2009a), and one was a RCT (Vercellini *et al.*, 2005a). Details of the characteristics of the selected studies are shown in Table I. Six studies were conducted in Italy, and one in Austria (Hefler *et al.*, 2005). A total of 217 cases of medically treated rectovaginal endometriosis were found, 68 in observational, non-comparative studies, 59 in the patient preference cohort study, and 90 in the RCT. The number of subjects enrolled in non-comparative studies ranged from 9 to 21. The women were all premenopausal. Generally, patients reported moderate or severe pelvic pain, and women with mild pain were also recruited in one study (Hefler *et al.*, 2005). Histological confirmation of endometriosis was reported in all studies. The rectovaginal lesion was assessed by transvaginal and/or transrectal ultrasonography in all studies, and by MRI in four.

An aromatase inhibitor was used in two of the observational, non-comparative studies (vaginal anastrozole suppository and oral letrozole in combination with an oral progestin), a GnRH agonist in one, a progestin in one [a levonorgestrel-releasing intrauterine device (LNG-IUD)], and danazol in one (danazol-containing vaginal capsules). Two estrogen–progestin combinations used transvaginally (ring) or transdermally (patch) were evaluated in the patient preference study, whereas an oral progestin and an estrogen–progestin combination were compared in the RCT.

The quality of the evidence provided was unanimously estimated as limited for the five observational, non-comparative studies, moderate for the patient preference cohort study, and adequate for the RCT. The main results observed in the selected studies are shown in Table II.

Table I Summary of study characteristics and interventions from individual reports included in systematic review of medical treatments for rectovaginal endometriosis

Author	Year	Study design	No. of subjects	Diagnostic modality	Intervention	Duration of treatment	Criteria for pain evaluation
Fedele *et al.*	2000	Prospective non-comparative	15	US, MRI, histology	Leuprolide acetate 3.75 mg i.m./28 day	6 months	VRS
Fedele *et al.*	2001	Prospective non-comparative	11	US, MRI, histology	Levonorgestrel-releasing IUD	12 months	VRS
Hefler *et al.*	2005	Prospective non-comparative	9	US, MRI, histology	Vaginal anastrozole 0.25 mg/day	6 months	VAS
Vercellini *et al.*	2005a	Randomized controlled trial	90	US, histology	Ethinyl estradiol 0.01 mg + cyproterone acetate 3 mg/day versus norethindrone acetate 2.5 mg/day per os	12 months	VAS and VRS
Razzi *et al.*	2007	Prospective non-comparative	21	US, histology	Vaginal danazol 200 mg/day	12 months	VRS
Remorgida *et al.*	2007b	Prospective non-comparative	12	US, MRI histology	Oral letrozole 2.5 mg/day plus 2.5 mg/day norethisterone acetate	6 months	VAS
Vercellini *et al.*	2009a	Patient preference study	59*	US, histology	Vaginal ethinylestradiol 0.015 mg + etonogestrel 0.12 mg/day versus transdermal ethinyl estradiol 0.02 mg + norelgestromin 0.15 mg/day	12 months	VAS and VRS

VAS = visual analogue scale; US = ultrasonography; MRI = magnetic resonance imaging; IUD = intrauterine device; VRS = verbal rating scale.
*Only subjects with rectovaginal endometriosis are considered.

Non-comparative studies

Gonadotrophin-releasing hormone agonist

Fedele *et al*. (2000) evaluated the effect of treatment with leuprolide acetate, 3.75 mg i.m./28 days for 6 months, in 15 women with symptomatic rectovaginal endometriosis, previously operated without excision of the deeply infiltrating lesion. At the end of therapy, dysmenorrhoea was abolished by induced amenorrhoea, non-cyclic pain persisted in only one subject in mild form, and deep dyspareunia varied from mild in three cases, moderate in eight, and severe in three at baseline, to mild in 11 subjects and moderate in two at 6-month treatment. Two women underwent surgery during medical therapy because of persisting severe pain, and another seven patients were operated during the 12-month follow-up period due to symptoms recurrence.

Levonorgestrel-releasing intrauterine device

To evaluate the effectiveness of the LNG-IUD as a therapy for rectovaginal endometriosis, Fedele *et al*. (2001) recruited 11 symptomatic women who had previously undergone conservative surgery without excision of deep lesions and assessed variations in pain symptoms and size of plaques.

At 1-year follow-up, nine women were oligomenorrhoeic and two experienced amenorrhoea; dysmenorrhoea, which had been moderate or severe in all cases, and non-menstrual pelvic pain were absent. Of notable interest was the reduction of deep dyspareunia, which had been moderate or severe in eight cases prior to IUD insertion, to absent or mild in all subjects throughout treatment. Dyschezia was relieved in four out of five women by the sixth month of treatment.

Transrectal ultrasonography showed a slight but significant reduction of rectovaginal lesions after 6 months of therapy. The use of the LNG-IUD was associated with headaches in four patients; breast tenderness in four; seborrhoea, oily hair, or acne in three; and weight increase in four.

Aromatase inhibitors

Hefler *et al*. (2005) administered anastrozole, 0.25 mg/day in a vaginal suppository for 6 months, to nine premenopausal women with histologically demonstrated rectovaginal endometriosis. A statistically significant reduction in dysmenorrhoea VAS score, of questionable clinical importance, was observed. Of note, mean menstrual pain at baseline was unusually low (3.6 cm) for these generally highly symptomatic patients. Dyspareunia and number of days on analgesic medications remained unchanged. The rectovaginal lesion regressed in three subjects, did not vary in three, and progressed in three. Mean (SD) estradiol serum level during treatment was 148 (68) pg/ml. Physical and social functioning, as assessed by the Short Form-36 questionnaire (SF-36), improved during the study period. Three women (33%) eventually underwent surgery after drug withdrawal.

Remorgida *et al*. (2007b) reported the results of a double drug regimen including the aromatase inhibitor letrozole (2.5 mg/day per os) and norethisterone acetate (2.5 mg/day per os) in 12 women with histologically diagnosed rectovaginal endometriosis. After 6 months of treatment, dysmenorrhoea, deep dyspareunia and chronic pelvic pain were significantly reduced, but recurred promptly after drug withdrawal. Significant improvement in health-related quality of life was observed during therapy in physical and emotional role limitations, mental health and social functioning SF-36 subscales. Five patients (42%) underwent surgery after 7 ± 5 months from completion of medical treatment due to recurrence of pain symptoms and lesion persistence, thus confirming that aromatase inhibitors do not 'cure' endometriotic foci. Moreover, the adoption of a double-drug regimen impedes an accurate estimate of the specific role of letrozole in improvement of pain symptoms.

Danazol

Razzi *et al*. (2007) treated 21 patients with post-operative persistence of deeply infiltrating rectovaginal endometriosis with vaginal danazol capsules, 200 mg/day for 12 months. Pain symptoms were consistently and significantly relieved during therapy, including five cases with dyschezia. Vaginal irritation was the main side effect reported by four women. Interestingly, the entire group of subjects remained regularly menstruating for the entire study period. Unfortunately, data on serum gonadotrophin, estradiol and progesterone levels were not reported. Metabolic and coagulative parameters did not vary significantly.

Patient preference cohort study

Very recently Vercellini *et al*. (2009a) evaluated the efficacy and tolerability of a contraceptive vaginal ring and transdermal patch in the treatment of endometriosis-associated pain. A total of 207 women with recurrent moderate or severe symptoms after conservative surgery were recruited and offered continuous, 12-month treatment with a vaginal ring supplying 0.015 mg of ethinyl estradiol and 0.12 mg of etonogestrel per day or a transdermal system delivering 0.02 mg of ethinyl estradiol and 0.15 mg norelgestromin per day. Treatment assignment of the two systems was based on patient preference.

Of the 59 patients with rectovaginal lesion, 38 chose the ring and 21 the patch. The ring was more effective than the patch in terms of pain reduction. In the former group, dysmenorrhoea was moderate in 9 (32%) cases and severe in 19 (68%) at baseline, and mild in 8 (29%) and moderate in 2 (7%) at the end of treatment. Corresponding figures in the transdermal patch group were mild, 3 (27%), moderate, 4 (36%), and severe, 4 (36%) at baseline, and mild, 3 (27%), moderate, 3 (27%), and severe, 1 (9%) at 12-month therapy, with a statistically significant difference in favour of the ring. Also deep dyspareunia decreased substantially. At baseline it was mild in 7 (26%) subjects in the ring group and in 3 (27%) in the patch group, moderate in, respectively, 14 (52%) and 2 (18%), and severe in 2 (7%) and 2 (18%). At completion of study dyspareunia was moderate in only 3 (11%) subjects using the ring, and mild in 5 (46%) and moderate in 3 (27%) in those wearing the patch. None of the patients reported moderate or severe non-cyclic pelvic pain at 12-month evaluation.

Patients who preferred the ring were significantly more likely to be satisfied and to comply with treatment than those who chose the patch. According to an intention-to-treat analysis, 30/38 (79%) patients in the vaginal ring group and 12/21 (57%) in the transdermal patch group were satisfied with the treatment received. Both systems were associated with poor bleeding control when used continuously.

Table II Main results of individual studies included in systematic review of medical treatments for rectovaginal endometriosis

Author	Year		Pain at baseline*	Pain during treatment*	Quality of life during treatment (instrument)	Satisfaction with treatment (%)	Mean lesion size pretreatment	Mean lesion size end of treatment
Fedele *et al.*	2000	Dysmenorrhoea	2.7 (0.5)‡	0	N.A.	N.A.	1.9 ml	1.7 ml
		Dyspareunia	2.0 (0.7)	1.2 (0.4)				
		Pelvic pain	2.1 (0.8)	0.8 (0.3)				
Fedele *et al.*	2001	Dysmenorrhoea	2.7 (0.5)‡	0	N.A	N.A.	1.6 ml	1.2 ml
		Dyspareunia	1.9 (0.9)	0.5 (0.5)				
		Pelvic pain	0.8 (1.0)	0				
Hefler *et al.*	2005	Dysmenorrhoea	3.6 (1.9)†	3.1 (1.6)	Improved (SF-36)	N.A.	4.2 ml	4.2 ml
Vercellini *et al.*	2005a EE+CPA							
		Dysmenorrhoea	72 (17)†	9 (21)	N.A	28/45 (62)	3.1 ml	2.2 ml
		Dyspareunia	46 (22)	11 (23)				
		Pelvic pain	52 (24)	25 (28)				
		Dyschezia	53 (16)	10 (17)				
	NETA							
		Dysmenorrhoea	76 (18)	3 (11)		33/45 (73)	3.0 ml	1.9 ml
		Dyspareunia	51 (25)	14 (23)				
		Pelvic pain	57 (24)	14 (21)				
		Dyschezia	53 (22)	7 (14)				
Razzi *et al.*	2007	Dysmenorrhoea	2.6 (0.5)‡	0.2 (0.3)	N.A.	N.A.	3.1 ml	1.2 ml
		Dyspareunia	1.9 (0.8)	0.1 (0.3)				
		Pelvic pain	1.8 (0.4)	0				
Remorgida *et al.*	2007b	Dysmenorrhoea	8.8 (1.0)†	3.7 (2.2)	Improved (SF-36)	N.A.	N.R.	N.R.
		Dyspareunia	7.6 (1.5)	2.2 (2.0)				
		Pelvic pain	5.6 (0.9)	2.4 (1.6)				
Vercellini *et al.*	2009a§							
	Vaginal ring							
		Dysmenorrhoea	82 (19)†	17 (21)	N.A	30/38 (79)	N.A.	N.A.
		Dyspareunia	71 (12)	30 (19)				
		Pelvic pain	65 (14)	20 (18)				
	Transdermal patch							
		Dysmenorrhoea	79 (14)	45 (22)		12/21 (57)		
		Dyspareunia	71 (22)	42 (26)				
		Pelvic pain	64 (16)	22 (22)				

N.A. = not available; N.R. = not reported; SF-36 = short form-36 questionnaire; EE + CPA = ethinylestradiol + cyproterone acetate; NETA = norethindrone acetate.
*Values are mean (SD), †visual analog scale scores, ‡VRS scale scores, §only subjects with rectovaginal endometriotic lesions are considered.

Randomized controlled trial

The only published RCT (Vercellini *et al.*, 2005a) was conducted on 90 women with recurrent moderate or severe pelvic pain after unsuccessful conservative surgery for symptomatic rectovaginal endometriosis, who were allocated to 12-month continuous treatment with oral ethinyl estradiol 0.01 mg plus cyproterone acetate 3 mg/day, or norethisterone acetate 2.5 mg/day. Seven subjects in the ethinyl estradiol plus cyproterone acetate arm and five in the norethisterone acetate arm withdrew due to side effects ($n = 5$), treatment inefficacy ($n = 6$) or loss to follow-up ($n = 1$). At 12 months, dysmenorrhoea, deep dyspareunia, non-menstrual pelvic pain and dyschezia scores were substantially reduced, without major between-group differences. In particular, moderate to severe deep dyspareunia was reported at baseline by 12 women in the ethinyl estradiol and cyproterone acetate group and by 13 women in the norethisterone acetate group. The symptom was not relieved in two subjects in each group. Moderate to severe dyschezia was present before treatment in, respectively, 10 and 15 patients, and regressed under therapy in all cases.

Among the women who completed the study, 17/38 (45%) who took the ethinyl estradiol plus cyproterone acetate combination achieved amenorrhoea compared with 29/40 (72%) given norethisterone acetate. Twenty-one women in the former group and 11 in the latter experienced erratic bleeding episodes (spotting in 14 and 9 subjects, respectively; breakthrough bleeding in seven and two).

Side effects were reported by 16/41 (39%) subjects allocated to ethinyl estradiol plus cyproterone acetate, and by 21/42 (50%) of those taking norethisterone acetate. Both regimens induced minor unfavourable variations in serum lipid profile.

At transrectal ultrasonography, the mean $\pm$ SD volume of rectovaginal plaques dropped from a baseline value of 3.1 ± 1.4 ml in the ethinyl estradiol plus cyproterone acetate group and of 3.0 ± 1.3 ml in the norethisterone acetate group to, respectively, 2.2 ± 1.0 and 1.9 ± 1.1 mL at the end of treatment.

According to an intention-to-treat analysis, 28/45 (62%) patients in the ethinyl estradiol plus cyproterone acetate group and 33/45 (73%) in the norethisterone acetate group were satisfied with the treatment received.

Comment

The present review showed that medical treatment in women with rectovaginal endometriosis was effective in terms of pain relief (Fedele *et al.*, 2000, 2001; Vercellini *et al.*, 2005a, 2009a; Razzi *et al.*, 2007; Remorgida *et al.*, 2007b), lesion reduction during therapy (Fedele *et al.*, 2000, 2001; Vercellini *et al.*, 2005a; Razzi *et al.*, 2007), improvement in health related-quality of life (Hefler *et al.*, 2005; Remorgida *et al.*, 2007b), and patient satisfaction (Vercellini *et al.*, 2005a, 2009a). However, these conclusions are limited by the paucity of published reports, the limited quality of the evidence presented in the non-comparative studies, the small numbers of subjects included in most trials, and the inherent risk of several types of biases. In particular, publication bias may constitute a major drawback, especially when considering case series, which are more prone to over-represent optimistic results. Moreover, several drugs have been used, with various modalities of administration, different dosages and diverse periods of treatment. In addition, therapies were occasionally combined, thus preventing assessment of the effect of specific medications.

It was sometimes unclear whether the recruited subjects were receiving treatment after unsuccessful surgery or if they were primary cases. The possibility that patients with recurrent disease constitute a subgroup with a particularly unfavourable prognosis cannot be excluded. Follow-up data were not available for some studies or referred to markedly different lengths of follow-up, a factor which may be important in a chronic disease with a high incidence of recurrence such as endometriosis. Thus, trying to obtain summary values from this type of report is unwarranted and unfeasible. However, the data included in our analysis were the only available evidence on which to base clinical understanding and therapeutic decision making, and to our knowledge, no systematic review of the data on the use of medical treatments for rectovaginal endometriosis has yet been published.

A thorough literature review was performed, adopting different article search modalities. To avoid major bias in data gathering, these were extracted from the reports of two independent observers, who admittedly were not blinded. Rejected studies and the reasons for their exclusion are described. Moreover, although different terms have been used to define rectovaginal endometriosis (i.e. rectovaginal septum endometriosis; rectovaginal endometriosis; deeply infiltrating endometriosis), the diagnostic modalities adopted, including histologic confirmation, indicate that all subjects recruited in the considered studies suffered from the same type of lesion involving vagina and rectum, and not simply from nodular and fibrotic Douglas foci.

Despite all the problems and difficulties in interpretation, the results of our review suggest that, with the exception of aromatase inhibitors used alone (Hefler *et al.*, 2005), the antalgic effect of the considered medical therapies is high for the entire treatment period (from 6 to 12 months), with 60% (Vercellini *et al.*, 2005a, 2009a) to 90% (Fedele *et al.*, 2001; Razzi *et al.*, 2007) of patients reporting considerable reduction or complete relief from pain symptoms. These estimates probably represent average evidence of the effect of medical intervention in various clinical conditions. The observed differences among various drugs appear limited in clinical terms and, in the absence of formal randomized comparisons, are difficult to interpret.

Considerable relief was obtained also in women experiencing an organic type of pain such as during intercourse or defecation. Dysmenorrhoea is a spontaneous and functional pain whereas deep-thrust dyspareunia and dyschesia are 'elicited' pain that ensue when the posterior fornix is struck during intercourse or when endometriotic rectal nodules are under pressure and stretched due to passage of hard stools (Vercellini *et al.* 1996, 2004; Vercellini, 1997a). The effect on organic symptoms may be due not only to the volumetric reduction of rectovaginal plaques but most probably also to reduced intra- and perilesional inflammation and to reduced production of prostaglandins and cytokines which stimulate pain fibres. However, periodic evaluations should not be reduced as a consequence of symptoms relief, because it cannot be excluded that lesions may progress in spite of decrease in pain.

Many women experienced side effects, but few withdrew because of them. This may be explained by the high degree of motivation of participants due to the severe symptomatology associated with rectovaginal

endometriosis and the awareness that the alternative treatment would have been surgery with the inherent risks and morbidity. Despite favourable results during treatment, pain recurrence was the rule at drug withdrawal and about half of the symptomatic patients evaluated at follow-up eventually underwent surgery (Fedele *et al*., 2000, 2001; Hefler *et al*., 2005; Remorgida *et al*., 2007b).

Some general conclusions on the medical management of symptomatic rectovaginal endometriosis can be drawn based on the evidence reviewed. In addition, individual drugs deserve specific considerations.

First, clarity is needed on the meaning of 'inefficacy' of medical treatment for rectovaginal endometriosis. 'Inefficacy' could be interpreted as lack of pain relief during drug use. In spite of the hypothesized causes for non-response, it has been repeatedly, consistently and definitively demonstrated that hormonal therapies are indeed effective in this form of the disease. However, there is another, more insidious explanation for 'inefficacy', i.e. recurrence of pain symptoms to a degree similar to that at baseline sometime after treatments are discontinued. This interpretation does not take into consideration the very nature of the disease as well as the characteristics of available drugs which, as reported innumerable times, are not cytoreductive. This means that suppression of endometriotic lesions is temporary and that no definitive 'cure' can be expected. Planning follow-up to demonstrate pain relapse at drug withdrawal means monitoring the inevitable. Active endometriosis can be compared with several other chronic inflammatory disorders such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, amongst others. In these conditions, no one would ever interpret recurrence of symptoms at drug interruption as a demonstration of inefficacy of medical therapies.

Accordingly, the second general conclusion is that medical therapies for rectovaginal endometriosis should be conceived in terms of years instead of months of treatment. Due to obvious reasons, periods of observation in a research setting are limited, but this by no means should be translated directly into clinical practice. Women should be counselled in detail on this specific aspect of the therapeutic program in order to increase compliance and avoid inopportune medical intervention in unfavourable circumstances. When patients are aware of the temporary effect of medications, they are in the best position to choose alternatives that best suit their expectations and planning.

Hormonal treatments must not be offered in the presence of obstructive uropathy, symptomatic bowel stenosis and adnexal mass of a doubtful nature. Also women seeking pregnancy should not undergo medical therapy, due to interference with ovulation. Medical therapy is reasonable when patients are delaying conception in the long-term future or choose to undergo IVF thus avoiding spontaneous attempts. The best candidates for long-term medical treatment are subjects not wanting pregnancy and those who have undergone unsuccessful operation. Non-responders, non-compliants, and those who are unwilling to take medications for years even if well tolerated, should consider surgery.

Specific considerations on individual drugs should take into account not only antalgic efficacy, but also safety, tolerability and cost. These issues are of major importance when evaluating the overall benefits of medical therapies for symptomatic rectovaginal endometriosis. Focusing only on pain relief can be misleading because drugs may well alleviate pain but can also be associated with important disadvantages or excessive costs. As an example, GnRH agonists appear unsuitable for long-term treatments when used alone, due to severe metabolic and subjective side effects. Combination with 'add-back' therapies may alleviate untoward consequences, but further increases the already high cost of this class of drugs.

Progestogens and estrogen–progestogen combinations have been repeatedly demonstrated to be safe, well tolerated and effective in the long-term treatment of women with symptomatic endometriosis. The oral route is generally better accepted than intravaginal or intrauterine administration (Vercellini *et al*., 1997b, 2003, 2008, 2009e). Norethisterone acetate (or norethindrone acetate) is a strong progestin derivative of 19-nortestosterone which offers various advantages for the long-term treatment of endometriosis. It allows good control of uterine bleeding as compared with other compounds, has a positive effect on calcium metabolism by producing greater increases in bone mineral density than alendronate, and at low dosages has limited effects on the lipoprotein profile (Riis *et al*., 2002). This may be partly due to the small conversion rate (0.20–0.33%) of norethisterone acetate to ethinyl estradiol (Chu *et al*., 2007). Norethisterone acetate is approved by the Food and Drug Administration and the Italian Ministry of Health for the therapy of endometriosis.

The use of progestins for symptomatic rectovaginal endometriosis is further supported by biological evidence on the essential role of mast cells in promoting inflammation (Kinet, 2007). Specifically, mast cells are involved in a variety of neuroinflammatory diseases, especially those worsened by stress, and sterile inflammatory conditions, such as interstitial cystitis and irritable bowel syndrome, in which pain is a predominant symptom (Theoharides and Cochrane, 2004). Mast cells can be activated by cytokines, growth factors, and hormones, leading to differential release of distinct mediators such as interleukin-6, vascular endothelial growth factor and nerve growth factor (Leon *et al*., 1994; Theoharides *et al*., 2007). In the sterile chronic peritonitis associated with endometriosis, mast cells could sustain inflammation, support neoangiogenesis, promote neurotrophism, sensitise nociceptors and induce neuropathic hyperalgesia. In particular, Anaf *et al*. (2006) demonstrated that deeply infiltrating endometriotic lesions show a significantly higher number of activated mast cells adjacent to sensory fibres compared with peritoneal and ovarian lesions. This abnormal condition may be influenced by progestin treatment, as it has been demonstrated that estradiol activates mast cells (Zaitsu *et al*., 2007), whereas progesterone inhibits their secretion (Vasiadi *et al*., 2006). This is in line with the observation that several disorders associated with mast cells activation ameliorate or subside in pregnancy.

The introduction of aromatase inhibitors in the therapeutic armamentarium for premenopausal patients with endometriosis raises perplexity. In fact, their use inhibits extraovarian estradiol synthesis, but stimulates ovarian estradiol production through FSH surge (Patwardhan *et al*., 2008) and induces cyst formation (Remorgida *et al*., 2007a). In fact, data from the only study reporting the use of an aromatase inhibitor alone (Hefler *et al*., 2005) were the least encouraging. Consequently, these compounds must be combined with additional drugs that effectively down-regulate the ovaries and, in turn, gonadal estradiol biosynthesis (Ailawadi *et al*., 2004; Soysal *et al*., 2004; Remorgida *et al*., 2007a). However, we challenge the hypothesis that suppression of both ovarian and extraovarian estradiol

production would lead to better results or even 'cure'. As an example, the magnitude of the effect of the combination of letrozole and norethisterone acetate (Remorgida *et al*., 2007b) appears substantially similar to that observed with the use of norethisterone acetate alone (Vercellini *et al*., 2005a). The concept itself, of pursuing the deepest possible hypo-estrogenism achievable through drug dosage increase or compound combinations with the objective of eradicating ectopic implants has been repeatedly demonstrated as erroneous: endometrium survives decades of post-menopausal hypo-estrogenism, let alone a few months of non-cytoreductive hypo-estrogenizing drug therapy. Moreover, such hormonal condition is not compatible with long-term treatments. Based on the available information, the combination of an aromatase inhibitor in addition to a standard regimen does not seem an appropriate choice as a first-line treatment for rectovaginal endometriosis.

The identification of safe and effective alternatives to prolong treatment constitutes an essential element in the current clinical research on symptomatic endometriosis. In this regard, the possibility of aiming the therapeutic action of drugs at specific organs, thus reducing general metabolic impact, is a subject of great interest. Three different 'topical' options have been studied in women with rectovaginal endometriosis, namely, danazol-loaded vaginal ring, suppositories and capsules; intrauterine levonorgestrel (as a medicated IUD), and a contraceptive ring releasing an estrogen–progestin combination.

It has been observed that, compared with the oral route, vaginal administration of danazol results in similar uterine and ovarian drug concentrations, but much lower serum levels (Mizutani *et al*., 1995). This seems to constitute the rationale for the treatment of symptomatic rectovaginal endometriosis with vaginal danazol, i.e. local effect with limited systemic absorption. However, it has been reported that this type of treatment does not interfere with ovulation (Igarashi *et al*., 1998; Razzi *et al*., 2007).

Also the use of a LNG-IUD in women with rectovaginal endometriosis may confer some advantages over other conventional systemic therapies, possibly increasing patients' compliance during long-term treatments. The mechanism of action may be a receptor-mediated effect of levonorgestrel that can reach endometriotic foci through blood circulation or direct diffusion from the uterus. Secondary oligoamenorrhoea may also play a role. However, a general effect secondary to uterine absorption of levonorgestrel cannot be excluded, as most reported side effects are typical of progestins. In fact, Lockhat *et al*. (2005) observed high levonorgestrel concentrations in the order of 300–400 pg/ml several months after LNG-IUD insertion and suggest that the progestin released by the IUD is rapidly absorbed by the subendometrial vascular network. Recently, doubts have been expressed on the overall satisfaction and continuation rate in LNG-IUD users due to unscheduled bleeding, lower abdominal pain and progestogenic side effects (Ewies, 2007). Moreover, also the LNG-IUD generally does not inhibit ovulation except in the first few months after insertion.

In light of the above considerations, the use of the LNG-IUD in women with symptomatic rectovaginal endometriosis should be limited to specific circumstances after careful counselling (Vercellini *et al*., 2005b). More data and comparative trials are needed also to confirm the effect on dyspareunia and dyschezia and to verify whether the good results reported are maintained during the entire 5-year period of system efficacy (Bahamondes *et al*., 2007).

Emphasis has been put on the possible direct effect of topical drugs on vaginal endometriotic lesions (Igarashi, 1990; Igarashi *et al*., 1998; Mizutani *et al*., 1995; Fedele *et al*., 2001; Vercellini *et al*., 2009a). However, there is no definitive demonstration of this hypothesis and it cannot be excluded that the systemic effect remains essential for the therapeutic success. In this regard, establishment of anovulation and of a steady hormonal environment with consequent amenorrhoea, may be revealed to be more important than the specific type of steroidal milieu achieved in terms of estrogens and/or progestins serum levels or drug-associated androgenic activity. An indirect demonstration of the above concept is derived from analysis of the results of the two available and included comparative studies (Vercellini *et al*., 2005a, 2009a). In fact, pain relief and satisfaction with treatment were no better with the use of a contraceptive ring delivering an estrogen–progestin combination directly onto vaginal lesions (Vercellini *et al*., 2009a) than with an estrogen–progestin combination or a progestin used orally (Vercellini *et al*., 2005a). Moreover, with the exception of the contraceptive ring, none of the locally acting drugs and systems seems to consistently inhibit ovulation. In theory, this may constitute a specific drawback of these regimens, as it has been demonstrated that ovulation plays a crucial role in the pathogenesis of ovarian endometriomas (Jain and Dalton, 1999; Vercellini *et al*., 2009f) and that ovulation inhibition dramatically reduce the likelihood of endometrioma development (Vercellini *et al*., 2008; Seracchioli *et al*., 2008). Finally, conception during vaginal danazol treatment (Igarashi *et al*., 1998) may be at higher teratogenic risk, if not promptly recognized.

Radical excision of rectovaginal endometriosis is almost invariably a traumatic procedure that entails extensive adhesiolysis, systematic vaginal opening, occasional rectal perforation or incidental resection and wide pelvic deperitonealization (Vercellini *et al*., 2004, 2009b). It is generally associated with post-operative pain reduction, but studies show an unacceptable rise in the number of women sent to referral centres because of relapsing excruciating pain and recurrence or, most probably, persistence of deep, infiltrating lesions after serial surgical procedures (Vercellini *et al*., 2009c). However, some women who have already undergone non-radical interventions might prefer to avoid further surgery and still others may want to postpone the operation or do not accept the risk of morbidity. Medical therapies may be considered for these difficult patients provided that no adnexal masses of doubtful nature, obstructive uropathy or bowel stenosis are present.

As only long-term treatments are strategically sound within this clinical setting, great care should be paid to the choice of drug. The use of aromatase inhibitors alone in premenopausal women is not based on sound rationale and has not been proven effective (Hefler *et al*., 2005). Danazol and GnRH analogues have been used successfully in women with symptomatic deeply infiltrating endometriosis (Fedele *et al*., 2000; Razzi *et al*., 2007), but side-effects and costs usually limit the feasibility of prolonged use. Progestogens, either alone or combined with estrogens, are safe, generally well tolerated, inexpensive, and can be prescribed for extended periods.

The cost in Italy for 12 months of treatment for rectovaginal endometriosis using the various drugs and systems considered in the present systematic review is shown in Table III. In this era of managed care, attention should also be paid to the economic aspects of pharmacologic therapies, especially when there is no

Table III Cost of 12 months of continuous medical treatment of rectovaginal endometriosis; Italy, 2009

Medication	Cost		
	€	£	$
Letrozole 2.5 mg/day*	2104	1868	2713
Anastrozole 1 mg/day*	2046	1817	2638
Depot GnRHagonist	1804–2160	1602–1918	2372–2784
Danazol 600 mg per os/day	821	729	1058
Danazol 200 mg per vaginam/day	274	243	353
Vaginal ring†	233	206	297
Transdermal patch‡	220	195	280
Low-dose monophasic OC§	80–260	71–230	101–331
Levonorgestrel-releasing IUD	38	34	49
Norethisterone acetate 2.5 mg/day**	18	16	22

*Cost probably higher owing to the need for combination with other standard regimens inhibiting ovulation.
**Partly reimbursed by the Italian National Health System with an overall yearly patient cost of €4–£3.6–$6.
†,‡Cost potentially higher owing to the need for system removal/replacement when breakthrough bleeding occurs.
§The least expensive OCs contain 30 μg of EE and are partly reimbursed by the Italian National Health System with an overall yearly patient cost of €18–£16–$28.

convincing demonstration of differences in terms of pain relief and patient satisfaction. The ultimate decision should be shared with the patient and based on her preference. In fact, compliance and adherence are decisive in determining the likelihood of treatment success, as for all chronic inflammatory conditions. Finally, it should be remembered that, although rectovaginal endometriosis is a benign condition with limited tendency to progress (Fedele *et al.*, 2004b), periodic evaluation to exclude silent obstructive uropathy (Carmignani *et al.*, 2009) should be systematically scheduled.

In conclusion, the results of several studies have demonstrated that rectovaginal endometriosis responds to various hormonal compounds and that considerable improvement in pain symptoms can be obtained with medical treatments (Fedele *et al.*, 2000, 2001; Vercellini *et al.*, 2005a, 2009a; Razzi *et al.*, 2007; Remorgida *et al.*, 2007b). All the different therapeutic options for this difficult condition should be described and offered to patients in an unbiased manner. Detailed information on the likelihood and extent of the effect achievable with medical treatment has been introduced in our patient's informed consent form to be signed before operating for this type of lesion. Indeed, women's consent to surgery should no longer be sought based solely on the purported uselessness of pharmacological therapies. Finally, in light of the considerable likelihood of post-operative pain and lesion recurrence (Vercellini *et al.*, 2009c), gynaecologists and patients should be aware that the real choice may not reveal to be between medical treatment and surgery, but instead between medical treatment alone and surgery followed by prolonged pharmacological therapy. However, only the results of an adequately designed randomized trial on hormonal therapy versus excision could definitively disentangle this issue.

Author's Role

P.V. contributed to the conception of the review, prepared the first draft and completed subsequent amendments. P.G.C. contributed to the conception of the review and subsequent amendments. E.S. contributed to the conception of the review and subsequent amendments. N.B. performed the literature search, selected the articles, and abstracted the data. G.B. performed the literature search, selected the articles and abstracted the data. L.F. contributed to the conception of the review and subsequent amendments.

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