Human Reproduction, Vol.25, No.1 pp. 94–100, 2010
Advanced Access publication on October 10, 2009 doi:10.1093/humrep/dep361

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Norethisterone acetate in the treatment of colorectal endometriosis: a pilot study

S. Ferrero[1,5], G. Camerini[2], N. Ragni[1], P.L. Venturini[3], E. Biscaldi[4], and V. Remorgida[1]

[1]Department of Obstetrics and Gynaecology, San Martino Hospital and University of Genoa, Largo R. Benzi 1, 16132 Genoa, Italy [2]Department of Surgery, San Martino Hospital and University of Genoa, Largo R. Benzi 1, 16132 Genoa, Italy [3]Department of Obstetrics and Gynaecology, Institute G. Gaslini, Largo G. Gaslini, 5, 16147 Genoa, Italy [4]Department of Radiology, Galliera Hospital, Via Mura delle Cappuccine 14, 16128 Genoa, Italy

[5]Correspondence address. Tel: +39-010511525; Fax: +39-010511525; E-mail: dr@simoneferrero.com

BACKGROUND: This pilot study evaluates the efficacy of norethisterone acetate in treating pain and gastrointestinal symptoms of women with colorectal endometriosis.

METHODS: This prospective study included 40 women with colorectal endometriosis, who had pain and gastrointestinal symptoms. Patients received norethisterone acetate (2.5 mg/day) for 12 months; in case of breakthrough bleeding, the dose of norethisterone acetate was increased by 2.5 mg/day. The degree of patient satisfaction with treatment (primary end-point) and the changes in symptoms (secondary end-point) were evaluated. Side effects of treatment were recorded.

RESULTS: Norethisterone acetate determined a significant improvement in the intensity of chronic pelvic pain, deep dyspareunia, dyschezia. Treatment determined the disappearance of symptoms related to the menstrual cycle (dysmenorrhea, constipation during the menstrual cycle, diarrhoea during the menstrual cycle and cyclical rectal bleeding). The severity of diarrhoea, intestinal cramping and passage of mucus significantly improved during treatment. On the contrary, the administration of norethisterone acetate did not determine a significant effect on constipation, abdominal bloating and feeling of incomplete evacuation after bowel movements. At the completion of treatment, 57% of the patients with diarrhoea or diarrhoea during the menstrual cycle continued the treatment with norethisterone acetate compared with 17% of the patients with constipation or constipation during the menstrual cycle.

CONCLUSIONS: In some patients with bowel endometriosis, the administration of norethisterone acetate may determine a relief of pain and gastrointestinal symptoms. This therapy has greater benefits in patients with gastrointestinal symptoms related to the menstrual cycle, diarrhoea and intestinal cramping.

Key words: bowel endometriosis / endometriosis / medical therapy / norethisterone acetate / prospective study

Introduction

Bowel endometriosis affects between 4 and 37% of women with endometriosis (Remorgida *et al*., 2007). It may cause a wide range of gastrointestinal complaints, including dyschezia, constipation, diarrhoea and symptoms mimicking irritable bowel syndrome (Ferrero *et al*., 2005; Remorgida *et al*., 2005a; Seracchioli *et al*., 2008). Several studies demonstrated that the surgical excision of bowel endometriotic nodules by either nodulectomy or segmental bowel resection improves pain symptoms, gastrointestinal function and quality of life (Dubernard *et al*., 2006; Daraï *et al*., 2007; Seracchioli *et al*., 2007; Minelli *et al*., 2009; Ferrero *et al*., 2009a). However, the excision of bowel endometriotic lesions infiltrating at least the muscular layer of the bowel wall is associated with the risk of severe complications such as ileostomy, post-operative urinary retention, rectovaginal fistula, iatrogenic ureteral injuries and *de novo* post-operative constipation (Ferrero *et al*., 2006; Ret Dávalos *et al*., 2007; Minelli *et al*., 2009; Ruffo *et al*., in press). In addition, some patients who do not undergo an adequate preoperative work-up may have a diagnosis of bowel endometriosis at the time of laparoscopy and, therefore, bowel surgery cannot be performed because of the lack of adequate preoperative consent or, in some cases, because of inexperience of the gynaecological surgeons in performing this type of procedures. Given this background, some patients with bowel endometriosis without subocclusive symptoms chose to either avoid or postpone surgery.

Medical therapies (particularly progestogens and estro-progestogen combinations) have been repeatedly demonstrated to be safe, well tolerated and effective in the long-term treatment of women with symptomatic endometriosis (Vercellini *et al*., 2009). However, surprisingly, few studies have specifically investigated the effects of hormonal therapies on bowel endometriosis. Gonadotrophin-releasing hormone agonists (GnRH-a) have been used with success in selected cases (Markham *et al*., 1991; Porpora *et al*., 2006); however, the length of treatment with GnRH-a is limited by side effects and bowel symptoms recur when medical therapy is interrupted (Markham *et al*., 1991; Thomassin *et al*., 2004). The administration of hormonal therapies to women with bowel endometriosis may have been limited by the observation that intestinal nodules often contain extensive fibrosis (Remorgida *et al*., 2005b) that might be unresponsive to hormonal manipulation (Remorgida *et al*., 2007).

Progestins are among the most commonly used medical treatments for endometriosis. Norethisterone acetate (or norethindrone acetate) is a strong progestin derivative of 19-nortestosterone. In the 1990s, it was shown to reduce the intensity of pain symptoms determined by pelvic endometriosis (Muneyyirci-Delale and Karacan, 1998). More recently, a randomized prospective study demonstrated that low-dose norethisterone acetate (2.5 mg/day) is effective in reducing the intensity of pain symptoms caused by rectovaginal endometriosis without causing severe adverse effects (Vercellini *et al*., 2005). Norethisterone acetate allows a good control of uterine bleeding as compared with other compounds, has a positive effect on bone metabolism, and at low dosages has limited effects on the lipoprotein profile (Riis *et al*., 2002; Vercellini *et al*., 2009). However, up to now, no study has examined the efficacy of progestins in the treatment of pain and gastrointestinal symptoms caused by bowel endometriosis.

This prospective study aimed to determine the efficacy of norethisterone acetate in treating pain and gastrointestinal symptoms of women with colorectal endometriotic nodules that did not cause subocclusive symptoms.

Materials and Methods

This prospective study included women of reproductive age with a diagnosis of colorectal endometriosis. The study was performed in an academic department specialized in the study and management of endometriosis.

Study population

Subjects of the study were recruited among patients referred to our centre because of persistent pain and gastrointestinal symptoms after prior surgery for endometriosis in other hospitals. In most of the patients, bowel endometriosis was undiagnosed before the diagnostic investigations at our centre.

The diagnosis of colorectal endometriosis was based on multidetector computerized tomography enteroclysis (MDCT-e), which has previously been shown to be accurate in the diagnosis of bowel endometriosis (Biscaldi *et al*., 2007a, b, 2009). The patients included in the study had bowel nodules estimated to infiltrate al least the muscularis propria of the bowel but did not have a stenosis of the bowel lumen greater than 60%. Patients that had additional bowel endometriotic nodules located on the cecum or the ileum were excluded from the study. The presence of colorectal cancer was excluded by colonoscopy before inclusion in the study.

Inclusion criteria for the study were: histological confirmation of pelvic or ovarian endometriosis at previous surgery, persistence of pain and gastrointestinal complains for at least 1 year after prior surgery, willingness to participate in the follow-up for 1 year.

Patients with subocclusive symptoms (such as nausea and vomiting during the menstrual cycle, small-calibre stools) were excluded from the study. Other exclusion criteria for the study were: previous use of norethisterone acetate, use of hormonal therapies for endometriosis in the 3 months before inclusion in the study (6 months for GnRH-a), desire for pregnancy in the 12 months after inclusion in the study, previous bowel surgery (other than appendectomy), infertility treatments in the 3 months before inclusion in the study.

Study design

The study protocol consisted in the administration of norethisterone acetate (Primolut-Nor; Schering, Milan, Italy), 2.5 mg/day, starting on the first day of the menstrual cycle, for 12 months. In case of breakthrough bleeding after 2 months of treatment, the dose of norethisterone acetate was increased by 2.5 mg/day (maximum dose of 5 mg/day).

In the 3 months before starting the use of norethisterone acetate and during the therapy, the patients were allowed to take non-steroidal anti-inflammatory drugs for the treatment of pain (naproxen sodium, 550 mg tablet, Synflex Forte 550, Recordati Industria Chimica e Farmaceutica, Milan, Italy) and lactulose (Laevolac, dose of 10 g per 15 ml, Roche, Milan, Italy) for the treatment of constipation. However, patients were requested to record the doses of these drugs used during the study period.

Subjects of the study were informed that surgery is currently considered the standard treatment of bowel endometriosis and it has been demonstrated to improve symptoms and quality of life (Remorgida *et al*., 2007). The patients were informed that medical treatments are effective in relieving pain symptoms caused by endometriosis, but that pain symptoms often recur to a degree similar to that at baseline after treatments are discontinued (Vercellini *et al*., 2009). Therefore, the administration of a 12-month therapy should not be considered definitively curative of endometriosis. Patients were informed that low-dose norethisterone acetate has previously been demonstrated to significantly reduce the intensity of pain symptoms caused by deep endometriosis (Vercellini *et al*., 2005; Ferrero *et al*., in press); however, they were informed that there is no evidence that this drug is effective in treating symptoms caused by bowel endometriosis. Patients were also informed that norethisterone acetate is approved by the Italian Ministry of Health for the treatment of endometriosis. Finally, patients were counselled regarding the potential side effects of the treatment; they were told that norethisterone acetate might cause irregular uterine bleeding, weight increase and decreased libido (Vercellini *et al*., 2005). The patients accepting to participate to the study signed a written consent form. The study was approved by the local Institutional Review Board.

Evaluation of symptoms

The primary end-point of the study was the degree of patient satisfaction with treatment. The secondary end-point of the study was the evaluation of changes in symptoms during treatment.

The presence of dysmenorrhea, deep dyspareunia, chronic pelvic pain and dyschezia were investigated in all the patients included in the study. The intensity of pain symptoms was rated on a 10 cm visual analogue scale, with the left extreme of the scale representing the absence of pain and the right extreme of the scale indicating the maximal intensity of pain. The presence of the following gastrointestinal symptoms was determined: diarrhoea (more than three bowel movements per day), diarrhoea during the menstrual cycle, constipation (fewer than three bowel movements per week), constipation during the menstrual cycle, abdominal bloating, intestinal cramping, feeling of incomplete evacuation after bowel

movements, passage of mucus in the stool and cyclic rectal bleeding. Patients completed a symptom analogue scale questionnaire (one indicated the absence of the symptom; 10 indicated the highest severity of the symptom) regarding each gastrointestinal symptom. The presence and intensity of symptoms were systematically evaluated before starting the treatment and after 6 and 12 months of treatment; however, the patients were allowed to have additional consultations to discuss the effects of treatment and report side effects.

After the completion of therapy, the women rated the overall degree of satisfaction with their treatment by answering to the following question: 'Taking into consideration the variations in pain symptoms, in overall well-being and quality of life, as well as the adverse effects experienced, if any, how would you define the level of satisfaction with your treatment?' as previously described by other authors (Vercellini *et al*., 2005) and by us (Ferrero *et al*., in press). Answers were based on a 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied). Furthermore, they were asked whether gastrointestinal symptoms changed during treatment with norethisterone acetate. The answers were based on a 7-point Likert scale (significantly worsened, worsened, slightly worsened, unchanged, slightly improved, improved, significantly improved). In addition, patients were asked whether they would continue the treatment after the completion of the study protocol.

Adverse effects experienced during treatment were recorded. Uterine bleeding was defined as spotting (scanty bleeding not requiring usual sanitary protection); breakthrough bleeding (light or moderate bleeding requiring sanitary protection); and metrorrhagia (more than normal menstruation).

Statistical analysis

Variations in grading of symptoms between baseline and follow-up were compared by using the Student's *t* test and the Signed Rank test according to data distribution. Categorical data were analyzed by using the χ^2 test or the Fisher's exact test. $P < 0.05$ was considered statistically significant. Data were archived using Excel 2007 (Microsoft, Redmond, WA, USA) and analysed using Sigma Stat software version 3.5 and SPSS software version 13.0 (SPSS Science, Chicago, IL, USA).

Results

Forty women were included in the study. Table I shows the characteristics of the study population. Among the patients included in the study, 85% ($n = 34$) had dysmenorrhea, 73% ($n = 29$) had chronic pelvic pain, and 68% complained of dyschezia. Thirty-three women were sexually active at the time of the study and 67% ($n = 22$) suffered deep dyspareunia.

Patients who interrupted the treatment were classified as having treatment failure in the evaluation of efficacy of treatment (the primary end-point), but were excluded from the evaluation of symptom course during treatment (secondary end-point). None of the patients was lost during the study period. The diagrammatic flow of the participants is given in Fig. 1.

At the 12-month mark, in the general assessment of the effects of therapy on the symptoms, 4 (10%) women very satisfied, 20 (50%) were satisfied, 8 (20%) were uncertain, 5 (13%) were dissatisfied and 3 (7%) were very dissatisfied. When only changes in gastrointestinal symptoms were considered, 53% (21/40) of the patients declared that the treatment determined some improvements (symptoms significantly improved, improved or slightly improved). In particular, Table II shows that the improvement in gastrointestinal symptoms was significantly higher in patients with diarrhoea than in those with constipation ($P < 0.001$). These analyses included all patients enrolled in the study.

Table I Characteristics of the study population

	***n* = 40**
Age (years, mean ± SD)	33.7 ± 4.4
Diagnosis of bowel endometriosis (before inclusion in the study)	
Laparoscopy and MDCT-e	9 (22%)
MDCT-e	31 (78%)
Location of the bowel endometriotic nodules	
Sigmoid colon	18 (45%)
Rectosigmoid junction	12 (30%)
Rectum	10 (25%)
Previous hormonal treatments	
GnRH analogues	7 (17%)
Oral contraceptive pill	26 (65%)
Vaginal ring (Nuvaring, Organon, Rome, Italy)	9 (23%)
Vaginal danazol (200 mg/day)	2 (5%)

The administration of norethisterone acetate determined a significant improvement in the intensity of chronic pelvic pain, deep dyspareunia and dyschezia (Table III). As expected, treatment determined the disappearance of symptoms related to the menstrual cycle such as dysmenorrhea, constipation during the menstrual cycle, diarrhoea during the menstrual cycle and cyclical rectal bleeding. The severity of diarrhoea, intestinal cramping and passage of mucus significantly improved during treatment (Table III). On the contrary, the administration of norethisterone acetate did not determine a significant effect on constipation, abdominal bloating and feeling of incomplete evacuation after bowel movements.

Two patients interrupted the study protocol before 6-month of therapy; another six patients interrupted the study protocol before 12-month of therapy. Therefore 32 (80%) women completed the study protocol. The reasons for interruption of treatment are shown in Fig. 1. Five women reported breakthrough bleeding after 2 months of treatment and the dose of norethisterone acetate was increased to 5 mg/day. Two of these patients interrupted the treatment because of breakthrough bleeding and other side effects (worsening of constipation in one patient, migraine attacks in the other patient).

Among the patients who completed the study, 78% (25/32) used naproxen sodium at baseline (mean number of naproxen sodium tablets used per patient each month, 7.9 ± 5.3). The mean number (± SD) of naproxen sodium tablets used per patient each month decreased significantly during treatment; it was 3.3 ± 3.1 at 6-month of treatment ($P < 0.001$ when compared with baseline values) and 2.4 ± 2.3 at 12-month of treatment ($P < 0.001$ when compared with baseline values). Fourteen women included in the study used lactulose for the treatment of constipation. The mean number of doses of 10 g of lactulose used per patient each month did not significantly change during the study period: baseline, 9.2 ± 5.9; 6-month of

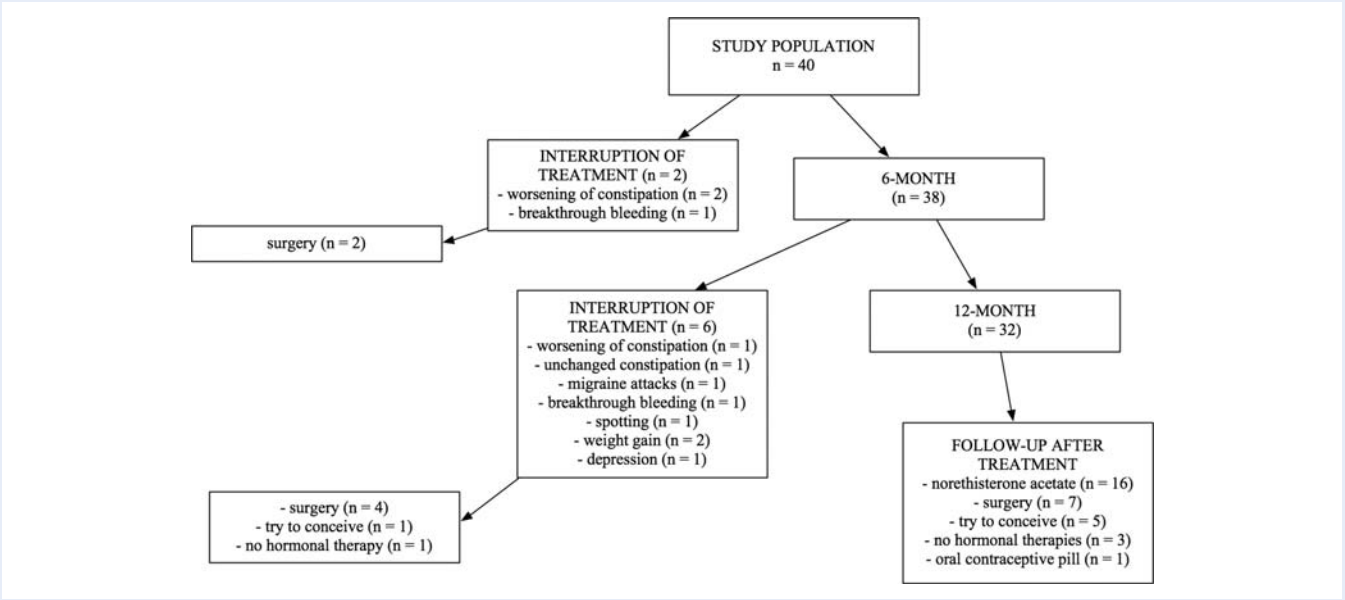

Figure 1 Flow chart showing women's progress through the study.

Table II Judgement of the patients on changes in gastrointestinal symptoms

	Study population (*n* = 40)	Patients with constipation or constipation during the menstrual cycle (*n* = 23)	Patients with diarrhoea or diarrhoea during the menstrual cycle (*n* = 14)
Significantly improved	4 (10%)	0 (0%)	4 (29%)
Improved	15 (38%)	4 (17%)	9 (64%)
Slightly improved	2 (5%)	2 (9%)	1 (7%)
Unchanged	13 (33%)	11 (48%)	0 (0%)
Worsened	4 (10%)	4 (17%)	0 (0%)
Slightly worsened	1 (2%)	1 (4%)	0 (0%)
Significantly worsened	1 (2%)	1 (4%)	0 (0%)

treatment, 9.6 ± 5.2 ($P = 0.542$ when compared with baseline values); 12-month of treatment, 9.8 ± 6.3 ($P = 0.644$ when compared with baseline values).

Thirteen women underwent surgery either after interruption of treatment ($n = 6$) or after completion of the treatment protocol ($n = 7$); in all the cases the presence of colorectal endometriosis was confirmed by surgery and histology.

After the completion of treatment, 16 patients declared that they wished to continue the treatment with norethisterone acetate. In particular, 57% (8/14) of the patients with diarrhoea or diarrhoea during the menstrual cycle continued the treatment with norethisterone acetate versus 17% (4/23) of the patients with constipation or constipation during the menstrual cycle ($P = 0.016$).

Discussion

This prospective study confirms the findings of previous investigations demonstrating that norethisterone acetate is effective in the treatment of pain symptoms related to the presence of deep endometriosis (Muneyyirci-Delale and Karacan, 1998; Vercellini *et al*., 2005; Ferrero *et al*., in press). In addition, the current study demonstrates for the first time that a continuous treatment with norethisterone acetate may improve the gastrointestinal symptoms of some women with colorectal endometriosis. Although 53% of the patients included in the study declared that the therapy determined some improvements in their gastrointestinal symptoms, 60% of the patients reported an overall improvement in the symptoms with the treatment. Interestingly, the administration of norethisterone acetate was effective in improving dyschezia, diarrhoea, and intestinal cramping, but it had no significant effect on constipation, feeling of incomplete evacuation and abdominal bloating (Table III).

Norethisterone acetate obviously does not represent a definitive treatment of deep endometriosis (Vercellini *et al*., 2009) and, in fact, intestinal endometriotic nodules persisted during treatment and were observed in all patients undergoing surgery ($n = 13$). Hormonal therapy cannot be proposed to patients wishing to conceive; on the contrary, laparoscopic surgical excision of bowel endometriosis may improve post-operative fertility (Daraï *et al*., 2005; Ferrero *et al*., 2008; Stepniewska *et al*., 2009). However, the administration of norethisterone acetate might be useful for young women desiring to postpone surgery or for older patients who wish to improve the severity of pain and gastrointestinal symptoms up to menopause and trying to avoid repeat surgery. As there is no evidence that hormonal therapies may affect the natural history of bowel endometriosis, it is possible that the disease progresses during long-term administration of

Table III Changes in pain and gastrointestinal symptoms during treatment

Symptom	Baseline	6-month	12-month
Dysmenorrhea	6.8 ± 1.9 ($n = 34$)	NA	NA
Chronic pelvic pain	5.5 ± 1.3 ($n = 29$)	4.1 ± 1.8 ($n = 28$); $P < 0.001$	3.5 ± 1.6 ($n = 24$); $P < 0.001$
Deep dyspareunia	5.7 ± 1.4 ($n = 22$)	3.1 ± 1.1 ($n = 20$); $P < 0.001$	2.8 ± 1.2 ($n = 20$); $P < 0.001$
Dyschezia	5.1 ± 1.9 ($n = 27$)	3.2 ± 1.2 ($n = 26$); $P < 0.001$	2.5 ± 1.4 ($n = 22$); $P < 0.001$
Constipation	7.6 ± 1.7 ($n = 15$)	6.9 ± 1.7 ($n = 14$); $P = 0.230$	6.8 ± 1.9 ($n = 12$); $P = 0.437$
Constipation during the menstrual cycle	7.6 ± 1.8 ($n = 8$)	NA	NA
Diarrhoea	7.3 ± 0.6 ($n = 3$)	2.7 ± 0.6 ($n = 3$); $P = 0.005$	1.7 ± 0.6 ($n = 3$); $P = 0.003$
Diarrhoea during the menstrual cycle	8.0 ± 0.9 ($n = 11$)	NA	NA
Intestinal cramping	7.1 ± 1.8 ($n = 23$)	4.0 ± 2.0 ($n = 22$); $P < 0.001$	3.0 ± 1.5 ($n = 19$); $P < 0.001$
Abdominal bloating	5.6 ± 1.6 ($n = 17$)	5.5 ± 2.0 ($n = 16$); $P = 0.926$	5.5 ± 2.5 ($n = 12$); $P = 0.674$
Feeling of incomplete evacuation	5.3 ± 1.9 ($n = 6$)	5.2 ± 2.2 ($n = 6$); $P = 0.867$	5.2 ± 2.8 ($n = 6$); $P = 0.895$
Passage of mucus	4.3 ± 1.5 ($n = 7$)	1.6 ± 0.8 ($n = 7$); $P < 0.016$	1.0 ± 0.0 ($n = 7$); $P = 0.001$
Cyclical rectal bleeding	3.8 ± 1.0 ($n = 4$)	NA	NA

NA, not available.
Intensity of symptoms at 6- and 12-month of treatment was compared with baseline values.

norethisterone acetate. Patients should be informed of this risk and monitored during treatment.

We are aware that some limitations characterize the current study. Firstly, this was not a randomized placebo-controlled trial; however, it would have been difficult to propose a placebo-controlled trial to highly symptomatic patients with a diagnosis of bowel endometriosis. In addition, no medical treatment is currently established for patients with bowel endometriosis and could be used for comparison with norethisterone acetate.

Secondly, the diagnosis of colorectal endometriotic nodules was based on MDCT-e and not on diagnostic laparoscopy. Although MDCT-e may be criticized for the exposure of reproductive age women to radiations and for the use of iodinated contrast medium, it has previously been shown to be accurate in diagnosing bowel endometriosis. A prospective study including 98 women demonstrated that MDCT-e has a sensitivity of 98.7%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 95.7% in identifying women with bowel endometriosis (Biscaldi *et al*., 2007a). Magnetic resonance imaging, which is one of the techniques most commonly used in the diagnosis of bowel endometriosis, has a sensitivity between 77 and 95%, a specificity between 89 and 100%, a positive predictive value between 94 and 100% and a negative predictive value between 77 and 99% for the diagnosis of bowel endometriosis (Bazot *et al*., 2004, 2007, in press; Chapron *et al*., 2004; Abrao *et al*., 2007; Chamié *et al*., 2009). In addition, MDCT-e allows the diagnosis of endometriotic nodules located on the cecum or the ileum (Biscaldi *et al*., 2007a, b), which was one of the exclusion criteria for the study. Finally, all study subjects had prior surgery for endometriosis and patients who underwent surgery after interruption or completion of treatment with norethisterone acetate ($n = 13$; 33%) had the presence of colorectal endometriosis confirmed by surgery and histology.

Thirdly, this study included a selected population of women with bowel endometriosis; in fact, these patients did not have subocclusive symptoms and had only colorectal nodules that determined a stenosis of less that 60% of the bowel lumen. These inclusion criteria were chosen in order to avoid including in the study patients at risk of bowel occlusion. On the basis of this study design, the findings of the current investigation cannot be generalized to all women with colorectal endometriosis.

A further limitation of this study consists of the fact that some gastrointestinal symptoms were reported only by a limited number of patients included in the study; this does not allow drawing definitive conclusions on the efficacy of norethisterone acetate in the treatment of these symptoms. The preliminary results of this study should therefore be confirmed in larger series of patients.

Finally, we cannot exclude that, in some of the patients included in the study, the intestinal symptoms were caused by concomitant irritable bowel syndrome and not by bowel endometriosis. However, specific biomarkers for irritable bowel syndrome are not available and the diagnosis of this condition requires the exclusion of organic intestinal disease (such as Crohn's disease, ulcerative colitic, colorectal cancer and bowel endometriosis) (American College of Gastroenterology Task Force on Irritable Bowel Syndrome, 2009; Ferrero *et al*., 2009b). Therefore, it is not possible to preoperatively discriminate whether bowel endometriosis or irritable bowel syndrome causes the intestinal symptoms suffered by the patients. However, previous investigations demonstrated that the surgical excision of bowel endometriosis improves intestinal symptoms mimicking irritable bowel syndrome (Minelli *et al*., 2009; Ferrero *et al*., 2009a); these findings suggest a pathogenic role of endometriotic lesions in determining these gastrointestinal complaints.

Modern radiological techniques (such as MDCT-e, magnetic resonance imaging, rectal endoscopic ultrasonography and transvaginal ultrasonography) allow a precise diagnosis of the presence and extent of bowel endometriotic lesions (Remorgida *et al*., 2007). Therefore, at the present time, surgery is not necessary for diagnosis and it should only be performed to treat the disease. On the basis of this, some patients might have a diagnosis of bowel endometriosis

without undergoing surgery. In some of these cases, the administration of norethisterone acetate may determine a temporary relief of pain and gastrointestinal symptoms. The administration of norethisterone acetate determines higher benefits in patients with gastrointestinal symptoms related to the menstrual cycle, diarrhoea and intestinal cramping. It remains to be established whether the long-term administration of norethisterone acetate might be associated with a progression of bowel endometriosis.

Author's Role

F.S. and R.V. had the original idea of the study. R.N. and V.P.L supervised the whole study procedure including design of the study and interpretation of results. B.E. performed the radiological diagnosis of bowel endometriosis. F.S., C.G., R.N. and R.V. recruited the patients enrolled in the study and performed the follow-up. F.S. performed the statistical analyses and prepared the draft of the manuscript. R.V. and V.P.L. revised the manuscript.

References

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.

American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EM. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009;**104**:S1–S35.

Bazot M, Daraï E, Hourani R, Thomassin I, Cortez A, Uzan S, Buy JN. Deep pelvic endometriosis: MR imaging for diagnosis and prediction of extension of disease. *Radiology* 2004;**232**:379–389.

Bazot M, Bornier C, Dubernard G, Roseau G, Cortez A, Daraï E. Accuracy of magnetic resonance imaging and rectal endoscopic sonography for the prediction of location of deep pelvic endometriosis. *Hum Reprod* 2007;**22**:1457–1463.

Bazot M, Lafont C, Rouzier R, Roseau G, Thomassin-Naggara I, Daraï E. Diagnostic accuracy of physical examination, transvaginal sonography, rectal endoscopic sonography, and magnetic resonance imaging to diagnose deep infiltrating endometriosis. *Fertil Steril* (in press).

Biscaldi E, Ferrero S, Fulcheri E, Ragni N, Remorgida V, Rollandi GA. Multislice CT enteroclysis in the diagnosis of bowel endometriosis. *Eur Radiol* 2007a;**17**:211–219.

Biscaldi E, Ferrero S, Remorgida V, Rollandi GA. Bowel endometriosis: CT-enteroclysis. *Abdom Imaging* 2007b;**32**:441–450.

Biscaldi E, Ferrero S, Remorgida V, Fulcheri E, Rollandi GA. Rectosigmoid endometriosis with unusual presentation at magnetic resonance imaging. *Fertil Steril* 2009;**91**:278–280.

Chamié LP, Blasbalg R, Gonçalves MO, Carvalho FM, Abrão MS, de Oliveira IS. Accuracy of magnetic resonance imaging for diagnosis and preoperative assessment of deeply infiltrating endometriosis. *Int J Gynaecol Obstet* 2009;**106**:198–201.

Chapron C, Vieira M, Chopin N, Balleyguier C, Barakat H, Dumontier I, Roseau G, Fauconnier A, Foulot H, Dousset B. Accuracy of rectal endoscopic ultrasonography and magnetic resonance imaging in the diagnosis of rectal involvement for patients presenting with deeply infiltrating endometriosis. *Ultrasound Obstet Gynecol* 2004;**24**:175–179.

Daraï E, Marpeau O, Thomassin I, Dubernard G, Barranger E, Bazot M. Fertility after laparoscopic colorectal resection for endometriosis: preliminary results. *Fertil Steril* 2005;**84**:945–950.

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

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

Ferrero S, Abbamonte LH, Remorgida V, Ragni N. Abdominal pain, bloating, and urgency. *Obstet Gynecol* 2005;**106**:195.

Ferrero S, Ragni N, Remorgida V. Post-operative digestive symptoms after colorectal resection for endometriosis. *Hum Reprod* 2006;**21**:1941–1942.

Ferrero S, Anserini P, Abbamonte LH, Ragni N, Camerini G, Remorgida V. Fertility after bowel resection for endometriosis. *Fertil Steril* 2008;**92**:41–46.

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

Ferrero S, Camerini G, Ragni N, Remorgida V. Endometriosis and irritable bowel syndrome: co-morbidity or misdiagnosis? *BJOG* 2009b;**116**:129.

Ferrero S, Camerini G, Seracchioli R, Ragni N, Venturini PL, Remorgida V. Letrozole combined with norethisterone acetate compared with norethisterone acetate alone in the treatment of pain symptoms caused by endometriosis. *Hum Reprod* (in press).

Markham SM, Welling DR, Larsen KS, Snell MJ. Endometriosis of the rectum treated with a long term GnRH agonist and surgery. *N Y State J Med* 1991;**91**:69–71.

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.

Muneyyirci-Delale O, Karacan M. Effect of norethindrone acetate in the treatment of symptomatic endometriosis. *Int J Fertil Womens Med* 1998;**43**:24–27.

Porpora MG, Pallante D, Ferro A, Crobu M, Cerenzia P, Panici PL. Intestinal endometriosis without evident pelvic foci treated with gonadotropin-releasing hormone agonist. *Eur J Obstet Gynecol Reprod Biol* 2006;**125**:265–266.

Remorgida V, Ragni N, Ferrero S, Anserini P, Torelli P, Fulcheri E. The involvement of the interstitial Cajal cells and the enteric nervous system in bowel endometriosis. *Hum Reprod* 2005a;**20**:264–271.

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* 2005b;**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.

Ret Dávalos ML, De Cicco C, D'Hoore A, De Decker B, Koninckx PR. Outcome after rectum or sigmoid resection: a review for gynecologists. *J Minim Invasive Gynecol* 2007;**14**:33–38.

Riis BJ, Lehmann HJ, Christiansen C. Norethisterone acetate in combination with estrogen: effects on the skeleton and other organs. A review. *Am J Obstet Gynecol* 2002;**187**:1101–1116.

Ruffo G, Scopelliti F, Scioscia M, Ceccaroni M, Mainardi P, Minelli L. Laparoscopic colorectal resection for deep infiltrating endometriosis: analysis of 436 cases. *Surg Endosc* 2009 (in press).

Seracchioli R, Poggioli G, Pierangeli F, Manuzzi L, Gualerzi B, Savelli L, Remorgida V, Mabrouk M, Venturoli S. Surgical outcome and long-term follow up after laparoscopic rectosigmoid resection in women with deep infiltrating endometriosis. *BJOG* 2007;**114**:889–895.

Seracchioli R, Mabrouk M, Guerrini M, Manuzzi L, Savelli L, Frascà C, Venturoli S. Dyschezia and posterior deep infiltrating endometriosis: analysis of 360 cases. *J Minim Invasive Gynecol* 2008;**15**:695–699.

Stepniewska A, Pomini P, Bruni F, Mereu L, Ruffo G, Ceccaroni M, Scioscia M, Guerriero M, Minelli L. Laparoscopic treatment of bowel endometriosis in infertile women. *Hum Reprod* 2009;**24**:1619–1625.

Thomassin I, Bazot M, Detchev R, Barranger E, Cortez A, Daraï E. Symptoms before and after surgical removal of colorectal endometriosis that are assessed by magnetic resonance imaging and rectal endoscopic sonography. *Am J Obstet Gynecol* 2004;**190**:1264–1271.

Vercellini P, Pietropaolo G, De Giorgi O, Pasin R, Chiodini A, Crosignani PG. Treatment of symptomatic rectovaginal endometriosis with an estrogen–progestogen combination versus low-dose norethindrone acetate. *Fertil Steril* 2005;**84**:1375–1387.

Vercellini P, Crosignani PG, Somigliana E, Berlanda N, Barbara G, Fedele L. Medical treatment for rectovaginal endometriosis: what is the evidence? *Hum Reprod* 2009;**24**:2504–2514.

Submitted on July 26, 2009; resubmitted on September 6, 2009; accepted on September 10, 2009