Surgical versus medical treatment for endometriosis-associated severe deep dyspareunia: I. Effect on pain during intercourse and patient satisfaction

P. Vercellini1,2,*, E. Somigliana3, D. Consonni4, M.P. Frattaruolo1,2, O. De Giorgi1,2, and L. Fedele1,2

1From Clinica Ostetrica e Ginecologica, Istituto 'Luigi Mangiagalli', Universita` Statale di Milano, 20122 Milan, Italy 2Fondazione IRCCS 'Ca' Granda - Ospedale Maggiore Policlinico, Via Commenda 12, 20122 Milan, Italy 3Infertility Unit, Fondazione IRCCS Ca’ Granda - Ospedale Maggiore Policlinico, Via M. Fanti 6, 20122 Milan, Italy 4Unit of Epidemiology, Department of Preventive Medicine, Fondazione IRCCS Ca’ Granda-Ospedale Maggiore Policlinico, Via San Barnaba 8, 20122 Milan, Italy

*Correspondence address: Tel: +39-02-5503-2917; Fax: +39-02-5503-2331; E-mail: paolo.vercellini@unimi.it

Submitted on June 1, 2012; resubmitted on July 21, 2012; accepted on July 30, 2012

STUDY QUESTION: Does surgical or medical treatment for endometriosis-associated severe deep dyspareunia achieve better results in terms of patients’ satisfaction (main study outcome), variation of coital pain and frequency of intercourse?

SUMMARY ANSWER: Surgery and progestin therapy were equally effective in the treatment of deep dyspareunia in women with rectovaginal endometriosis, whereas medical therapy performed significantly better than excisional treatment in those without deeply infiltrating lesions.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS: Conservative surgery and hormonal therapies have been used independently for endometriosis-associated deep dyspareunia with inconsistent results. This study reports a direct comparison between the two treatment options in women with severe pain during intercourse.

DESIGN: Patient preference, parallel cohort study with a 12-month follow-up. The effect of conservative surgery at laparoscopy was compared with treatment with a low-dose of norethisterone acetate per os (2.5 mg/day) in women with persistent/recurrent severe deep dyspareunia after first-line surgery.

PARTICIPANTS AND SETTING: A total of 51 patients chose repeat surgery and 103 progestin treatment. Patient satisfaction was graded according to a five-category scale. Variations in pain during intercourse were measured by means of a 100-mm visual analogue scale.

MAIN RESULTS AND THE ROLE OF CHANCE: In the surgery group, a marked and rapid short-term dyspareunia score reduction was observed, followed by partial recurrence of pain. The pain relief effect of the progestin was more gradual, but progressive throughout the study period. At a 12-month follow-up, the frequency of intercourse per month (mean ± SD) was 4.6 ± 1.8 in the surgery group and 5.3 ± 1.5 in the norethisterone acetate group (P = 0.02). A total of 22/51 (43%) women were satisfied in the surgery group compared with 61/103 (59%) in the progestin group [adjusted odds ratios (OR), 0.36; 95% confidence interval (CI), 0.16–0.82; P = 0.015]. Corresponding figures in women with and without rectovaginal endometriotic lesions were, respectively, 13/24 (54%) versus 18/35 (51%; adjusted OR, 0.77; 95% CI, 0.22–2.67; P = 0.68), and 9/27 (33%) versus 43/68 (63%; adjusted OR, 0.23; 95% CI, 0.07–0.76, P = 0.02).

BIAS, CONFOUNDING, AND OTHER REASONS FOR CAUTION: Treatments were not randomly assigned, and distribution of participants as well as of dropouts between study arms was unbalanced. However, the possibility of choosing the treatment allowed assessment of the maximum potential effect size of the interventions.

GENERALIZABILITY TO OTHER POPULATIONS: Caucasian patients able to choose their treatment.

STUDY FUNDING/COMPETING INTEREST(S): This study was supported by a research grant from the University of Milan School of Medicine (PUR number 2009-ATE-0570). None of the authors have a conflict of interest.

Key words: endometriosis / deep dyspareunia / surgery / medical treatment

© The Author 2012. Published by Oxford University Press on behalf of the European Society of Human Reproduction and Embryology. All rights reserved.
For Permissions, please email: journals.permissions@oup.com
Introduction

The prevalence of deep dyspareunia is significantly higher in women with endometriosis than in the general female population of corresponding age (Ballard et al., 2008). Pain during coital activity has been associated with deep endometriotic lesions infiltrating the uterosacral and cardinal ligaments, the pouch of Douglas, the posterior vaginal fornix and the anterior rectal wall (Vercellini et al., 1991, 1996, 2004, 2007; Vercellini, 1997; Fauconnier et al., 2002; Fauconnier and Chapron, 2005). During complete penetration the penis fills up the posterior fornix (Schultz et al., 1999). In these conditions, deep dyspareunia may be caused by traction of scarred and inelastic parametria, by pressure on endometriotic nodules embedded in fibrotic tissue, and by immobilization of postero-uterine pelvic structures (Vercellini, 1997, Ferrero et al., 2008; Vercellini et al., 2011a).

Excision of deep endometriotic foci has been reported to reduce pain during intercourse and improve the quality of sex life (Anaf et al., 2001; Vercellini et al., 2006; Ferrero et al., 2007). However, surgery for deep lesions requires a high level of technical competence, is associated with potentially severe morbidity, and may reveal only partially or temporarily effective (Vercellini et al., 2009a,b; De Cicco et al., 2011; Kondo et al., 2011). Several hormonal compounds have been used successfully for endometriosis-associated deep dyspareunia (Vercellini et al., 2008, 2009c,d). In this regard, low-dose norethisterone acetate has demonstrated a particularly favourable profile in terms of efficacy, safety, tolerability, costs and possibility of indefinitely extending the treatment period (Vercellini et al., 2005, 2011b; Remorgida et al., 2007; Ferrero et al., 2009, 2010). However, pharmacologic therapies fail in approximately one woman out of three, because of side effects, and may interfere with sexual desire and arousal (Vercellini et al., 2005, 2008, 2009c,d; Remorgida et al., 2007; Ferrero et al., 2009, 2010).

To our knowledge, surgical and medical treatments have never been directly compared in endometriosis patients reporting severe deep dyspareunia as their main complaint. Given this background, we sought to compare the effect of laparoscopic versus progestin treatment for the management of severe deep dyspareunia associated with persistent or recurrent endometriosis after unsuccessful first-line conservative surgery. The primary end-point was patient satisfaction at a 1-year follow-up. Variations in pain symptoms and in the frequency of intercourse were also assessed. Data regarding additional study end-points, namely, sexual functioning, psychological status and health-related quality of life, have been described elsewhere.

Materials and Methods

This patient preference, parallel cohort study compared two alternative therapeutic options, i.e. second-line laparoscopic excision of lesions and an oral progestin, for the treatment of severe deep dyspareunia associated with persistent or recurrent endometriosis after unsuccessful first-line conservative surgery. The study was conducted considering available information about the medical problem in question, and reaching a decision on treatment choice based on patient preference. Two groups of recruits were thus generated in whom motivational factors were optimized by allowing them to receive their preferred treatment (Cooper et al., 1997). The investigation was performed in an academic department and the local institutional review board approved the study. All patients were informed and provided written consent before enrolment.

At baseline screening demographic information and a medical history were obtained. We considered 18–40-year-old women not wanting pregnancy, and who had undergone laparoscopy or laparotomy for Stage III and IV endometriosis (Revised American Fertility Society, 1985) in the previous 24 months. Patients in whom rectovaginal lesions were not excised were also included. In our centre, the diagnosis of rectovaginal endometriosis is based on vaginal and rectal examination, transvaginal and transrectal ultrasonography, and histological demonstration of endometriosis in specimens taken during previous surgery or at biopsy of the posterior fornix. In these cases, the diagnostic work-up includes kidney and urinary tract ultrasonography and rectosigmoidoscopy.

Subjects with persistent, severe deep dyspareunia of more than 6 months’ duration were deemed eligible. Exclusion criteria were obstructive uropathy or symptomatic bowel stenosis; evidence of complex adnexal cysts or an ovarian endometrioma of diameter > 4 cm at vaginal ultrasonography; therapies for endometriosis other than non-steroidal anti-inflammatory drugs (NSAIDs) in the 3 months before study entry (6 months for GnRH analogues); the typical contraindications to progestins; the use of drugs that interfere with ovarian steroid metabolism; allergy to components of the study medication or to NSAIDs; abnormal findings at breast examination and mammary ultrasound scan; an abnormal cervical smear; a diagnosis of concomitant pelvic inflammatory disease, pelvic varices or genital malformations at previous surgery; known gastrointestinal, urologic and orthopedic diseases; psychiatric disturbances; history of drug or alcohol abuse; and unwillingness to tolerate menstrual changes.

After an introductory explanation, the women were informed that the evidence supporting the efficacy of conservative surgery for the relief of endometriosis-associated deep dyspareunia, although generally favourable and consistent, is derived from non-comparative trials in which most subjects were undergoing first-line procedures (Anaf et al., 2001; Ferrero et al., 2005, 2007). Information on the effect of second-line conservative surgery on pain during intercourse is scanty and scattered. Moreover, patients were told that repeat operations can be technically difficult and carry an increased risk of complications and of further symptoms and/or lesions recurrence (Vercellini et al., 2009e). They were also informed that medical therapies for endometriosis are usually effective in reducing pain during intercourse in about two-thirds of cases (Vercellini et al., 2005, 2008, 2009c,d; Remorgida et al., 2007; Ferrero et al., 2009; Somigliana et al., 2009). However, drugs induce only temporary relief, are not expected to be definitively curative, and may cause side effects including depressed mood and decreased libido. Finally, when hormonal treatments are to be continued for long periods, progestins appear to be among the compounds that most favourably balance benefits, harm and costs (Vercellini et al., 2009c,d, 2011b). On the basis of the above information, a shared decision was taken on whether to undergo second-line conservative surgery at laparoscopy or start progestin treatment.

Each patient was asked to complete a questionnaire on the presence and severity of deep dyspareunia, dysmenorrhoea, dyschezia (painful defecation sometimes associated with constipation, diarrhoea or cyclic haematochezia) and non-menstrual pelvic pain graded using a 100-mm visual analogue scale, the left extreme of which indicates the absence of pain and the right extreme pain as bad as it could be. A score of 1–50 was considered mild pain, 51–80 moderate pain and 81–100 severe pain. Cut-off points defining different categories of pain were chosen on the basis of a previous correlation analysis with the Biberoglu and Behrman (1981) multi-dimensional categorical rating scale (Vercellini et al., 1996). They were also requested to indicate the mean frequency of intercourse per month.

Subjects were recruited who reported severe deep dyspareunia.

Baseline fasting peripheral blood samples were obtained to measure concentrations of glucose, aspartate and alanine aminotransferases, total bilirubin, lactate dehydrogenase, alkaline phosphatase, total, high- and
low-density-lipoprotein cholesterol and triglycerides. Only women with normal values were considered for medical therapy.

Conservative surgery at laparoscopy was performed with mechanical instruments and electrotherapy only. Adhesions were sectioned with microscissors, the ovaries were completely mobilized, and endometriomas were excised and cauterized by means of countershock applied to the pseudocapsule and normal gonadal cortex with atrumatic microforces. Haemostasis was achieved by selective application of bipolar current. Superficial peritoneal implants were fulgurated with low-power unipolar current or excised with microscissors. In order to excise rectovaginal lesions, the accessible portion of the pouch of Douglas was explored, the ureters were bilaterally identified and isolated, and pararectal spaces were developed. After insertion of tampons mounted on ring forceps in the vaginal apex and in the rectal ampulla, the anterior rectal wall was detached from the posterior fornix with microscissors. The fornix was then opened by cutting along the attachment of the vaginal cuff to the posterior part of the cervix. Once free margins were reached both laterally and caudally, the plaque was excised and the vagina re-attached to the anterior part of the cervix. Once free margins were reached both laterally and caudally, the plaque was excised and the vagina re-attached to the anterior part of the cervix. Once free margins were reached both laterally and caudally, the plaque was excised and the vagina re-attached to the anterior part of the cervix.

Participants who chose hormonal treatment were instructed to take 2.5 mg of oral norethisterone acetate once a day, starting on the first day of menstruation. In case of prolonged spotting (≥ 7 days) or breakthrough bleeding, the women were advised to suspend treatment for 1 week. Compliance was assessed by checking personal diaries and questionnaires at each visit. Subjects in both study groups were invited to use barrier contraception and were allowed to take NSAIDs when needed (naproxen sodium, one 550-mg tablet twice a day).

At the 3-, 6- and 12-month evaluation the patients underwent clinical assessment, vaginal and rectal examination, and transvaginal ultrasonography, and were requested to indicate the frequency of intercourse (number per month), and to complete the pain questionnaire again. In women who chose progestin treatment, pain during both erratic or regular withdrawal bleeding was considered as dysmenorrhoea. Analgesic use and adverse events were also recorded. At 6- and 12-month assessment, fasting peripheral blood samples were obtained to measure the blood chemistries determined at baseline.

At the same time points, the women rated the overall degree of satisfaction with their treatment on a five-category scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied) by answering the following question: "Taking into consideration the variation in pain during intercourse, in sexual functioning, in overall physical and psychological well-being and in quality of life, how would you define the level of satisfaction with your treatment?"

In calculating the sample size required, the primary consideration was the rate of satisfied patients (very satisfied plus satisfied) at 12-month evaluation. Based on our previous experience on low-dose norethisterone acetate used continuously (Vercellini et al., 2005), we hypothesized that about 60% of the subjects treated with the progestin would be satisfied. Limited literature data are available on the effect of repeat conservative surgery on endometriosis-associated deep dyspareunia. In order to justify the morbidity and risks associated with operative laparoscopy, the outcome after excision of endometriotic lesions should be expected to be better than that during medical treatment. We considered a difference of 25% in satisfaction rate between the study groups as clinically relevant. To have an 80% chance of detecting such a difference at an overall significance level of 5%, 50 patients per group are required. As treatment allocation was based on patient preference, no anticipation could be made on a balanced distribution of participants between the two study arms. Accordingly, the recruitment phase continued until the pre-planned sample size was reached in the least numerous group.

Categorical variables were compared with the Fisher’s exact test. Drop-outs were considered as treatment failures (dissatisfied) and included in this analysis. In order to estimate the adjusted effect of treatment on patient satisfaction, a dichotomization of the outcome into treatment success (very satisfied plus satisfied subjects) and treatment failure (uncertain plus dissatisfied plus very dissatisfied subjects) was done. This variable was inserted into a multivariate logistic regression model including age, previous pregnancies, BMI, endometriosis stage, ovarian endometriotic cysts, rectovaginal lesions, type of treatment chosen and NSAID use and the adjusted odds ratios (OR) for satisfaction and corresponding 95% confidence intervals (CIs) were calculated. Visual analogue scale score across treatment at baseline, 3, 6 and 12 months were analysed using a linear regression random intercept model, adjusted for age, to take into account the intra-individual correlation of repeated measurements over time (Rabe-Hesketh and Skrondal, 2008). We then fitted similar models separately in women with and without a rectovaginal plaque. The analyses were performed with Stata, version 11 (StataCorp LP, College Station, TX, USA).

The independent Student’s t-test was adopted to compare number of sexual intercourses per month and analgesic use. All statistical tests were two-sided. Probability values of < 5% were considered statistically significant.

Results

A total of 192 women evaluated at our endometriosis outpatient clinic in the period 2007–2010 were eligible for the study, but 21 were lost to further contacts and 17 declined the proposed treatments. Fifty-one (33%) of the remaining patients chose surgical treatment and 103 (67%) chose medical treatment. The mean interval (± SD) between previous surgery and the start of the study was 15.2 ± 4.5 months in the former group and 16.5 ± 3.2 months in the latter. The baseline clinical characteristics of the enrolled women are shown in Table I. The age and BMI (mean ± SD) of women who underwent surgery and of those who received NETA were, respectively, 35.0 ± 4.7 and 34.3 ± 5.0 years and 21.0 ± 2.3 and 22.1 ± 3.0 kg/m². The distribution of the variables considered was similar in the two groups. Fifty-five subjects (36%) had ovarian endometriomas, 20 in the surgery group (unilateral, 14; bilateral, 6; mean ± SD cyst diameter, 3.1 ± 0.6 cm) and 35 in the progestin group (unilateral 26; bilateral 9; mean ± SD cyst diameter, 2.8 ± 0.5 cm). Fifty-nine patients (38%) had rectovaginal lesions.

In the surgery group, all the 24 rectovaginal plaques were excised, ovarian endometriomas were removed in all the 20 affected women, and the posterior parametria were resected in 15 cases owing to infiltrating lesions. Peritoneal implants were treated in all subjects. Two patients with rectovaginal endometriosis underwent colorectal resection with end-to-end staple anastomosis because of dyschezia, cyclic haematochezia and detection of endometriotic foci at histological examination of biopsies taken at rectosigmoidoscopy. One woman with a full-thickness endometriotic detrusor nodule underwent segmental bladder resection. No major intra-operative complications occurred. Post-operatively, a rectovaginal fistula developed in a woman who underwent excision of a rectovaginal plaque combined with rectal resection. She was treated with a temporary colostomy and subsequent surgical repair at laparotomy.

Twenty-one women in the progestin group and four in the surgery group withdrew from the study for various reasons (Fig. 1). All these
women were included as failures (dissatisfied) in the evaluation of satisfaction with treatment, the primary end-point of our study.

At 3-month evaluation, the degree of patient satisfaction was significantly better in the surgery group independently of endometriotic lesion types (Table II). However, the differences were no more significant at a 6-month follow-up. At the end of the study period, no significant between-group difference was observed in patients with rectovaginal lesions, whereas norethisterone treatment performed significantly better than surgery in women without such lesions.

Overall, at 12-month assessment, 22/51 (43%) of the women in the surgery group were satisfied or very satisfied compared with 61/103 (59%) in the progestin group (adjusted OR, 0.36; 95% CI, 0.16–0.82; \( P = 0.015 \)). Corresponding figures in the subgroup of women with rectovaginal lesions were, respectively, 13/24 (54%) and 18/35 (51%); adjusted OR, 0.77; 95% CI, 0.22–2.67; \( P = 0.68 \), and, respectively, 9/27 (33%) and 43/68 (63%); adjusted OR, 0.23; 95% CI, 0.07–0.76, \( P = 0.02 \) in those without rectovaginal lesions.

In order to identify predictive factors for satisfaction, we compared baseline characteristics of subjects who were satisfied or very satisfied and those who were not. None of the studied variables was significantly associated with this outcome (data not shown).

Pain symptom variations during the study period are shown in Figs 2 and 3. Considering all the subjects followed at 12 months, a substantial decrease in deep dyspareunia VAS scores was observed in both groups, although the treatment effect was significantly greater in the medical treatment group. In the surgery group, the mean dyspareunia score fell from 89 ± 9 at baseline to 51 ± 27 at the end of the study period. Corresponding figures in the progestin group were, respectively, 89 ± 8 and 39 ± 26 (between-group difference at 3 months = −32, \( P = 0.001 \); at 6 months = −15, \( P = 0.001 \); at 12 months = +11, \( P = 0.001 \), random intercept model adjusted for age; Fig. 2A). At the end of follow-up, deep dyspareunia was still severe in 8 (17%) women in the surgery group and in 4 (5%) in the progestin group (\( P = 0.03 \), Fisher’s exact test). The mean decrease in deep dyspareunia scores at a 12-month follow-up in women with rectovaginal endometriotic lesions was identical in the two study groups (51), thus resulting in similar final dyspareunia scores (respectively, 42 and 40, \( P = 0.60 \), Table III and Fig. 2B). However, in patients without rectovaginal lesions, the mean decrease in deep dyspareunia score was almost double in the progestin compared with the surgery group (50 versus 26), so that the mean final score was 38 in the former group and 59 in the latter (\( P < 0.001 \), random intercept model adjusted for age, Table III and Fig. 2C).

In the surgery group, the mean number of sexual intercourses per month increased quickly, being significantly higher at 3- and 6-month evaluation compared with that reported by patients in the progestin group. However, women using norethisterone acetate improved progressively until the end of follow-up, whereas women who underwent surgical treatment experienced a decline in sexual activity in the second half of the study period. At 12-month assessment, a significant benefit in favour of the medical therapy group was observed. In the surgery and progestin group, the mean number of monthly intercourses was, respectively, 3.6 ± 1.6 versus 3.8 ± 1.7 at baseline, 5.8 ± 1.6 versus 4.3 ± 1.7 at 3 months (\( P < 0.01 \)), 5.4 ± 1.8 versus 4.6 ± 1.6 at 6 months (\( P = 0.01 \)) and 4.6 ± 1.8 versus 5.3 ± 1.5 at 12 months (\( P = 0.02 \)).

At baseline, 80% of women in the surgery group used NSAIDs compared with 90% in the progestin group. Percentages at 3-, 6- and 12-month evaluation were, respectively, 27 versus 43%, 34 versus 21% and 34 versus 12% (12 months, \( P = 0.003 \), Fisher’s exact test).

Untoward effects in the norethisterone acetate group were common (60/98, 61%), but generally well tolerated by the majority of patients. The most frequently reported side effect was weight gain (\( n = 35 \)), followed by breakthrough bleeding (\( n = 21 \)), decreased libido (\( n = 20 \)), vaginal dryness (\( n = 12 \)), spotting (\( n = 11 \)), breast tenderness (\( n = 6 \)), bloating/swelling (\( n = 5 \)), headache (\( n = 4 \)), depression (\( n = 4 \)) and nausea (\( n = 2 \)). Three subjects withdrew because of erratic bleeding, two because of weight gain, two because of decreased libido and one owing to headache. No major alterations were observed in periodic blood tests in norethisterone acetate users.

**Discussion**

Our findings suggest that, overall, surgery and progestin therapy were both effective in relieving endometriosis-associated deep dyspareunia, although with a different temporal trend, and with a greater improvement in the medical therapy group at the end of the follow-up period. Excision of lesions is followed by a rapid and substantial decrease in pain, with short- and medium-term advantage over medical treatment, but a gradual recurrence of the symptom after 6 months since surgery. Given the chronic and relapsing nature of endometriosis, this is

---

**Table I** Distribution of study patients according to age, parity, body mass index, endometriosis stage at previous surgery, presence of endometriotic cysts or rectovaginal lesions and preferred treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgery group (n = 51)</th>
<th>Progestin group (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>16/51 (31%)</td>
<td>17/103 (16%)</td>
</tr>
<tr>
<td>≥30</td>
<td>35/48 (75%)</td>
<td>86/100 (84%)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>78/44 (70%)</td>
<td>81/100 (80%)</td>
</tr>
<tr>
<td>≥1</td>
<td>22/7 (27%)</td>
<td>26/100 (25%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21</td>
<td>33/17 (20%)</td>
<td>31/103 (30%)</td>
</tr>
<tr>
<td>21–22</td>
<td>35/18 (20%)</td>
<td>36/103 (35%)</td>
</tr>
<tr>
<td>23–24</td>
<td>22/11 (20%)</td>
<td>21/103 (20%)</td>
</tr>
<tr>
<td>≥25</td>
<td>10/5 (10%)</td>
<td>15/100 (15%)</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>33/17 (20%)</td>
<td>47/103 (46%)</td>
</tr>
<tr>
<td>IV</td>
<td>67/34 (64%)</td>
<td>56/103 (54%)</td>
</tr>
<tr>
<td>Endometriotic cysts</td>
<td>39/20 (60%)</td>
<td>35/103 (34%)</td>
</tr>
<tr>
<td>Rectovaginal endometriosis</td>
<td>47/24 (60%)</td>
<td>35/103 (34%)</td>
</tr>
</tbody>
</table>

**Note:**

+ None of the between-group differences is statistically significant (Fisher’s exact test).
+ According to the revised American Fertility Society classification (1985) as assessed at first-line surgery.
expected, as surgery does not interfere with the pathogenic mechanisms of the disease. Conversely, the use of norethisterone acetate determines a less impressive effect at the beginning of therapy, but followed by gradual amelioration with time, probably because of a progressive decrease in pelvic inflammatory status (Tokushige et al., 2009).

Subgroup analysis indicates that patients with and without rectovaginal lesions respond differently. During deep penetration the glans impacts on the posterior fornix and adjacent structures (Schultz et al., 1999; Barnhart et al., 2006), thus explaining the observed relationship between deep lesions and pain during intercourse (Vercellini et al., 1996, 2004, 2007; Fauconnier et al., 2002; Fauconnier and Chapron, 2005; Ferrero et al., 2008). Therefore, the best surgical results were observed specifically in this group of patients with a clear-cut ‘organic’ origin of the symptom. In fact, the 12-month mean dyspareunia VAS score reduction was 51 mm in subjects with rectovaginal nodules, and only 26 in those without this type of lesion. Moreover, the trend towards pain recurrence in the second half of the study period was less marked in the former than in the latter group. On the other hand, progestin treatment was equally, and gradually, effective in both clinical conditions. In women with rectovaginal endometriosis, no significant between-group difference was observed in severity of pain during intercourse at 12-month evaluation, whereas in subjects without rectovaginal lesions progestin treatment was associated with a better outcome compared with surgery. These findings suggest that second-line surgery should be carefully restricted to women with recurrent deep lesions.

The trend in variation of dysmenorrhoea and non-menstrual pain intensity was similar to that observed with deep dyspareunia. Interestingly, mean baseline dyschesia VAS scores were substantially lower compared with the other pain symptoms considered. Moreover, a
major between-group difference in favour of surgery was observed only at 3-month assessment, whereas afterwards mean scores remained similar and generally low and stable in both study groups.

Also the variation in the mean number of monthly intercourses followed the same pattern of dyspareunia. In fact, women who underwent surgery reported an immediate benefit that, however, was not long-lasting, whereas those who used norethisterone acetate reported a more gradual, but steady increase in coital frequency. This is most probably due to dyspareunia recurrence during time in women who underwent endometriosis excision.

The incidence of side effects in norethisterone acetate users seems high in our series. However, we did not only record the complaints spontaneously reported by patients, but specifically investigated their occurrence at each study visit. The main untoward effects were erratic bleeding, weight gain, and decreased libido. The progressively rising number of intercourses in the progestin group may appear in contradiction with the desire reduction observed in one fifth of the subjects (20/98). Possibly, drug-induced relief of pain is more important than the detrimental effect on libido, thus tipping the overall balance toward enhancement of sexual activity in women using norethisterone acetate. Bleeding control is a classic problem of progestin therapy. In this regard, norethisterone acetate appears to perform better than other progestins, as in this as well as in a previous study (Vercellini et al., 2005), two-thirds of the women experienced amenorrhea during treatment. Discontinuing the progestin for 1 week in case of prolonged or heavy bleeding revealed successful in the management of most cases.

In our opinion, tolerability is of major importance when evaluating the benefit of long-term medical treatment for a chronic condition such as symptomatic endometriosis (Vercellini et al., 2011b). The choice of satisfaction with treatment as the primary study end-point was based on the presupposition that women would evaluate not only pain-related benefits, but also untoward effects of hormonal therapy. After inclusion of all subjects withdrawn for any reason as dissatisfied, 43% women who chose surgery were satisfied with their treatment, compared with 59% women who chose progestin therapy. In general, these data emphasize the limits of our current understanding and treatment modalities for this clinical condition, as almost half of the recruited women were dissatisfied at the end of the study. Overall, the pattern of patient satisfaction with treatment during the study period followed the trend of variation of coital pain in the two study groups. In fact, women in the surgery group were significantly more satisfied than those in the progestin group at 3-month assessment. This difference vanished at a 6-month follow-up, and reversed at 12-month evaluation, although only in women without rectovaginal lesions.

It is difficult to compare our findings with those available in the scientific literature. In fact, although relief of endometriosis-associated deep dyspareunia has been repeatedly reported after both surgical and medical treatments (Anaf et al., 2001; Abbott et al., 2003; Table II Grading of satisfaction with treatment in patients with and without rectovaginal endometriosis during the study period according to treatment allocation.

| Follow-up | Rectovaginal endometriosis | | | | No rectovaginal endometriosis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Surgery | Progestin | P-value* | Surgery | Progestin | P-value* |
| | group | group | | | group | group | | | |
| | (n = 24) | (n = 35) | | | (n = 27) | (n = 68) | | | |
| 3 months | | | | | | | | | | |
| Very satisfied | 10 | 42 | 2 | 6 | 7 | 26 | 6 | 9 | 0.005 | 0.02 |
| Satisfied | 6 | 25 | 19 | 54 | 14 | 52 | 30 | 44 | | |
| Uncertain | 6 | 25 | 8 | 23 | 3 | 11 | 23 | 34 | | |
| Dissatisfied | 1 | 4 | 5 | 14 | 3 | 11 | 4 | 6 | | |
| Very dissatisfied | 1 | 4 | 1 | 3 | 0 | 0 | 5 | 7 | | |
| 6 months | | | | | | | | | | |
| Very satisfied | 9 | 38 | 4 | 12 | 7 | 26 | 17 | 25 | 0.06 | 0.95 |
| Satisfied | 7 | 29 | 19 | 54 | 13 | 48 | 30 | 44 | | |
| Uncertain | 5 | 21 | 6 | 17 | 4 | 15 | 9 | 13 | | |
| Dissatisfied | 2 | 8 | 6 | 17 | 3 | 11 | 9 | 13 | | |
| Very dissatisfied | 1 | 4 | 0 | 0 | 0 | 0 | 3 | 5 | | |
| 12 months | | | | | | | | | | |
| Very satisfied | 7 | 29 | 7 | 20 | 2 | 7 | 17 | 25 | 0.92 | 0.001 |
| Satisfied | 6 | 25 | 11 | 31 | 7 | 26 | 26 | 38 | | |
| Uncertain | 6 | 25 | 9 | 26 | 13 | 48 | 6 | 9 | | |
| Dissatisfied | 5 | 21 | 7 | 20 | 4 | 15 | 16 | 24 | | |
| Very dissatisfied | 0 | 0 | 1 | 3 | 1 | 4 | 3 | 4 | | |

*Fisher’s exact test.
Vercellini et al., 2005, 2006), we are not aware of studies focusing specifically on women with severe pain during intercourse. In most reports, variation in dyspareunia was a secondary study outcome, and in the few in which dyspareunia was a selection criterion, also women with moderate pain were recruited (Ferrero et al., 2007). We confirm the effect of low-dose norethisterone acetate on dyspareunia observed by us (Vercellini et al., 2005) and others (Ferrero et al., 2009) in women with rectovaginal lesions. Conversely, our results after surgery compares unfavourably with those reported by other authors in women with symptomatic endometriosis in general (Abbott et al., 2003), as well as specifically in those with dyspareunia as their main complaint (Ferrero et al., 2007). However, these latter studies evaluated the effect of first-line surgery, whereas our patients underwent second-line surgery because of persistent/recurrent...
disease, and the results of repeat laparoscopy are usually worse than those at primary procedure (Vercellini et al., 2009e).

Non-random allocation of treatment alternatives constitutes the most important methodological drawback of our study. The choice of undergoing surgery or using a progestin was based on patients’ preference after detailed counselling. The unbalanced distribution between the two treatment arms is explained by the expected preference of most women for a medical therapy, especially after a first-line surgical procedure. On the other hand, patients with more severe symptoms or lesions could have been more prone to choose surgery instead of medical treatment, although no significant baseline difference between-group difference was observed in this regard.

Setting up a formal randomized controlled trial (RCT) in case of very diverse treatment alternatives associated with major differences in terms of risks and morbidity, would have almost certainly lead to insurmountable recruiting difficulties (McCulloch et al., 2002; Carragee, 2006). This is true particularly when comparing surgery with a non-surgical therapy (Weinstein et al., 2006a,b; Crowther et al., 2012).

The main difference between an observational study comparing two case series and a patient preference, parallel cohort trial is the modality of treatment allocation, by the clinicians in the former case and by patient choice in the latter. Whereas clinicians are prone to recruit different types of women to the two different arms, depending on their belief about the effectiveness of different options, allocation by the patients themselves may offer some reassurance that the results could be extrapolated to a wider group of subjects. Moreover, it has been reported that the results of well-designed observational studies are generally similar to those of formal RCTs (Benson and Hartz, 2000; Concato et al., 2000).

Although preference arms comparisons have the potential limitations of observational studies, including selection bias, it has been recognized that such research environment may be more similar to ‘real world’ conditions (Brocklehurst, 1997), and that preference-based treatment allocation may optimize cost-effectiveness of intervention (Sculpher, 1998). This effect is largely dependent on the type of outcome being measured, with minimal or no effect for hard outcomes (survival), but a potential major influence if the outcome is patient satisfaction. In the latter case, a comparison between two groups of patients who have chosen their treatment, thereby emphasizing their satisfaction, may represent the maximum effect size of the intervention (Schmoor et al., 1996). However, the effect observed under these conditions can be referred exclusively to patients who specifically choose that treatment (Brewin and Bradley, 1989). We have managed the data in the two non-randomized groups controlling for known confounding factors. In this regard, multivariate logistic regression analysis identified the chosen treatment as the sole factor influencing the main study outcome.

The observed proportion of satisfied women in the progestin group was as anticipated. At study planning, we hypothesized a higher satisfaction rate in women choosing surgery with respect to those choosing medical therapy, because we expected that physical elimination of endometriotic lesions would have revealed particularly successful in women with a mainly organic type of pain such as deep-thrust dyspareunia. However, the rate of satisfied patients 1 year after surgery was almost half with respect to the pre-planned figure. This invalidates the calculation of the sample size and may affect interpretation of the results.

In theory, imbalance in dropouts may result in overestimation of the progestin effect in a ‘per protocol’ analysis. However, satisfaction with the treatment chosen, the main study end-point, was based on all the recruited subjects, as all dropouts were included as failures. On the other hand, as the outcome of operative laparoscopy is strictly operator-dependent, it cannot be excluded that in a less specialized environment the surgical results could have been even worse or the complication rate higher.

The medical personnel caring for women followed in our endometriosis outpatient clinic are extensively trained in counselling with a tolerant attitude, and are able to dedicate unlimited time to provide information, assistance and reassurance. This may partly explain the relatively limited number of dropouts observed, especially in the surgery group, and constitutes another factor limiting the generalizability of our findings. Although it is very difficult to weigh the impact of this aspect, it is probably substantial. If this is true, our findings should be considered as the combination of the effect of surgery or medical therapy plus psychological support. This part of medical intervention appears particularly important in a population afflicted by an intimate problem such as dyspareunia. Here the quality of the patient–physician relationship may play a major role in the overall management of this difficult clinical condition. Therefore, in a less experienced or dedicated setting, the outcome of treatment may be worse than observed by us.

Exclusion of women seeking pregnancy could be considered a further limitation of our study. We decided to include only patients

<table>
<thead>
<tr>
<th>Rectovaginal endometriosis</th>
<th>No rectovaginal endometriosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery group (n)</strong></td>
<td><strong>Progestin group (n)</strong></td>
</tr>
<tr>
<td>Baseline</td>
<td>93 ± 8 (22)</td>
</tr>
<tr>
<td>3 months</td>
<td>23 ± 20 (22)</td>
</tr>
<tr>
<td>6 months</td>
<td>29 ± 23 (22)</td>
</tr>
<tr>
<td>12 months</td>
<td>42 ± 28 (22)</td>
</tr>
</tbody>
</table>

All values are mean ± standard deviation. *From random intercept model adjusted for age.

Table III: Variation of intensity of dyspareunia as assessed on a visual analogue scale in patients with and without rectovaginal endometriosis during the study period according to treatment allocation.
who did not want to get pregnant based on the hypothesis that those desiring a conception would have declined prolonged ovulation suppression anyway. Moreover, it is not possible to exclude that the motivation to get pregnant could result in better dyspareunia tolerance with respect to women not seeking conception.

The role of additional or alternative sources of deep dyspareunia, such as adenomyosis, was not investigated in our study. Moreover, we did not take into account the potential impact of post-operative desafferentation pain. This syndrome appears to be caused by transection of sympathetic somatic and visceral afferent axons, followed by the death of axotomized afferent neurons (central deafferentation) and persistent sensitization of spinal nociceptive neurons, probably due to viscerosomatic convergence or collateral sprouting of afferents (Kramis et al., 1996). Finally, the specific effect of peritoneal and ovarian lesions associated with rectovaginal endometriosis on pain was not measured. This would have been impossible anyway in women who chose progestin therapy.

In the medical treatment group, we cannot exclude some misdiagnosis of rectovaginal endometriosis. Our study design did not allow us to rule out the possibility that some subjects classified in the category ‘non-rectovaginal endometriosis’ may instead have harboured milder, unrecognized, deep lesions. On the other hand, in women previously managed by advanced surgery, fibrous post-operative sequelae could mimic deep endometriotic lesions, both clinically and radiologically. However, based on our selection criteria, affected cases were those with more florid plaques, i.e. those whose diagnosis was based on direct visualization of bluish nodules in the posterior fornix and/or histological examination of biopsies. The conclusions of our study are thus valid only for this group of women.

Finally, we were unable to discriminate between patients who underwent incomplete first-line surgery and those in whom new lesions developed after radical excision. In fact, the majority of the recruited subjects underwent primary surgery elsewhere. This limits a reliable assessment of the actual degree of radicality, and thus the correct identification of persistent versus recurrent lesions, even after careful checking of surgical reports. Therefore, it is uncertain if our findings may apply to both subgroups of patients.

In conclusion, based on our observations we suggest that both surgical and progestin treatment are offered to women with deep dyspareunia and rectovaginal endometriotic lesions, i.e. in those with a mainly organic type of pain, whereas we strongly support the use of medical therapy as a first-line alternative for those without rectovaginal lesions, i.e. with a predominant inflammatory and functional component. Surgery remains the only possible option for women desiring a spontaneous conception. The combination of surgical and long-term adjuvant medical therapy deserves further research. In fact, such association may reveal the best available treatment, and the results of the present study appear to provide new arguments in favour of this strategy.

Authors’ roles

P.V., L.F.: conception and design. M.P.F., O.D.G.: acquisition of data. P.V., E.S., D.C.: analysis and interpretation of data. P.V.: drafting the article. All authors: critical revision of the article for intellectual content. All the authors approved the final version of the manuscript.

Funding

Supported in part by the University of Milan School of Medicine Research Grant PUR number 2009-ATE-0570.

Conflict of interest

None declared.

References


Concato J, Shah N, Horwitz I. Randomized, controlled trials, observational studies, and the hierarchy of research designs. NEJM 2000; 342:1887–1892.

Cooper KG, Grant AM, Garrat AM. The impact of using a partially randomised patient preference design when evaluating alternative management for heavy menstrual bleeding. BJOG 1997; 104:1367–1373.


