Surgical versus low-dose progestin treatment for endometriosis-associated severe deep dyspareunia II: Effect on sexual functioning, psychological status and health-related quality of life

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STUDY QUESTION: Does surgical and low-dose progestin treatment differentially affect endometriosis-associated severe deep dyspareunia in terms of sexual functioning, psychological status and health-related quality of life?

SUMMARY ANSWER: Surgery and progestin treatment achieved essentially similar benefits at 12-month follow-up, but with different temporal trends.

WHAT IS ALREADY KNOWN: Conservative surgery and hormonal therapies have been used independently for endometriosis-associated deep dyspareunia with inconsistent results.

STUDY DESIGN, SIZE, DURATION: Patient preference, parallel cohort study with 12-month follow-up. The effect of conservative surgery at laparoscopy versus 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 was compared.

PARTICIPANTS/MATERIALS AND SETTING, METHODS: A total of 51 patients chose repeat surgery and 103 progestin treatment. Variations in sexual function, psychological well-being and quality of life were measured by means of the Female Sexual Function Index (FSFI), the Hospital Anxiety and Depression Scale (HADS) and the Endometriosis Health Profile-30 (EHP-30).

MAIN RESULTS AND THE ROLE OF CHANCE: Four women in the surgery group and 21 women in the progestin group withdrew from the study for various reasons. Total FSFI scores, anxiety and depression scores and EHP-30 scores improved immediately after surgery, but worsened with time, whereas the effect during progestin use increased more gradually, but progressively, without overall significant between-group differences at 12-month follow-up. A tendency was observed towards a slightly better total FSFI score after surgery at the end of the study period.

LIMITATIONS, REASONS FOR CAUTION: Treatments were not randomly allocated, 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.

WIDER IMPLICATIONS OF THE FINDINGS: Both surgery and medical treatment with progestins are valuable options for improving the detrimental impact of endometriosis-associated dyspareunia on sexual functioning and quality of life. Women should be aware of the pros and cons of both options to decide which one best suits their needs.
**Introduction**

Endometriosis is the most frequent cause of deep dyspareunia (Ferrero et al., 2008; Meana and Yitzchak, 2011), and patients with the disease have a 9-fold increase in risk of experiencing this symptom when compared with the general female population (Ballard et al., 2008). Deep dyspareunia due to endometriosis has been associated with lesions infiltrating the pouch of Douglas, the uterosacral and cardinal ligaments, the posterior vaginal fornix and the anterior rectal wall (Fauconnier et al., 2002; Vercellini et al., 2004, 2007; Fauconnier and Chapron, 2005; Ferrero et al., 2005). Pain during coital activity may originate from pressure on endometriotic nodules embedded in fibrotic tissue, traction of scarred and inelastic parametria and immobilization of posterior uterine pelvic structures (Vercellini, 1997; Ferrero et al., 2008; Vercellini et al., 2011a).

Pain at intercourse is among the factors that impact mostly on sexual functioning that is an important aspect of health and quality of life (Garratt et al., 1995). Painful sex also has personal and intimate implications, including substantial psychological and relational distress (Meana and Lykins, 2009), as well as unfavourable emotional impact in partners (Fernandez et al., 2006). However, only limited information is available on the consequences of endometriosis-associated deep dyspareunia, as well as on the effect of medical and surgical treatment alternatives for this condition, in terms of variations in sexual functioning, psychological status and health-related quality of life (Ferrero et al., 2005, 2007a, 2007b, 2009; Meana and Yitzchak, 2011; Vercellini et al., 2011b).

Conservative surgery for endometriosis has been suggested to relieve pain at intercourse and ameliorate quality of sex life (Vercellini et al., 2000, 2006; Anaf et al., 2001; Ferrero et al., 2007a). However, a high level of technical competence is required to deal with deeply infiltrating lesions. Moreover, the effect of surgery is generally partial or temporary (Vercellini et al., 2000, 2009a, 2009b). As an alternative, some hormonal therapies have been used successfully for endometriosis-associated deep dyspareunia, including oral contraceptives, progestins, GnRH agonists and aromatase inhibitors (Vercellini et al., 1993, 2005, 2008, 2009c, 2009d). Unfortunately, medical treatment is effective in no more than two-thirds of women. In addition, among the several untoward effects reported, interference with sexual desire and arousal may be particularly distressing in this patient population (Vercellini et al., 2005, 2008, 2009c, 2009d; Remorgida et al., 2007; Ferrero et al., 2009, 2010). Finally, surgical and medical treatments for endometriosis have not yet been directly compared in women complaining specifically of pain at intercourse.

Given this background, we sought to compare the effect of laparoscopic treatment versus therapy with low-dose norethisterone acetate (NETA), a progestin with a particularly favourable efficacy/safety/tolerability/cost profile (Vercellini et al., 2005, 2008, 2009c, 2009d, 2011b; Remorgida et al., 2007; Ferrero et al., 2009, 2010), for the management of severe deep dyspareunia associated with persistent or recurrent endometriosis after unsuccessful first-line conservative surgery. Variations in pain at intercourse, other types of pelvic pain and patient satisfaction with treatment have been described elsewhere (Vercellini et al., 2012). We here report the results regarding the additional study end points, namely, sexual functioning, psychological status and health-related quality of life during a 1-year follow-up period.

**Materials and Methods**

This patient preference, parallel cohort study was conducted considering two alternative therapeutic options, i.e. second-line laparoscopic excision of lesions and an oral progestin, for the treatment of deep dyspareunia associated with persistent or recurrent endometriosis. Allocation to treatment was decided after detailed information and mutual agreement. Therefore, two groups of recruits were generated in whom motivational factors were optimized by allowing them to receive their preferred therapy (Cooper et al., 1997). The investigation was performed in an academic department, and the local institutional review board approved the study (approval code no. 1465). All patients provided written consent before enrolment.

We selected 18–40-year-old women not wanting pregnancy who had undergone laparoscopy or laparotomy for stage III and IV endometriosis (American Fertility Society, 1985) in the previous 2 years. Patients in whom rectovaginal lesions were not excised were also included. Subjects with persistent severe deep dyspareunia of more than 6 months duration were deemed eligible. Women were excluded in case of obstructive uropathy or bowel stenosis; evidence of complex adnexal cysts or an ovarian endometrioma of diameter $>$4 cm at vaginal ultrasonography; use of therapies for endometriosis other than non-steroidal anti-inflammatory drugs in the 3 months before study entry (6 months for GnRH analogues); typical contraindications to progestins; allergy to components of the study medication; abnormal findings at breast examination and mammary ultrasound scan; abnormal cervical smear; diagnosis of concomitant pelvic inflammatory disease, pelvic varices or genital malformations at previous surgery; known gastrointestinal, urologic and orthopaedic diseases; psychiatric disturbances; history of drug or alcohol abuse; and unwillingness to tolerate menstrual changes.

After an introductory explanation, the women received detailed information on treatment alternatives in terms of morbidity, risks, expected benefits and costs. A shared decision was then taken on whether to undergo second-line conservative surgery at laparoscopy or to start progestin treatment. Subjects were recruited who reported severe deep dyspareunia defined as $>$81 mm on 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. Participants were asked to complete the Female Sexual Function Index (FSFI), the Hospital Anxiety and Depression Scale (HADS) and the Endometriosis Health Profile-30 (EHP-30) questionnaire.

The FSFI questionnaire is a 19-item, validated, multidimensional, self-report instrument for assessing the major categories of female sexual dysfunction and sexual satisfaction (Rosen et al., 2000; Meston, 2003). The

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**Key words:** endometriosis / deep dyspareunia / sexual functioning / psychological well-being / health-related quality of life
FSFI has proven an acceptable internal consistency and test–retest reliability. Domains include desire, arousal, lubrication, orgasm, satisfaction and pain. Each question is answered using a five-point Likert scale, and scores are transformed by multiplying domain scores by a factor of 0.3–0.6 to equally weigh each domain depending on the number of question per domain. The transformed maximum score for each domain is 6, and the maximum transformed full-scale score is 36, with a minimum full-scale score of 2.0. Women with a FSFI total score below 26.55 are categorized as experiencing sexual dysfunction, whereas those above this cut-off score are categorized as functionally normal (Wiegel et al., 2005).

The HADS questionnaire is a self-assessment mood scale specifically designed for use in non-psychiatric hospital outpatients to determine states of anxiety and depression. It comprises 14 items, 7 in anxiety subscale and 7 for the depression subscale. Five mutually exclusive answers, rated from 0 to 4 according to increasing psychiatric severity, are provided for each of the 14 questions. The points are summed to give anxiety and depression subtotals and a total score. The HADS has been shown to be a reliable instrument for screening for clinically significant anxiety and depression and a valid measure of severity of these mood disorders (Zigmond and Snaith, 1983).

The EHP-30 questionnaire is a reliable, valid and responsive, patient-generated instrument that measures disease-specific health-related quality of life in women with endometriosis (Jones et al., 2001, 2004, 2006). In this study, the official Italian version of the questionnaire was used. The EHP-30 consists of two parts: a core questionnaire that is applicable to all women with endometriosis, containing 30 items in 5 domains (pain, control and powerlessness, emotional well-being, social support and self-image), and a modular questionnaire that does not necessarily apply to all women with endometriosis, containing 23 items in 6 domains (work, sexual intercourse, relationship with children, medical profession, treatment and infertility). As an example, the domain ‘medical profession’ includes the following questions: ‘Felt doctor(s) seen not doing anything for you? Felt doctor(s) think it is all in your mind? Felt frustrated at doctor(s) lack of knowledge about endometriosis? Felt like you are wasting the doctor(s) time?’ For a detailed description of the other questions included in the different core and modular domains, the reader is referred to the original publication by Jones et al. (2001). The items, both in the core and in the modular questionnaire, have five possible response levels. Each scale is standardized on a range from 0 (indicating the best health status) through to 100 (indicating the worst health status). Each scale is calculated as follows: scale score is equal to the total of the raw scores of each item in the scale divided by the maximum possible raw score of all the items in the scale, multiplied by 100 (Jones et al., 2001). If an item in a scale is not answered, no score is calculated for that scale (Jones et al., 2006). The EHP-30 has been shown to be sensitive to change in clinical pharmacology studies (Wayne et al., 2008) and also when assessing the outcome of conservative surgery (Jones et al., 2004).

Conservative surgery at laparoscopy was performed with mechanical instruments and electrosurgery only, according to previously described techniques (Vercellini et al., 2006). Briefly, adhesions were sectioned and plaque excision, the vagina was sutured to the cervix. The anterior rectal wall was treated according to the shaving technique, and the rectum reinforced with interrupted sutures, unless a low anterior rectal resection was deemed necessary.

Participants who chose hormonal treatment were instructed to take 2.5 mg of oral NETA once a day, starting on the first day of menstruation. In case of prolonged spotting (≥7 days) or breakthrough bleeding, they were advised to suspend treatment for 1 week. Compliance was assessed by checking personal diaries and questionnaires at each visit. Women in both study groups were invited to use barrier contraception and were allowed to take non-steroidal anti-inflammatory drugs when needed (naproxen sodium, one 550-mg tablet twice a day unless contraindicated). At the 3-, 6- and 12-month of evaluation, the patients underwent clinical assessment, vaginal and rectal examination and transvaginal ultrasonography and were requested to complete the FSFI, the HADS and the EHP-30 again.

Statistics

The power calculation was based on the main study outcome, i.e., satisfaction with treatment at 12-month follow-up evaluation, and is reported in a previous publication (Vercellini et al., 2012). Briefly, 50 participants per group were required to identify a difference of 25% in satisfaction rate (very satisfied plus satisfied) between women who chose surgery and those who chose progestin treatment.

Variations in sexual functioning, psychological status and health-related quality of life were assessed by computing scores on, respectively, the FSFI, the HADS and the EHP-30 scales. Scores across treatment at baseline, 3, 6, and 12 months were analysed using linear regression random intercept models, adjusted for age, parity, BMI, endometriosis stage, ovarian endometriomas and rectovaginal lesions to take into account the intra-individual correlation of repeated measurements over time (Rabe-Hesketh and Skrondal, 2008). To compare the time trend between the two treatment groups, we included in all models three interaction terms between treatment and time and reported the corresponding probability values that, therefore, refer to changes in the clinical effect of treatment at each follow-up visit against the baseline value. We also evaluated interaction between treatment and selected variables (age, parity, BMI, endometriosis stage, ovarian endometriomas and rectovaginal lesions) by including a product term in the regression models, and, in case of significant interactions (P < 0.05), we performed stratified analyses. The analyses were performed with Stata, version 12 (StataCorp LP, College Station, TX, USA).

Results

A total of 192 women evaluated at our endometriosis outpatient clinic in the period 2007–2010 were eligible for this 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 low-dose progestin 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 1. The differences between the study groups in the distribution of the variables considered were not statistically significant. The mean ± SD age and BMI in women operated and those receiving 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. Proportions of women with BMI under 21 or over 25 were, respectively, 33% (n = 17) and 10% (n = 5) and 30% (n = 31) and 15% (n = 15). Ovarian endometriomas
and rectovaginal lesions were present in 20 (39%) and 24 (47%) women in the surgery group. Corresponding figures were 35 (34%) and 35 (34%) among participants who chose medical therapy.

In the surgery group, an attempt to remove all endometriotic lesions was systematically performed. Based on surgical records, this was always achieved. Two patients with rectovaginal endometriosis underwent colorectal resection with end-to-end anastomosis. No major intra-operative complications occurred. Post-operatively, a rectovaginal fistula developed in one 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. Four women in the surgery group and 21 women in the progestin group withdrew from the study for various reasons (surgery group: medical treatment for pain, 2; oral contraceptive for recurrent endometrioma, 1; lost to follow-up, 1; progestin group: side effects, 8 (erratic bleeding, 3; weight gain, 2; decreased libido, 2; headache, 1); lost to follow-up, 5; preferred oral contraceptives, 4; surgery for persistent pain, 2; and desire for conception, 2).

The FSFI score variation is shown in Fig. 1. A within-group significant increase in total score was observed in both study groups (surgery group, \( P < 0.0001 \); progestin group, \( P = 0.002 \); adjusted random intercept model; Fig. 1A), with a tendency towards a slightly better total score after surgery at the end of the study period (\( P = 0.05 \)). At 3 months, both the total score and the subscores for each of the six domains were significantly higher (better) in the surgery group than in the progestin group (Fig. 1B–G). This was confirmed also at 6 months, except for orgasm scores, which was similar in the two groups (Fig. 1E). At 12 months, desire, arousal and lubrication scores were still significantly higher in the surgery group, but the between-group difference in satisfaction and pain at intercourse observed at 3 and 6 months had vanished (Fig. 1F and 1G). In spite of the observed improvements, the mean total FSFI score remained below the threshold for sexual dysfunction in both study groups during the entire study period.

Interaction analyses between treatment and selected variables (age, parity, BMI, endometriosis stage, ovarian endometriomas and rectovaginal lesions) demonstrated some statistically significant results (Wald’s test, \( P < 0.05 \)). At stratified analyses, the difference in favour of surgery in lubrication was limited to nulliparous women, whereas a benefit of NETA over surgery on orgasm was observed in parous participants only. The effect of NETA on pain at intercourse was significantly higher than that of surgery in women without rectovaginal plaques, whereas no difference was observed in those with this lesion type. Finally, a slightly higher benefit of surgery on desire was observed in women without ovarian endometriomas.

Variations in anxiety and depression scores are shown in Fig. 2. Both total and subscale scores decreased substantially in both study groups (\( P < 0.0001 \), adjusted random intercept model). Similarly, to findings relative to sexual functioning, women in the surgery group reported an immediate major benefit at the 3-month assessment that was confirmed at 6 months, but partly receded at the 12-month follow-up. In contrast, the improvement in psychological status in the medical treatment group was gradual but, at the end of the study period, lead to an essentially similar effect without a significant between-group difference (\( P = 0.22 \), adjusted random intercept model).

The EHP-30 score variation during the study period is shown in Fig. 3. At baseline, the subjects in the progestin treatment group performed significantly worse than those in the surgery group in three dimensions (pain, control and powerlessness and medical profession) (Fig. 3A, B and I). At the 3-month evaluation, the women who underwent surgery scored significantly better in emotional well-being, social support, self-image, sexual intercourse, treatment and infertility (Fig. 3C–E, G, L and M). At 6 months, the comparison was more balanced, as a significant difference in favour of the surgery group was observed only in three modular dimensions, namely, control and powerlessness, self-image and sexual intercourse (Fig. 3B, E and G). Health-related quality of life further improved in the progestin group during the second half of the study period, and, at final assessment, significant differences were observed in control and powerlessness, work and relationship with children in favour of women who chose medical therapy (Fig. 3B, F and H). Only the score relative to the modular domain medical profession was better in the surgery group (Fig. 3I). In summary, a significant amelioration in average EHP scores from baseline to 12-month follow-up was observed for all domains in both the surgical and the progestin group. For women who underwent surgery, mean scores showed a dramatic reduction at 3 months, but crept back at 12 months, whereas for those

### Table I Distribution of study patients according to age, parity, BMI, endometriosis stage at previous surgery, presence of endometriotic cysts or rectovaginal lesions, baseline FSFI total scores, baseline HADS total scores 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>8 (16)</td>
<td>17 (16)</td>
</tr>
<tr>
<td>≥30</td>
<td>43 (84)</td>
<td>86 (84)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40 (78)</td>
<td>81 (79)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>11 (22)</td>
<td>22 (21)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21</td>
<td>17 (33)</td>
<td>31 (30)</td>
</tr>
<tr>
<td>21–22</td>
<td>18 (35)</td>
<td>36 (35)</td>
</tr>
<tr>
<td>23–24</td>
<td>11 (22)</td>
<td>21 (20)</td>
</tr>
<tr>
<td>≥25</td>
<td>5 (10)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Disease stagea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>17 (33)</td>
<td>47 (46)</td>
</tr>
<tr>
<td>IV</td>
<td>34 (67)</td>
<td>56 (54)</td>
</tr>
<tr>
<td>Endometriotic cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 (39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectovaginal endometriosis</td>
<td>24 (47)</td>
<td></td>
</tr>
<tr>
<td>Baseline FSFI total score (mean ± SD)</td>
<td>19.0 ± 4.3</td>
<td>20.1 ± 4.7</td>
</tr>
<tr>
<td>Baseline HADS total score (mean ± SD)</td>
<td>22.9 ± 9.6</td>
<td>20.3 ± 8.6</td>
</tr>
</tbody>
</table>

\(^{a}\)None of the between-group differences is statistically significant (Fisher’s exact test or unpaired two-sample t-test).

\(^{b}\)According to the revised American Fertility Society (1985) classification as assessed at first-line surgery.
Figure 1  Variation of FSFI overall scores and domain scores in the two treatment groups during the study period. Values are mean ± SD shown by vertical bars. Red line, surgery group; violet line, NETA group. (A) Total scores. (B) Desire domain scores. (C) Arousal domain scores. (D) Lubrication domain scores. (E) Orgasm domain scores. (F) Satisfaction domain scores. (G) Pain domain scores. FSFI, female sexual function index.
women who underwent progestin treatment, the EHP-30 score reduced slowly over time.

Discussion

Our findings suggest that, overall, surgery and low-dose progestin therapy are both effective in improving sexual functioning, psychological well-being and health-related quality of life in women with endometriosis-associated deep dyspareunia, although with a different chronological pattern. Excision of lesions is followed by a rapid and substantial benefit, with a greater immediate effect with respect to progestin treatment. However, the gradual recurrence of pain at intercourse after 6 months since surgery, combined with progressive amelioration of clinical conditions in women using NETA, lead to a final practical equipoise in the considered functional outcomes at 1-year follow-up.

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 study participants underwent primary surgery elsewhere. This limits a reliable evaluation of the actual degree of radicality at primary surgery and, thus, the proper identification of persistent versus recurrent lesions. Therefore, we are unable to demonstrate that our findings may apply to both subgroups of patients, i.e. those who underwent incomplete surgery, and those in whom recurrences developed de novo after actual radical excision.

Given the complete lesion excision obtained at second-line surgery, it appears reasonable to ascribe pain relapse in women in the surgery group to endometriosis recurrence, as removal of lesions does not interfere with the pathogenesis of the disease. However, a psychogenic component cannot be excluded, as after surgery, patients may expect worsening of symptoms over time anyway. On the other hand, the progressive effect observed in progestin users is probably related to a gradual decrease in pelvic inflammatory status (Tokushige et al., 2009).

In both groups, the mean total FSFI score never exceeded the ‘normality’ cut-off limit of 26.55 at any time point (Wiegel et al., 2005). Therefore, the sexual dysfunction observed at baseline was completely corrected neither by surgery nor by medical treatment. In particular, performance in the surgery group improved substantially in the short term, then gradually deteriorated. However, at 12-month of evaluation, desire, arousal and lubrication scores were still significantly higher than in the NETA group, resulting in a tendency towards better total FSFI score after surgery. This could also reflect the adverse impact of progestins on libido (Vercellini et al., 2002, 2005). In other words, women using NETA probably experience a drug-induced decrease in desire, arousal and lubrication, but once intercourse initiates, orgasm capacity and overall satisfaction are not worse than in the surgical group. Conversely, 1 year after surgery, women maintained an unaffected sexual predisposition, but experienced slightly more pain during intercourse.

We evaluated possible treatment effect modifications by selected variables by including product terms in the model. Despite a few statistically significant differences, we looked at mean effect over time in stratified analyses and observed results that, with the exception of the effect of NETA on women without rectovaginal lesions (Vercellini et al., 2012), are probably of modest clinical relevance or potentially due to random fluctuation of data (e.g. a slightly higher benefit of surgery on desire in women without ovarian endometriomas). Moreover, we feel that the generalizability of this subgroup analyses is somewhat uncertain.

Anxiety and depression constitute important factors in the evaluation of sexual problems in women with chronic pelvic pain. In fact, it has been demonstrated that both psychological conditions

Figure 2

Variation of HADS overall scores and anxiety and depression subdomain scores in the two treatment groups during the study period. Values are mean ± SD shown by vertical bars. Red line, surgery group; violet line, NETA group. (A) Total scores. (B) Anxiety subscale scores. (C) Depression subscale scores. HADS, hospital anxiety and depression scale.
mediate the effect of pain on sexual disorders (ter Kuile et al., 2010). We observed a remarkable improvement in overall psychological status and in anxiety and depression subscales in women in both study groups. In the present study, only women suffering from severe limitation in sexual activity were included. Living with this symptom may result in more frustrating in comparison with dysmenorrhoea that is usually associated with less important psychological consequences (Vercellini et al., 2002, 2005). This could explain the high HADS scale scores reported by our patients at baseline. However, it is not possible to exclude that other forms of pelvic pain could have influenced the anxiety and depression scores throughout the study period.

Endometriosis is associated with debilitating pelvic pain, impairment of psychological as well as social functioning and reduction in quality of life as well as sexual satisfaction (Tripoli et al., 2011). The use of a disease-specific instrument to assess the health-related quality of life burden of endometriosis has been repeatedly suggested (Khong et al., 2010; Vincent et al., 2010). The EHP-30 questionnaire is a user-friendly self-report tool suitable for use in endometriosis-related clinical research (Khong et al., 2010). According to literature data, both surgical and pharmacological treatments improve patient’s physical and psychological functioning, vitality, pain level and general health (Gao et al., 2006). In our study, variations of the EHP-30 questionnaire scores in both study groups followed a substantially similar temporal pattern with respect to the other considered study outcomes. This further emphasizes the importance of being relieved from dyspareunia and the possibility to resume a better sex life in the overall quality of a woman’s life.

We recruited only women with severe pain at intercourse. In this regard, the findings of our study are difficult to compare with literature data, as in most reports variation in dyspareunia was a secondary study outcome, and in the few in which dyspareunia was a selection criterion, women with moderate pain were also recruited. Overall, we confirm the results observed by Ferrero et al. (2007a) on the effect of radical surgery for endometriosis in women with moderate to severe deep dyspareunia. Also in their study, reduction in pain at intercourse and improvement in quality of sex life resulted more marked in patients with deep lesions.

We used NETA in a low dose. Other investigators have suggested that higher doses are required to obtain pain relief (Muneyyirci-Delale and Karacan, 1998; Kaser et al., 2012). Therefore, it is certainly possible that had higher doses been used, a larger effect could have resulted. Other medical therapies have been demonstrated to benefit women with endometriosis-associated deep dyspareunia. In

**Figure 3** Variation of EHP-30 scores in the two treatment groups during the study period. Values are mean ± SD shown by vertical bars. EHP subdomains scores range from 0 to 100. Lower score indicates fewer negative symptoms. Red line, surgery group; violet line, NETA group. (A) Pain domain scores. (B) Control and powerlessness domain scores. (C) Emotional well-being domain scores. (D) Social support domain scores. (E) Self-image domain scores. (F) Work domain scores. (G) Sexual intercourse domain scores. (H) Relationship with children domain scores. (I) Medical profession domain scores. (L) Treatment domain scores. (M) Infertility domain scores. P-values are from random intercept model adjusted for age, parity, BMI, endometriosis stage, ovarian endometriomas and rectovaginal lesions. EHP-30, endometriosis health profile-30.
a randomized controlled trial, a GnRH agonist was more effective than an estrogen–progesterin on pain at intercourse (Vercellini et al., 1993), and the combination of NETA with an aromatase inhibitor (letrozole) reduced deep dyspareunia to a larger extent than NETA alone in some women with rectovaginal endometriosis (Ferrero et al., 2009). Moreover, Ferrero et al. (2007b) suggested that the best results can be obtained with surgery, followed by post-operative medical treatment. The findings of our study appear to support this view, and the combination of surgical and long-term adjuvant pharmacological therapy deserves further research.

The most important methodological drawback of our study is the non-random allocation of treatments. The choice of undergoing surgery or using a progestin was based on patients' preference, and the unbalanced distribution between the two study arms is almost certainly due to the refusal of most women to undergo further surgery after an unsuccessful first-line procedure. In theory, a study based completely on patient preference introduces a major selection bias, thus limiting interpretation of the results. In fact, the profile of patients selecting such different options may vary in several and undefined aspects, including psychological pattern, attitude towards sexual activity and ability to cope with a stressful, painful and chronic condition. The observed similarity in baseline clinical characteristics of subjects in the two study groups may reduce, but not eliminate this potential bias. In addition, lack of statistically significant differences in the considered demographic aspects may be due to lack of power relative to the small sample size.

Moreover, the number of dropouts was unbalanced, as substantially more subjects withdrew from the progestin arm. This is partly expected, as women may easily decide to interrupt drug use even for minor problems (e.g. erratic bleeding or weight gain), whereas withdrawal from the surgery arm is usually dictated only by important reasons (e.g. development of an ovarian cyst and recurrence of severe symptoms). This could result in overestimation of the progestin effect in a ‘per protocol’ analysis.

In spite of the above methodological implications, the results of two systematic literature reviews demonstrated that estimates of treatment effects in well-designed cohort studies are not consistently larger than or qualitatively different from those obtained in RCT on the same topic (Benson and Hartz, 2000; Concato et al., 2000). In addition, we consider that in case of very diverse treatment alternatives associated with major differences in terms of risks and morbidity, the study design adopted by us may reveal more practical and feasible, and potentially more representative, ‘real world’ conditions than a formal RCT (Brocklehurst, 1997). In fact, it has been repeatedly demonstrated that setting up a RCT in these circumstances may easily lead to insurmountable recruiting difficulties (McCulloch et al., 2002; Carragee, 2006; Weinstein et al., 2006a, 2006b; Crowther et al., 2012).

Women are more and more willing to be informed on the therapeutic options and to decide which one best suits their needs. The alternative health outcome paradigm is becoming the ‘goal-oriented’ perspective (Schmoor et al., 1996), and the combination of NETA with an aromatase inhibitor (letrozole) reduced deep dyspareunia to a larger extent than NETA alone in some women with rectovaginal endometriosis (Ferrero et al., 2009). Moreover, Ferrero et al. (2007b) suggested that the best results can be obtained with surgery, followed by post-operative medical treatment. The findings of our study appear to support this view, and the combination of surgical and long-term adjuvant pharmacological therapy deserves further research.

In conclusion, surgery and low-dose oral NETA demonstrated a similar final beneficial outcome in women with endometriosis-associated deep dyspareunia in terms of improvement of sexual functioning, psychological well-being and health-related quality of life at 1-year follow-up. The findings should be considered with caution owing to lack of randomization, potential between-group heterogeneity and difference in dropout rates. Moreover, in light of the observed differences in the temporal pattern of the effect, further comparative studies with longer follow-up are warranted.

**Authors’ roles**

Conception and design: P.V. and L.F. Acquisition of data: M.P.F. and D.A. Analysis and interpretation of data: P.V., M.P.F., E.S., G.L.J., D.C. and D.A. Drafting the article: P.V. Critical revision of the article for intellectual content: all authors. All the authors approved the final version of the manuscript.

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**Conflict of interest**

None declared.

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