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Full length article

Efficacy and acceptability of long-term norethindrone acetate for the treatment of rectovaginal endometriosis

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ABSTRACT

Objective: To study the efficacy of long-term treatment with norethindrone acetate (NETA) in patients with rectovaginal endometriosis.
Study design: This retrospective cohort study included 103 women with pain symptoms caused by rectovaginal endometriosis. Patients received NETA alone (2.5 mg/day up to 5 mg/day) for 5 years. Primary outcome was the degree of satisfaction with treatment after 5 years of progestin therapy. Secondary outcomes were the assessment of any variation in pain symptoms and the volumetric assessment of the disease by magnetic resonance imaging (MRI).
Results: Sixty-one women completed the 5-year follow-up (61/103, 59.2%) with 16 women withdrawing because of adverse effects (38.1%). Overall, 68.8% (42/61) of the women who completed the study were satisfied or very satisfied of this long term NETA treatment. This represents a 40.8% (42/103) of the patients enrolled. Intensity of chronic pelvic pain and deep dyspareunia significantly decreased during treatment ($p < 0.001$ versus baseline at 1 and 5 year). Dyschezia improved after 1-year respect to baseline ($p = 0.008$) but remained stable between first and second year ($p = 0.409$). At the end of 5 years treatment, a radiological partial response was observed in 33 patients (55.9%, n 33/59); a stable disease in 19 patients (32.2%, n 19/59). Seven women (7/59, 11.9%) displayed a volumetric increase of rectovaginal endometriosis under NETA treatment.
Conclusion: Five-year therapy with NETA is safe and well tolerated by women with rectovaginal endometriosis. Due to its low cost and good pharmacological profile, it represents a good candidate for long-term treatment in this setting.

Introduction

Endometriosis is an estrogen-dependent chronic inflammatory disease [1]. The optimal treatments for endometriosis have not been completely standardized yet and for this reason several women undergo medical and/or surgical treatment during their life to treat the disease. Current medical regimens (hormonal treatments) act improving disease symptoms through the suppression of estrogens circulation [2]; however, due to the lack of response or compliance to long-term hormonal treatment, many women opt during their life for the surgical removal of the disease [3].

Laparoscopic surgical excision of pelvic endometriotic nodules might represent a definitive treatment in some patients [4], however this "radical" surgery is technically demanding and deep endometriotic lesions may not be completely excised by inexperienced surgeons. Furthermore, even in experienced hands, it may cause long and short term complications [5] which may not be easily accepted by young women undergoing surgery for a benign disease [6,7].

For those women, who do not accept primary or secondary surgical treatment or just want to postpone this option, a medical therapy (hormonal therapy), possibly for long-term periods, is necessary [8]. Thus, it becomes a key objective ensuring that

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hormonal therapies are being accepted for long periods of time, with a good pain control and with few side effects.

Hormonal therapies (particularly progestins and estro-progestins combinations) have been repeatedly demonstrated to be safe, well tolerated and effective in the treatment of women with symptomatic endometriosis but, unfortunately, very few studies have investigated the effects of long-term treatment in women with endometriosis-related pelvic pain (>12 months) [9]. Furthermore, it is common clinical experience that patients with extensive deep endometriosis (such as intestinal and bladder nodules) have used hormonal therapies for years to control pain and/or for contraception; however, the impact of these therapies on the progression of unoperated deep nodules remain to be elucidated. Limited data showed that, in some patients, deep endometriosis can progress despite the use of hormonal therapies [10,11].

Norethindrone acetate (NETA) has been used widely in women with rectovaginal endometriosis up to 12 months follow-up, demonstrating a good pain control, with tolerable clinical (weight gain, reduce libido) and haematological (lipid profile alteration) side effects and it appears a good candidate for long-term single drug management in this setting [12–19].

This retrospective study aimed to assess the efficacy and the volumetric control of five years therapy with NETA alone in treating pain symptoms of women with rectovaginal endometriotic nodules that did not infiltrate the rectum.

Materials and methods

This study was based on a retrospective analysis of a database that was prospectively collected between October 2004 and August 2016. The local Ethic Committee approved the study protocol. All women signed an informed written consent to record their data for scientific purposes.

The study included patients who had a diagnosis of rectovaginal endometriosis between October 2004 and July 2011 and suffered pain symptoms requiring hormonal treatment.

The diagnosis of rectovaginal endometriosis was suspected on the basis of vaginal and rectal examination and it was confirmed by magnetic resonance imaging (MRI). Infiltration of the muscularis mucosae of the rectum was also excluded by at least one of the following techniques: rectal water-contrast transvaginal ultrasonography [20,21] or multidetector computerized tomography enema [22]. All these techniques were previously shown to be accurate in the diagnosis of rectosigmoid endometriosis.

We included in the study patients who, at the time of starting the treatment with NETA, had persistence of pain symptoms of

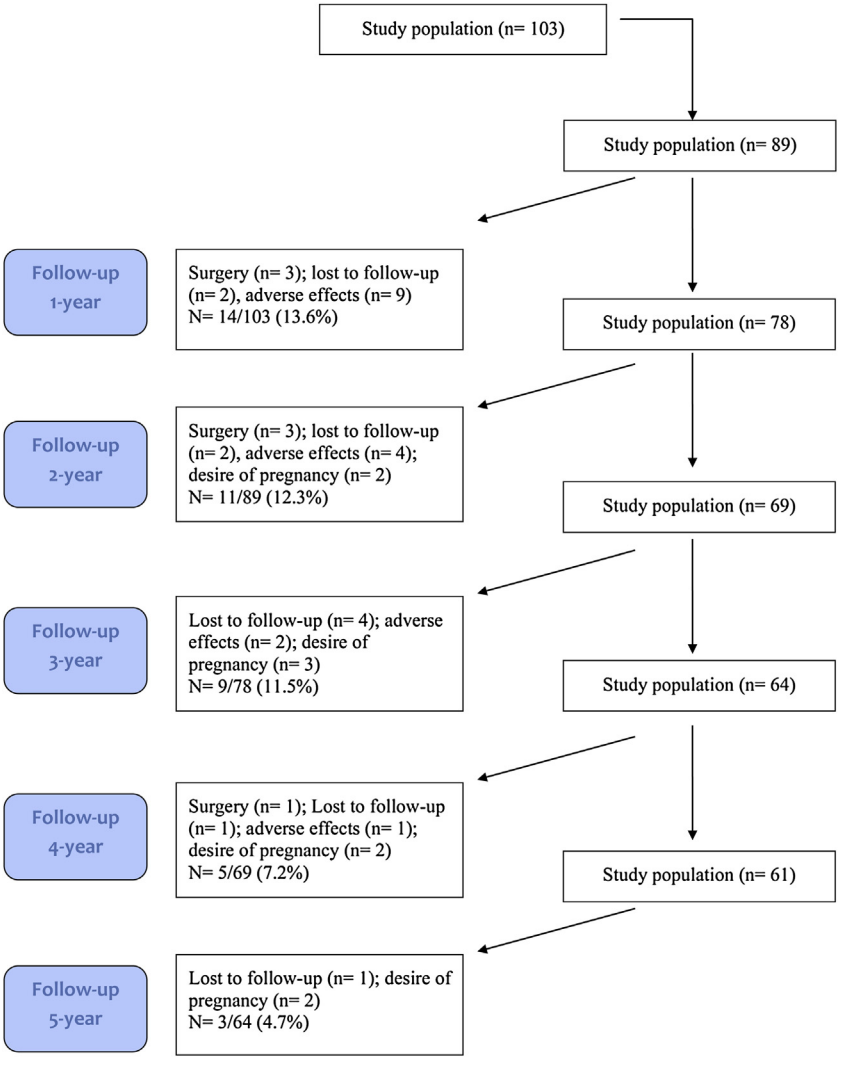


Fig. 1. Flow chart showing women's progress through the study.

more than 6-months, desired to avoid surgery, to receive a long-term hormonal treatment for endometriosis, and did not wish to conceive. We did not include in this study patients with the following characteristics: previous treatment with NETA; use of hormonal therapies for endometriosis in the 3 months before starting the treatment with NETA; endometriotic nodules infiltrating at least the muscularis mucosae of the rectosigmoid and psychiatric disturbances. Furthermore, during the study period, NETA was not prescribed to patients with complex adnexal cysts of uncertain nature, hepatic disease, BMI >30 kg/m^2, breast nodules of uncertain nature, unwillingness to tolerate menstrual changes.

Patients received NETA (Primolut-Nor®; Schering, Milan, Italy), 2.5 mg/day, starting on the first day of the menstrual cycle. In case of breakthrough bleeding after 30 days of treatment, the dose of NETA was increased to 5 mg/day.

The primary end-point of the study was the evaluation of changes in pain symptoms during treatment. Other parameters evaluated were: the degree of patient satisfaction with treatment and volumetric nodules changes during NETA assessed by MRI.

Each patient was asked to complete a 10 cm visual analogue scale (VAS) on the presence and severity of dysmenorrhea, deep dyspareunia, chronic pelvic pain and dyschezia before starting the treatment, and every year of treatment. After five years of treatment, 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 [13]. Answers were based on a 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied).

MRI was performed before starting NETA treatment and after five years of treatment in order to assess the extent of deep endometriosis. MRI was performed on a 1.5 T magnet (Signa Excite HDx, GE Medical Systems, Waukesha, WI, USA) using an 8 channels phased array coil. Endometriotic nodules are detectable as solid mass outside the sigmoid or rectal wall, frequently with a hypointense signal due to their fibrous nature [23].

To evaluate the nodules changes over time we used RECIST criteria [24,25] and we defined partial response (PR) at least a 30% decrease in the sum of the longest diameters (LD) of target lesions, taking as reference the baseline sum LD. Stable Disease (SD) indicated neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD). PD was defined at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started [25].

Statistical analysis

The comparison of pain intensity during the treatment was performed by using one-way ANOVA with Dunnett's multiple comparisons test according to data distribution when comparing three or more categories. The volumetric changes of the rectovaginal nodules were assessed by using the Student's *t*-test (paired and unpaired) according to the data distribution. The normal distribution of continuous variable data was evaluated with the Kolmogorov-Smirnov test. Categorical data were analysed by using the x^2 test or the Fisher's exact test. $P < 0.05$ was considered statistically significant. Data were analysed using GraphPad Software version 6 (La Jolla, CA, USA) and SPSS software version 21.0 (SPSS Science, Chicago, IL, USA).

Table 1
Characteristics of the study population.

Age, y (mean ± SD)	30.5 ± 3.5 years n = 103
BMI (mean ± SD)	21.5 ± 2.0
Current or ex-smokers (n,%)	47 patients (45.6%)
Parity (mean ± SD)	0.66 ± 0.5
Previous hormonal therapy (n, %)	COC: 45 patients (43.6%) GnRH: 8 patients (7.7%) Vaginal ring: 5 patients (4.8%) Vaginal danazol: 4 patients (3.8%) Levonorgestrel-IUD: 2 patients (1.9%)

Results

One hundred and three patients were included in the study. The diagrammatic flow of the participants is given in Fig. 1. Table 1 shows the characteristics of the study population. Among the patients included in the study, 79.6% (82/103) had dysmenorrhea, 64.1% (66/103) had chronic pelvic pain, 63.1% (65/103) had dyspareunia and 25.2% had dyschezia (26/103).

At 5-year follow-up 61 women (59.2%, 61/103) were still using NETA. The reasons for treatment interruption are shown in Fig. 1 and Table 2. Most of the women withdrew in the first two years of treatment compared to the last three years but without reaching statistic significance (25/42, 59.5% vs. 17/42, 40.5%; p = 0.081) (Suppl. Table I). However, we found that in the first two years it was more common to withdraw for adverse effects related to treatment (13/25, 52.0% vs. 3/17, 17.6%, p = 0.024) compared with the last three years. While in the latter years it was more common to withdraw for desire of pregnancy compared to the previous two years (7/17; 41.2% vs. 2/25, 8.0%, p = 0.010) (Fig. 1, Suppl. Table I). The cumulative continuation rates of NETA during 5 years is shown in Fig. 2a.

Effects on pain

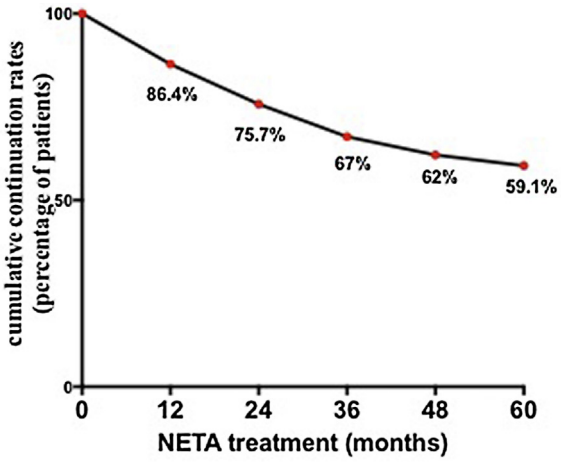
Regarding the primary end-point, the administration of NETA caused a significant improvement in the intensity of chronic pelvic pain, deep dyspareunia and dyschezia ($p < 0.001$ respectively) after five years treatment (Table 3, Suppl. Fig. 1). As expected, treatment caused the disappearance of symptoms related to the menstrual cycle such as dysmenorrhea. In particular, chronic pelvic pain and deep dyspareunia improved statistically between baseline and subsequent years of treatment. ($p < 0.001$, respectively). Dyschezia improved statistically between baseline and first-year treatment (p = 0.007), and then remained stable throughout the study (Table 3, Suppl. Fig. 1).

Seven women underwent surgery after interruption of treatment (7/103, 6.8%). In all cases the women opted for this option, as pain control under NETA was not effective. In all cases (7/7, 100%)

Table 2
Causes of interrupting treatment with NETA (n = 42 women).

Adverse effects, (n, %)	n = 16 women (16/42, 38.1%) Breakthrough bleeding (n = 5, 29.4%) Weight gain (n = 3, 18.7%) Migraine attacks (n = 3, 18.7%) Depression (n = 2, 12.5%) Lipids alteration (n = 2, 12.5%) Decreased libido (n = 1, 6.2%)
Lost to follow-up, (n, %)	n = 10 women (10/42, 23.8%)
Desire of pregnancy, (n, %)	n = 9 women (9/42, 21.4%)
Surgery, (n, %)	n = 7 women (7/42, 16.7%)
Total	42 women (100%)

a.



b.

ENDOMETRIOSIS RELATED SYMPTOMS (5-year)	MRI EVALUATION (5-year)			
	Partial Response (PR)	Stable disease (SD)	Progressive disease (PD)	TOTAL
No symptoms	6 (10.2%)	4 (6.8%)	2 (3.3%)	12 (20.3%)
Unchanged	8 (13.5%)	6 (10.2%)	3 (5.1%)	17 (28.9%)
Improved	19 (32.2%)	9 (15.3%)	2 (3.3%)	30 (50.8%)
Worsened	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TOTAL	33 (55.9%)	19 (32.2%)	7 (11.9%)	59 (100%)

No symptoms: VAS < 3 and a VAS baseline – VAS 5-years >2 in all symptoms
Unchanged: VAS baseline - VAS 5-year ≤ 2 in all symptoms

Fig. 2. a) The cumulative continuation rates of NETA treatment during 5 years b) changes in the volume of the endometriotic nodules during NETA therapy and their correlation with symptoms at the end of the treatment.

the presence of rectovaginal endometriosis was confirmed by surgery and histology.

At the end of 5 years treatment, 14 (22.9%, 14/61) women were very satisfied with their treatment, 27 (44.2%, 27/61) were satisfied, 15 (24.6%, 15/63) were uncertain, 5 (8.2%, 5/61) were

Table 3
Changes in pain symptoms during treatment.

	Baseline (n = 103)	1-year (n = 89)	2-year (n = 78)	3-year (n = 69)	4-year (n = 64)	5-year (n = 61)
Dysmenorrhea (mean ± SD) (n, %)	7.2 ± 1.7 (n = 82/103; 79.6%)	NA	NA	NA	NA	NA
Chronic pelvic pain (mean ± SD) (n,%)	5.3 ± 1.1 (n = 66/103; 64.1%)	3.8 ± 0.9 p < 0.001 (n = 57/89; 64%)	3.1 ± 0.7 p < 0.001 p < 0.001 (n = 50/78; 64.1%)	2.8 ± 0.8 p < 0.001 p = 0.208 (n = 41/69; 59.4%)	2.7 ± 0.9 p < 0.001 p = 0.594 (n = 35/64; 54.7%)	2.5 ± 1.0 p < 0.001 p = 0.344 (n = 31/61; 50.8%)
Deep dyspareunia (mean ± SD) (n,%)	5.4 ± 1.3 (n = 65/103; 63.1%)	4.2 ± 0.9 p < 0.001 (n = 58/89; 65.2%)	3.4 ± 0.7 p < 0.001 p < 0.001 (n = 50/78; 64.1%)	3.0 ± 0.8 p < 0.001 p = 0.069 (n = 45/69; 65.2%)	2.8 ± 0.9 p < 0.001 p = 0.523 (n = 43/64; 67.2%)	2.6 ± 1.0 p < 0.001 p = 0.320 (n = 41/61; 67.2%)
Dyschezia (mean ± SD) (n,%)	3.9 ± 1.3 (n = 26/103; 25.2%)	3.0 ± 0.9 p = 0.098 (n = 21/89 23.6%)	2.6 ± 0.5 p = 0.0004 p = 0.141 (n = 17/78; 21.8%)	2.4 ± 0.7 p = 0.0009 p = 0.353 (n = 13/69; 18.8%)	2.4 ± 0.8 p = 0.002 p = 0.959 (n = 11/64; 17.2%)	2.4 ± 1.0 p = 0.006 p = 0.953 (n = 11/61; 18.0%)

NA: not available.
First line: Intensity of symptoms of treatment were compared with baseline values.
Second line: Intensity of symptoms of treatment were compared with the year before.

Table 4
Adverse effects reported in the study.

Adverse effects (number of patients: 66)	Number of adverse effects	Percentage of adverse effects per all patients (n = 103) in the study
Weight gain	31	30.1% (31/103)
Vaginal bleeding	24	23.3% (24/103)
Lipids alterations	12	11.6% (12/103)
Decreased libido	11	10.7% (11/103)
Headache	9	8.7% (9/103)
Bloating or swelling	8	7.8% (8/103)
Depression	7	6.8% (7/103)
Acne	5	4.8% (5/103)
Erythematous cutaneous reaction	1	1.0% (1/103)
	108	

dissatisfied. Overall, 68.8% (42/61) of the women were satisfied or very satisfied of this long term NETA treatment, this represents a 40.8% (42/103) of all patients in the intention to treat analysis (ITT). Total number of adverse effects were 108 events in 66 patients (64.1%; 66/103) (Table 4). More common adverse effects were: weight gain (30.1%; 31/103); vaginal bleeding (23.3%; 24/103) and lipids alterations (11.6%; 12/103).

Radiological assessment

After 5-year treatment, fifty-nine patients (59/61, 96.7%) underwent a pelvic MRI to estimate the extent of the disease (Table 5). There was a significant reduction in the volume of the endometriotic nodules between baseline (n = 98) and the end of treatment (n = 59) ($4.58 \pm 0.86\,cm^3$ and $3.81 \pm 0.90\,cm^3$, $p < 0.0001$, unpaired *t*-test). Evaluating only patients who continued the treatment (n = 59) the results were similar ($4.45 \pm 0.80\,cm^3$ and $3.81 \pm 0.90\,cm^3$, $p < 0.0001$, paired *t*-test, Suppl. Fig. 2).

We found that NETA treatment caused a PR in 33 patients (55.9%, n 33/59); a SD was noted in 19 patients (32.2%, n 19/59) while a PD in seven patients (11.9%, n 7/59) (Fig. 3b). In three patients with PD we noted a rectal infiltration reaching the muscolaris mucosa. Interestingly, in patients with PD we found an improvement in pain symptoms in 2 patients (28.6%, n 2/7), a degree of symptoms similar to baseline in 3 patients (42.8%, n 3/7), while two patients had reduced symptoms compared to baseline (28.6%, n 2/7). Similar results in term of pain symptoms were seen in patients with SD (Fig. 2b).

Discussion

To the best of our knowledge, this is the first study evaluating a long-term progestin therapy (5 years with NETA) in women with rectovaginal endometriosis. This study confirms that NETA is effective in the treatment of pain symptoms caused by deep endometriosis (14–21) even in long-term treatment with acceptable side effects. We showed that 59.2% of the patients (61/103) were able to continue the five years NETA administration and 40.8% of the patients (42/103, in the ITT analysis) was satisfied or very satisfied with the drug at the end of the treatment. These results are lower compared to the literature where a reduction or complete relief from pain symptoms and satisfaction with NETA treatment ranged from 50% to 80%; however, in all these studies the administration period varied from 6 to 12 months of treatment (14–21). Overall the adverse effects were frequent and reported by a total of 66 women (66/103; 64.1%) (Table 4); however, only 16 women (15.5%, 16/103) withdrew the study because of adverse effects related to treatment (Fig. 1, Table 2). These results are slightly higher than those reported before by Vercellini et al. (50% of women reporting side effects after 12 months of NETA treatment) [19]. Again the longer treatment time in this study might be the cause for these discrepancies.

Interestingly, the higher percentage of exit from the study was seen within the first two years of treatment (59.5%; 25/42, Fig. 1) with 13 patients (13/103; 12.6%) withdrawing for adverse effects and nine patients (9/103; 8.7%) opting for a surgical intervention. This data suggests that these first two years of treatment are the more important for selecting those women who will accept long-term NETA treatment. In fact, the majority of the patients who tolerated NETA in the first two years were then able to continue the treatment in the three subsequent years (61/78, 78.2%) of the patients), (Figs. 1 ; 2 a, Table 2), suggesting that the first years of treatment might represent a sort of “window” period to evaluate the long-term acceptance to progestin treatment.

We are aware that adverse effects related to treatment should not be used as a surrogate biomarkers to identify those patients who might benefit for a specific drug [26], however we think that these findings might be useful in the discussion when planning long-term medical treatment for endometriosis.

We found that single NETA regimen is able to control the endometriotic disease (volume of nodules), evaluated by MRI, in term of PR or SD in 88.1% of the patients (52/59) after 5 years treatment (Fig. 2). These results confirmed that NETA treatment is able to control pain symptoms and, in some patients, the progression of the disease; but it is not able to induce significant regression of the lesions and thus it does not represent a definitive treatment for deep endometriosis [2].

Unfortunately, we found that in 11.9% of the patients (n = 7/59) who continued NETA treatment, a PD evaluated by MRI was found, with three cases showing rectal infiltration (Fig. 2). These results are in line with Guo et al. who found a 9.0% of the patients not responding to NETA [27]. This is an interesting and potentially dangerous finding, as although NETA is able to control pain symptoms (66.6%, 4/6 of these patients had stable or improved pain control) a progression of deep nodules is possible. This is particular important as pelvic PD might led to medical complications such as hydroureteronephrosis or a more extensive, difficult and morbid surgery in the future.

These findings indirectly suggest that NETA can act on several mechanisms of pain transmission (neuroinflammation, central nervous system mechanisms), which are independent of the volumetric increase of the disease [28–30].

More importantly, we think that these results suggest the need for a continuous monitoring of patients under NETA treatment, thus allowing the early detection of patients with PD. Moreover, imaging exams should not be performed only when patients report clinical symptoms, as we showed that the progression of the

disease might not be positively correlated with worsening of clinical symptoms (Fig. 2).

The reasons for a failed response to NETA in this 11.9% of the patients are beyond the findings of this study. The presence of the estrogen receptor (ER) and progesterone receptor (PR) are well-known as prerequisites for progestin action [31] and several molecular mechanisms, such as the imbalance of ER and PR subtypes, as well as adhesion molecules imbalance or might contribute to the mechanisms involved in the progesterone resistance have been implicated in progestin resistance in estrogen-driven diseases [32]. At the moment, as no biomarkers for NETA or progestin resistance has been proposed, a dynamic monitoring of response to NETA is warranted in order to switch the treatment of this "resistance population" to other medical treatments, such as dienogest [33], or to discuss in the right time the surgical option.

This is the first study reporting the long-term use of NETA, one of the therapies most commonly administered for the treatment of symptoms caused by deep endometriosis [34]. Despite the retrospective design, a strength of this study is that the data were prospectively collected in a standardized fashion for clinical follow-up.

We are aware that several limitations characterize the current study. The diagnosis of rectovaginal nodules was based on pelvic MRI and not on diagnostic laparoscopy and histology. These results cannot be generalized to all women; in fact, the women included in this study were highly motivated to start a medical treatment due to the severe symptomatology associated with rectovaginal endometriosis and refused alternative treatments, such as surgery. This high motivation could also explain the low withdrawal rate despite the high percentage of side effects recorded during the treatment.

In conclusion, our study showed for the first time that a long-term therapy with NETA determines a good control of the disease in patients with rectovaginal endometriosis. We showed that NETA is well tolerated with acceptable adverse effects and due to its low cost, it represents a good medication for long-term prescription. Patients who tolerate the first two years of NETA treatment are usually keen to continue the drug for other years, however during long-term administration a monitoring of the disease is warranted as a volumetric progression of rectovaginal nodules is possible in about 10% of the patients.

Author's roles

S.F. conceived and supervised the study, performed the follow-up and took lead on writing the manuscript.

M.M. recruited the patients enrolled in the study and performed the follow-up; performed the statistical analyses; prepared the draft of the manuscript.

A.R and L.C. assisted with patient enrolment, data acquisition, data management, and manuscript preparation. E.B. performed all the MRI examinations. C.S took part in the surgical component of the study. V.G.V performed the pathological examination of the surgical specimens and revised the manuscript. P.L.V. supervised the whole study procedure including the design of the study and interpretation of results; revised the manuscript.

All authors participated in the conception and drafting of the manuscript and all give final approval of this article.

Fundings

None.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejogrb.2017.03.033.

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