IS SHIFTING TO A PROGESTIN WORTHWHILE WHEN ESTROGEN-PROGESTINS ARE INEFFICACIOUS FOR ENDOMETRIOSIS-ASSOCIATED PAIN?

Running Head: From estrogen-progestins to progestins for inefficacy on endometriosis-associated pain

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ABSTRACT

The purpose of this study was to assess the proportion of patients satisfied with their treatment after a change from a low-dose oral contraceptive (OC) to norethisterone acetate (NETA) because of inefficacy of OC on pain symptoms.

To this end, prospective, self-controlled study was conducted on 153 women using OC as a treatment for endometriosis, and with persistence of one or more moderate or severe pain symptoms. At baseline and during 12 months after a shift from OC to oral NETA, 2.5 mg/day, pelvic pain was measured by means of a 0 to 10-point numerical rating scale and a multidimensional categorical rating scale. Variations in health-related quality of life, psychological status, and sexual function were also evaluated with validated scales. At the end of the study period participants indicated the degree of satisfaction with their treatment according to a 5-degree scale from very satisfied to very dissatisfied.

A total of 28 women dropped out of the study, the main reason being intolerable side effects (*n*=15). At 12-month assessment, 70% of participants were very satisfied or satisfied with NETA treatment (intention-to-treat analysis). Statistically significant improvements were observed in health-related quality of life, psychological status, and sexual function. At per-protocol analysis, almost half of the patients (58/125) reported sub-optimal drug tolerability. However, complains were not severe enough to cause dissatisfaction, drug discontinuation, or request for surgery.

These encouraging results could be used to counsel women with symptomatic endometriosis not responding to OC, and inform their decisions on modifications of disease management.

KEYWORDS: endometriosis; pelvic pain; medical treatment; combined oral contraceptives; progestins.

INTRODUCTION

Estrogen-progestins and progestins are currently considered as first-line treatments for symptomatic endometriosis in women not seeking pregnancy and without absolute surgical indications, such as adnexal masses of doubtful ultrasonographic appearance or large endometriomas, ureteral stenosis with hydronephrosis, and bowel stenosis causing persistent subocclusive symptoms.[1-5]

In women with endometriosis-associated pelvic pain, some authors suggest starting treatment with low-dose, combined, monophasic, oral contraceptive pills (OCs), and shifting to progestin monotherapy in case OCs are inefficacious or not tolerated.[6] This stepwise pharmacologic approach is based on metabolic, psychological, and practical considerations. Low-dose OCs have been proven safe when used in women without definite contraindications,[7-9] whereas the most popular progestins used for endometriosis treatment may alter the serum lipid profile[10,11] or affect bone mineralization.[12-15] As OCs are generally not perceived as medications for an illness, their use may limit the psychological burden of disease labelling.[16,17] Finally, when used continuously, OCs allow easy management of erratic bleeding through tailored cycling, whereas this modality may result less successful with progestin monotherapy.

However, this approach has been recently criticized as, based on published biological and clinical evidence, OCs might reveal less effective than progestins in controlling endometriosis, relieving associated pain symptoms, and preventing lesion progression.[18] Indeed, OCs have been indicated even as a risk factor for the development of deep, infiltrating lesions.[19] The issue here would be the supra-physiologic concentrations of estrogens contained in OCs, as 5 mg of ethinyl-estradiol (EE) are equivalent to around 1 mg of micronized estradiol or 0.625 mg of conjugated equine estrogen.[18] Thus, even low-dose OCs containing only 15-20 mg of EE would create a hyper-estrogenic environment resulting in suboptimal lesion and symptom control despite adequate combined progestin doses.[18]

Given this background, we deemed of interest to investigate which degree of pain symptom improvement and satisfaction with treatment could be obtained by shifting to a progestin monotherapy in women in whom low-dose OCs use did not relieve pain.

MATERIALS AND METHODS

The manuscript was prepared according to the Strengthening the Reporting of Observational studies in Epidemiology guidelines for reporting observational studies.[20] The main objective of the present study was to assess the proportion of patients satisfied with their treatment after a change from a low-dose, monophasic OC to norethisterone acetate (NETA) because of inefficacy of OC on pain symptoms (persistence of one or more moderate or severe pain symptoms, including dysmenorrhea, deep dyspareunia, non-menstrual pain, and dyschezia). Secondary objective was the evaluation of variations in pain symptoms, health-related quality of life, psychological status, and sexual function associated with the shift from OC to NETA.

The investigation was performed in an academic department, and the competent Institutional Review Board approved the study (Comitato Etico Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, determination #786/2013). Patients signed an informed consent form before enrolment. Women who denied their consensus were excluded.

Design

A prospective, self-controlled study design was adopted with the objective of assessing within-person comparisons before and after the shift from OC to NETA. With this study design each participant acts as her own control, in order to avoid the inherent biases caused by differences between patients.[21] In fact, the objective of the study was to assess variations in efficacy when shifting to NETA not in a general population of patients taking OC, but specifically in those patients who were dissatisfied because of inefficacy of OC and that would have otherwise discontinued medical therapy.

Study participants

We considered 18- to 40-year old women, not seeking conception, with a surgical diagnosis of endometriosis in the previous 24 months or with a current non-surgical diagnosis of endometriosis,[22] and using an OC for pelvic pain, but unwilling to continue or modify (change of OC type or modality of assumption) the current treatment because of inefficacy on symptoms and overall dissatisfaction with OCs.

Non-surgical diagnoses were based on ultrasonographic criteria in patients with ovarian endometriomas;[23,24] on visual inspection of the posterior fornix and biopsy of vaginal lesions in those with rectovaginal endometriosis;[10,25] on ultrasonographic criteria,[26] cystoscopic findings, and biopsy of vesical lesions in those with bladder detrusor endometriosis; on physical signs at recto-vaginal examination and ultrasonographic criteria[27,28] in those with deep lesions infiltrating the Douglas pouch and parametria; and on ultrasonographic criteria[23,28] double contrast barium enema and rectosigmoidoscopy or colonoscopy findings in those with full-thickness bowel lesions. Magnetic resonance imaging was performed in selected circumstances.

Women were referred or self-referred to our tertiary-care outpatient clinic for the treatment of endometriosis. Patients were excluded in case of 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 disorders that may cause pelvic pain independently of endometriosis presence (e.g., pelvic inflammatory disease or pelvic varices or genital malformations at previous surgery; known urologic and orthopedic diseases); psychiatric disturbances; and history of drug or alcohol abuse. Participants were recruited during the period August 2014 – July 2015.

Women were informed that OCs are considered by some authors as the first-line treatment for endometriosis-associated pelvic pain, but that further medical therapy steps are available in case of inefficacy. They were also informed that medical therapies for endometriosis are usually effective in reducing various types of pain in more than two thirds of patients.[29-31] However, drugs

induce only temporary relief, are not expected to be definitively curative, and may cause several side effects (listed, with percentages derived from previous studies conducted in our centre). Finally, when hormonal treatments are to be continued for long periods, estrogen-progestins and progestins appear to be among the compounds that most favourably balance benefits, harm and costs.[17,32-34]

In case of pain persistence, it was explained that the estrogen included in OCs on one hand may prevent potentially detrimental effects of hypo-estrogenizing treatments (e.g., decrease in bone mineral density and unfavourable modifications in serum lipid pattern), but on the other hand may limit the therapeutic efficacy on endometriotic implants that, being estrogen-sensitive, may retain part of their metabolic activity. Women were informed that other drugs for symptomatic endometriosis were available but, owing to severe untoward effects and/or high costs, generally they were not suggested for prolonged treatment periods. Finally, patients were also informed that laparoscopic surgery was a reasonable alternative in case they declined switching from a OC to a progestin, but that pain and lesion recurrence was about 10% a year without long-term postoperative medical therapy.[35,36]

Treatments

The OCs used in our centre were monophasic formulations containing ethinyl-estradiol 0.015 mg and gestodene 60 mg or, in case of spotting, ethinyl-estradiol 0.02 mg and desogestrel 150 mg. In smokers and in those with a BMI $\geq$ 30, a combination of ethinyl-estradiol 0.02 mg and levonorgestrel 100 mg was prescribed.

Norethisterone acetate, a 19-nortestosterone derivative progestin, has been repeatedly evaluated in women with endometriosis,[37-43] and has been routinely used in our referral centre for several years.[6,10,25,44] Norethisterone acetate is approved by the FDA and the Italian Ministry of Health for the treatment of endometriosis and is reimbursed by the Italian National Health System. Norethisterone acetate was prescribed at the dose of 2.5 mg once a day, *per os*. The progestin was

started after 4-7 days since OC discontinuation, depending on the type of OC previously used, and it was continued without preplanned time limits. However, for the purpose of the present study, only the first 12 months of use have been evaluated. In case of prolonged spotting (≥ 7 days) or breakthrough bleeding, the patients were advised to discontinue treatment for one week. When needed, naproxen sodium was the standard non-steroidal anti-inflammatory drug prescribed (one 550-mg tablet twice a day unless contraindicated).

Measurements

All patients assisted in our centre systematically undergo clinical and ultrasonographic evaluation every six months. On these occasions, women are routinely asked to complete five questionnaires, two on pain (a numerical rating scale, NRS; and a multi-dimensional categorical rating scale, MCRS), one on quality of life (the Short Form-12 questionnaire, SF-12), one on psychological status (the Hospital Anxiety and Depression scale, HADS), and one on sexual functioning (the Female Sexual Function Index, FSFI). Women are also asked to indicate drug tolerability using a NRS and to rate the degree of satisfaction with their treatment.

The above scales and questionnaires have been described previously in detail.[6,10,25,44,45] The presence and severity of dysmenorrhea, deep dyspareunia, non-menstrual pelvic pain, and dyschezia were assessed using an 11-point NRS, with 0 indicating absence of pain and 10 pain as bad as it could be. Patients were also asked to grade the severity of the above symptoms using a 0- to 3-point MCRS modified from that devised by Biberoglu and Behrman.[46] Irregular bleeding during treatment was defined as spotting (scanty bleeding requiring ≤ 1 pad or tampon per day) or breakthrough bleeding (light or moderate bleeding requiring ≥ 2 pads or tampons per day). Pain during spotting or breakthrough bleeding was considered as dysmenorrhea.

The SF-12 health survey, developed from the original SF-36 questionnaire,[47,48] is a well know, validated self-administered 12-item instrument. It measures health dimensions covering functional status, well-being, and overall health. Information from the 12 items is used to construct

177 physical (PCS-12) and mental (MCS-12) component summary measures,[49,50] with higher scores
178 indicating better health perception.

179 The HADS questionnaire is a self-assessment mood scale specifically designed for use in
180 non-psychiatric hospital outpatients to determine states of anxiety and depression. It comprises 14
181 questions, 7 for the anxiety subscale and 7 for the depression subscale. Lower scores indicate better
182 psychological status.[51]

183 The FSFI questionnaire is a 19-item, multidimensional, self-report instrument for evaluating
184 the main categories of female sexual dysfunction and sexual satisfaction.[52-54] The transformed
185 maximum score for each domain is 6, and the maximum (best) transformed full-scale score is 36,
186 with a minimum full-scale score of 2.0.

187 Occurrence of side effects associated with medical treatments is actively investigated in our
188 endometriosis outpatient clinic, and the overall tolerability of hormonal therapies is measured using
189 a 0- to10-point NRS, with 0 indicating absolutely intolerable untoward effects and 10 absence of
190 adverse effects. Scores are then categorized, with 9-10 indicating that a drug is very well tolerated;
191 7-8, well tolerated; 5-6, moderately tolerated; 3-4, poorly tolerated; 0-2, not tolerated.[6]

192 Patients rated the degree of satisfaction after the modification of their treatment according to
193 a five-category scale (very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very
194 dissatisfied) by answering the following question: “Taking into consideration the variations
195 occurred in pain symptoms, overall physical and psychological well-being, health-related quality of
196 life, and sexual functioning, how would you define the level of satisfaction with your current
197 treatment?” For this study, only women that were dissatisfied or very dissatisfied with their OC
198 treatment because of inefficacy on pain (one or more persistent pain symptom > 5 points as
199 measured by the NRS) were considered. In order to limit the potential effect of confounding,
200 satisfaction with treatment, the main study outcome, was dichotomized into “satisfied” (very
201 satisfied plus satisfied) and “dissatisfied” (neither satisfied nor dissatisfied plus dissatisfied plus
202 very dissatisfied).

Data management

The focus of the investigation was not a head-to-head comparison between OC and NETA but, instead, quantification of the proportion of women who were satisfied with NETA treatment 12 months after OC discontinuation because of inefficacy. No study is available to define the potential benefits of progestins over OCs in this clinical condition. Therefore, a pre-planned power calculation was not performed, and we decided to include all the eligible patients evaluated in a 1-year period.

Data were archived using Excel 2003 (Microsoft Corporation, Redmond, Washington, U.S.A.) and exported in SPSS 18.0 (SPSS, Inc, Chicago, IL, U.S.A.) or SAS software 9.4 (SF-12 data; SAS Institute Inc., Cary, NC, U.S.A.) for statistical analysis. Estimate of patient satisfaction rate was performed according to the intention-to-treat principle, considering as dissatisfied all patients who dropped out of the study for any reason except conception seeking, thus including request for surgery and lost to follow-up. Variations in pelvic pain symptoms, health-related quality of life, psychological status, sexual functioning, and drug tolerability between baseline and 12-month values were evaluated by using the paired Student *t* test for normally distributed data, the non-parametric Wilcoxon matched pairs test for non-normally distributed data, the McNemar test for categorical variables, and the Fisher Exact test in case of cells without numerical data. Determinants of satisfaction with treatment were investigated with unpaired tests (Student *t* test for normally distributed continuous variables, Wilcoxon test for non-normally distributed continuous variables, and the chi-squared test for categorical variables). All statistical tests were two-sided. A *P* value < 5% was considered statistically significant. When appropriate, 95% confidence intervals (CIs) of proportions were calculated by applying a binomial distribution model.

RESULTS

A total of 153 women evaluated during the recruitment period were enrolled in the study (Figure 1). The baseline demographic and clinical characteristics of the patients are shown in Table 1. Two

thirds of women previously underwent surgery for endometriosis, and all had stage III-IV disease according to the revised American Society for Reproductive Medicine (ASRM) classification[55], except one patient who had stage II endometriosis. A total of 116 (76%) patients had deep endometriotic lesions, and 91 (60%) had ovarian endometriomas. The median [interquartile range, IQR] duration of previous OC use was 9 [5–24] months. One hundred-two women (67%) were using OC cyclically and 51 (33%) continuously. Sixty-four subjects (42%) were dissatisfied with OC use also because of side effects in addition to inefficacy on pain symptoms. However, inefficacy was the main reason for dissatisfaction also in these 64 subjects independently of intolerance. The most frequent side effects were headache (15%) and spotting/breakthrough bleeding (15%).

A total of 125 women completed the preplanned 12-month study period, whereas 28 (18%) dropped out of the study before the 6-month follow-up evaluation (n = 2), or between the 6- and the 12-month assessment (n = 26; Figure 1). Overall, 15 women referred one or more intolerable side effects with NETA as the reason for abandoning the study (headache n = 7; erratic bleeding, n = 6; weight increase, n =4; abdominal bloating, n = 4; acne, n = 2; mood nausea, decreased libido, vaginal dryness, breast tenderness, depressed mood, n = 1 each).

A significant reduction in symptoms' severity as measured by both the NRS and the MCRS scales was observed when comparing baseline and 12-month measurements (Table 2). Median [IQR] dysmenorrhea NRS scores decreased from 8 [6-9] to 0 [0-0] after 1 year of NETA treatment. According to the MCRS, menstrual pain was moderate or severe in 94/125 (75%) women at baseline evaluation, but in only one at 12-month follow-up assessment. The variations in deep dyspareunia, non-menstrual pain, and dyschezia followed a similar pattern. In particular, median [IQR] deep dyspareunia NRS scores, evaluated in the 114 women who were sexually active both at baseline and 12-month follow-up, decreased from 7 [1-8] to 0[0-5]. According to the MCRS 54/114 (47%) women suffered from moderate-to severe pain at intercourse at baseline, compared with 15/114 (13%) after 1 year of NETA treatment (Table 2).

Only the physical component of the SF-12 improved at the end of the study period, whereas no substantial variation was observed in the mental component of the health-related quality of life questionnaire (Table 2). However, when the psychological status was evaluated by means of HADS, significant reductions were observed in the scores of both anxiety and depression questionnaire components. According to the FSFI, a statistically significant amelioration of sexual functioning was observed in the 114 sexually active women at baseline and end of follow-up (Table 2).

At final per-protocol analysis, almost half of the patients (58/125) reported sub-optimal drug tolerability. However, complains were not severe enough to cause dissatisfaction, drug discontinuation, or request for surgery. Side effects referred at baseline and at 12-month evaluation are shown in Table 3. After switching from OC to NETA, the prevalence of headache, spotting, and nausea decreased significantly. The mean ± SD tolerability score as assessed by the NRS increased from 5.4 ± 2.6 during OC use to 6.9 ± 2.5 after 12 months of NETA treatment. Overall, 34% (42/125) women scored their tolerability as good or very good (NRS $\geq$ 7), compared with 54% (67/125) at 12-month assessment.

When evaluating the degree of satisfaction with NETA treatment at the end of the study period, four women who discontinued the drug between 6- and 12-month follow-up visits because of pregnancy desire were excluded, as variation in satisfaction with treatment during time is unpredictable. Eventually, 105/149 patients (70%; 95% C.I., 63% to 77%) were satisfied or very satisfied with NETA treatment, whereas 44/149 (30%; 95% C.I., 23% to 37%) were neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied. The baseline demographic and clinical characteristics of the 105 patients satisfied with NETA treatment and those of the 44 dissatisfied ones were substantially similar. A statistically significant difference was observed only for non-menstrual pain, which was more severe at both the NRS and the MCRS in the group of dissatisfied patients (Supplemental Tables 1 and 2).

The impact of the two potentially relevant variables, i.e., the modality of OC use (cyclic versus continuous) before switching to NETA, and type of endometriotic lesions (deep lesions versus ovarian endometriomas) was investigated. The proportion of satisfied patients was 24/33 (73%; 95% C.I., 57% to 86%) in women with deep lesions and previous continuous OC use; 54/80 (68%; 95% C.I., 57% to 77%) in those with deep lesions and previous cyclic OC use; 11/17 (65%; 95% C.I., 42% to 84%) in those with ovarian endometriosis and previous continuous OC use; and 16/19 (84%; 95% C.I., 64% to 96%) in those with ovarian endometriosis and previous cyclic OC use.

DISCUSSION

According to the results of the present study, slightly more than two thirds of women with endometriosis experiencing pelvic pain symptoms despite OC use were satisfied one year after shifting to NETA treatment. The satisfaction rate at the end of the study period was not significantly influenced neither by the modality of previous OC use, nor by the type of endometriotic lesion present, thus supporting the consistency of the general results. However, with one exception, all the patients who underwent previous surgery had ASRM stage III-IV endometriosis, and all those who were recruited based on non-surgical criteria had ovarian endometriomas or deep infiltrating lesions. Therefore, our results may not be generalizable to women with early stage disease.

Pain symptoms' scores decreased during NETA treatment. The reduction of dysmenorrhea scores was expected as most participants experienced progestin-induced amenorrhea. The effect of NETA on deep dyspareunia is worthier of note and confirms our previous findings on patients with severe pain at intercourse.[25,44] Only a tiny minority of women referred moderate or severe non-menstrual pain and dyschezia at the end of the study period. Overall, except some women with deep dyspareunia as their main complaint, the shift from an OC to NETA was of substantial benefit for patients who were still moderately or severely symptomatic despite OC use. This seems important because, in similar circumstances, this “third way” can be chosen as an alternative to stepping-up by

using drugs with less favorable therapeutic profiles (e.g., GnRH agonists and danazol) or undertaking surgery. Moreover, this finding supports the view that, in some women, the estrogen component of OCs may not allow sufficient inhibition of ectopic endometrium metabolism, thus occasionally limiting the efficacy of these medications in relieving endometriosis-associated pelvic pain symptoms.[18]

Also the increased tolerability of NETA compared with that of OC may have influenced the likelihood of being satisfied with the treatment received. Indeed, as medical therapy for endometriosis is not definitively curative, the issue of tolerability, in addition to that of safety and efficacy, is crucial, because long periods of treatment should be foreseen. The reduction in the frequency of nausea and headache after shifting from OC to NETA was expected, as these side effects are typically associated with estrogens.[56] The decrease in the frequency of spotting confirms the good control of NETA on erratic uterine bleeding.[6,10,39,40,43]

Nevertheless, slightly less than half of the patients who completed the study period (per-protocol analysis) referred that NETA was moderately, poorly, or not tolerable, although not to the point of causing dissatisfaction, drug discontinuation, or request for surgery. Moreover, the majority of participants who dropped out of the study did so because of side effects. Tolerance is a determinant of patient compliance and adherence to drugs, and should receive more focus in future trials on medical treatment for endometriosis. In fact, according to major international guidelines, the efficacy of various hormonal compounds on pain is similar, whereas side effects vary.[1-4]

The physical component of the SF-12 questionnaire improved significantly during NETA treatment, whereas the mental component did not. This last finding is at odds with the ameliorations observed in both the anxiety and depression dimensions of the HADS scale. We do not have an explanation for this apparent discrepancy, and random fluctuation of data, or incapacity of the SF-12 scale to capture differences in this particular domain, cannot be excluded.

Also sexual function, as measured by the FSFI, improved significantly. However, as repeatedly observed,[6,44,57] the mean score remained well below the cut-off for a physiologic

condition. We have previously interpreted this finding as a demonstration that impacting on a single dimension, i.e., pain at intercourse, of a multifactorial experience such as sexual life, may not completely restore a complex physiological function. Moreover, NETA reduced libido and lubrication in some women. However, also it may not be excluded that the FSFI cut-off may be inappropriate for a population of endometriosis patients. Therefore, observing the overall trend in FSFI scores' variation during treatment might be more opportune than focusing on the achievement of the exact and potentially arbitrary cut-off score of 26.55.

The self-controlled design may appear as a limitation of our study. However, this model was chosen because our aim was not to compare OC and NETA in a parallel-group, randomized, controlled trial (RCT), but rather to evaluate sequentially the effect of NETA used as a second-line treatment modality specifically in a selected group of non-responders to OC. In this setting, recruited patients acted as their own control, thus limiting the effect of confounding inherent to other designs. In fact, relevant characteristics that can influence study outcomes may differ between patients.[21] The use of multivariable analyses should account for these differences in observational studies, but residual confounding may not be excluded. Moreover, the intention-to-treat analysis adopted to investigate patient satisfaction included all drop-outs except women who discontinued treatment to seek a conception. Thus, overoptimistic results should have been avoided. Moreover, even if a placebo effect cannot be excluded, it is presumably limited given that this is a population of women who already experienced a treatment failure and were thus presumably less prone to a placebo effect. Noteworthy, given the pragmatic approach of this study, i.e., reflecting real world clinical management, the existence of a placebo component in the determinisms of the observed findings would not invalidate the general conclusions.

However, the "regression toward the mean" phenomenon could theoretically explain at least partly the results observed in a self-controlled study. In fact, extreme values are likely unduly influenced by random variation and, when re-measured, they tend to be closer to the mean of the original population from which the study subjects were drawn.[58,59] Therefore, when the patients'

conditions are worse than average and they are enrolled in a self-controlled study of a new therapy because standard regimens seem to have lost efficacy, some general amelioration may occur that has nothing to do with improved treatment.[58] Despite this, the impact of regression toward the mean should have been limited in our study, as we considered patients complaining of chronic and fairly stable pain symptoms that were measured on more than one occasion during the pre-enrollment phase.[58]

Observational studies are not suited to assess efficacy, that is whether a new, experimental treatment can work. For this purpose, the explanatory RCT is the standard investigational modality. However, observational studies can be used to assess whether interventions that have already been proven to work under ideal circumstances, work also in real life.[60,61] Therefore, observational studies are useful to evaluate effectiveness and efficiency and, in case of medical treatment for endometriosis, to define the prospective role of the available medications in different clinical conditions.[61]

A pre-planned power analysis was not performed, but the sample size of our study was larger than that theoretically required to detect as statistically significant the observed difference between baseline and 12-month follow-up values in most outcome measures. The relatively high dropout rate (28/153, 18%) was not surprising, given that the study population was generally at unfavourable prognosis considering the persistence of moderate to severe pain symptoms despite OC use, and the related patient dissatisfaction status. In this regard, it may be hypothesized that the use of dienogest instead of NETA could have led to greater efficacy[57] and/or better tolerability,[6] and thus higher degree of satisfaction with treatment. However, we have selected NETA because many patients in our centre cannot afford the much higher cost of dienogest.[6] In fact, our general policy is to prescribe dienogest only in case of intolerance to NETA.

In our opinion, the results of the present study should not lead to systematic prescription of progestins as the first-line treatment for endometriosis, but should rather be used when counselling non-respondents to OCs. Progestin treatment for years may raise some safety concerns.[11,14-16,62,63]

Therefore, these drugs should be chosen to step-up when OC are not effective on pain (or not tolerated or contraindicated), or in presence of severely infiltrating lesions, when a more profound inhibition of ectopic endometrium metabolism is desirable. More in general, we believe that the current approach to management of endometriosis, characterized by selection, among available alternatives, of the purportedly most efficacious intervention on the basis of head-to-head comparisons, should be substituted by a stepwise approach that takes into consideration not only absolute efficacy, but also safety, tolerability, and costs, in order to define an overall therapeutic profile. Medications with the most favorable therapeutic profile should be chosen first, stepping-up, in non-responders only, to medications that, although with a less favourable overall therapeutic profile, are more effective on pain.[16]

We are convinced that women suffering from endometriosis badly need answers to questions that matter to them. These questions are those that physicians face in their everyday practice. Performance of RCTs is nowadays problematic for independent investigators, owing to unreasonable increase in administrative bureaucracy and often unaffordable insurance costs.[61] On the other hand, industry supported, explanatory RCTs have almost exclusively registration purposes and may not provide those answers that are important to patients.[34,64,65] Indeed, we are not aware of RCTs investigating medical or surgical alternatives specifically for symptomatic women not responding to OC use. With this study we have tried to provide a pragmatic description of what could be obtained by simply shifting from an OC to an inexpensive progestin. In this frequently encountered clinical situation, two out of three patients benefitted from this change of medication, and were satisfied with the new treatment after one year of use. Precisely because our investigation was not conducted under ideal experimental conditions, our data should be generalizable and could be used to counsel non-responders to OC, in order to help informing their decisions on how to modify the management of their disease.

AUTHOR CONTRIBUTIONS

PV: conception and design of the study, manuscript preparation; FO, MPF, and LB: acquisition and analysis of data; AR: analysis and interpretation of health-related quality of life data; ES: conception and design of the study, analysis and interpretation of data; all the authors: critical revision of the article for important intellectual content, and approval of the final version of the manuscript.

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CONFLICT OF INTEREST

PV, FO, MPF, LB, and AR declare that there is no conflict of interest. ES received grants from Ferring and Serono.

ETHICAL APPROVAL

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

429 FIGURE LEGENDS

430 Figure 1. Flow-chart showing recruitment and progression through the study of women who shifted
431 from OC to NETA because of inefficacy on pain symptoms.

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Table 1. Distribution of baseline demographic and clinical characteristics of women who shifted to norethisterone acetate for inefficacy of low-dose oral contraceptive (*n* = 153).

Characteristic	Enrolled patients (*n* = 153)
Age (years)	33.4 ± 5.4
BMI (Kg/m^2)	21.4 ± 3.7
Smoking	31 (20.3%)
Previous deliveries	37 (24%)
Previous interventions for endometriosis[a]	
None	51 (33%)
1	79 (52%)
2	18 (12%)
≥ 3	5 (3%)
Endometriotic lesion type[b]	
Deep infiltrating endometriosis	116 (76%)
Ovarian endometriomas	91 (60%)
Estroprogestin use	
Duration [months]	9 [5-24]
Continuous use	51 (33%)
Cyclic use	102 (67%)

Data is reported as mean ± SD, or number (percentage), or median [interquartile range].

BMI = body mass index.

[a] A total of 101/102 of the women who underwent previous surgery had stage III-IV endometriosis according to the revised American Society for Reproductive Medicine classification[55].

[b]The sum does not add to the total as some women had both lesion types.

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Table 2. Per-protocol analysis[a] of pain symptoms, health-related quality of life, psychological status, and sexual functioning scores variation between baseline and 12-month evaluation in patients (*n* = 125) shifting from low-dose oral contraceptive to norethisterone acetate for inefficacy on pain.

Symptoms / Questionnaires	Baseline	12 months	*P*
Dysmenorrhea			
NRS	8 [6-9]	0 [0-0]	<0.001
MCRS ≥ 2	94 (75%)	1 (1%)	<0.001
Deep dyspareunia [b]			
NRS	7 [1-8]	0 [0-5]	<0.001
MCRS ≥ 2	54 (47%)	15 (13%)	<0.001
Non-menstrual pelvic pain			
NRS	5 [0-7]	0 [0-2]	<0.001
MCRS ≥ 2	48 (38%)	4 (3%)	<0.001
Dyschezia			
NRS	4 [0-7]	0 [0-0]	<0.001
MCRS ≥ 2	52 (42%)	5 (4%)	<0.001
SF-12			
Physical component	30.7 ± 11.0	53.4 ± 6.7	<0.001
Mental component	45.0 ± 9.7	46.3 ± 9.9	NS
HADS			
Anxiety	12.3 ± 6.6	9.5 ± 6.4	<0.001
Depression	6.2 ± 3.3	5.0 ± 3.2	0.001
Total	6.1 ± 3.6	4.5 ± 3.6	<0.001
FSFI total score[b]	21.4 ± 6.3	24.5 ± 6.4	<0.001

Data is reported as mean ± SD, or number (percentage), or median [interquartile range].

NRS = 0-10-point Numerical rating scale. MCRS = 0-3-point multidimensional categorical rating scale modified from that devised by Biberoglu and Behrman[46]. SF-12 = Short Form-12[50]. HADS = Hospital Anxiety and Depression Scale[51]. FSFI = Female Sexual Function Index[52,53]. NS = not significant.

[a]Women who withdrew before 12-month follow-up assessment (n = 28) were excluded.

[b]Eleven women did not have sexual intercourses either at baseline and/or at 12-month evaluation.

Table 3. Per-protocol analysis of frequency of side effects reported at baseline and at 12-month evaluation by patients (n = 125) shifting from oral contraceptive to norethisterone acetate.

Side effects[a]	Baseline	12 months	*P*
Headache	42 (34%)	28 (22%)	0.03
Spotting	39 (31%)	11 (9%)	<0.001
Breakthrough bleeding	4 (3%)	0 (0%)	NS
Weight gain	32 (26%)	38 (30%)	NS
Nausea	11 (9%)	2 (2%)	0.001
Decreased libido	35 (28%)	45 (36%)	NS
Vaginal Dryness	37 (30%)	44 (35%)	NS
Bloating or swelling	17 (14%)	13 (10%)	NS
Breast tenderness	6 (5%)	5 (4%)	NS
Acne	1 (1%)	3 (2%)	NS
Alopecia	0 (0%)	3 (2%)	NS
Mood disorders	9 (7%)	17 (14%)	NS
Others	13 (10%)	14 (11%)	NS

[a]Some women reported more than one side effect.

Data are number (percentage).

Supplemental Table 1. Comparison of the baseline demographic and clinical characteristics of women who were satisfied and women who were not satisfied after 12 months of treatment with norethisterone acetate (*n* = 149).

Characteristic	Satisfied *n* = 105	Not satisfied *n* = 44	*P*
Age (years)	33.4 ± 5.5	33.5 ± 5.4	NS
BMI (Kg/m^2)	21.3 ± 3.6	21.4 ± 4.3	NS
Smoking	20 (69%)	9 (31%)	NS
Previous deliveries	25 (67%)	12 (33%)	NS
Previous interventions for endometriosis[a]	75 (74%)	26 (26%)	NS
Endometriotic lesion type[b]			
Deep infiltrating endometriosis	78 (69%)	35 (31%)	NS
Ovarian endometriomas	68 (76%)	21 (24%)	NS
Estroprogestin use			
Duration [months]	9 [6-14]	10 [4-24]	NS
Continuous use	35 (70%)	15 (30%)	NS
Cyclic use	70 (71%)	29 (29%)	
Pain symptoms			
Dysmenorrhea	83 (71%)	33 (29%)	NS
Deep dyspareunia[c]	57 (70%)	24 (30%)	NS
Non-menstrual pelvic pain	59 (68%)	28 (32%)	NS
Dyschezia	37 (66%)	19 (34%)	NS
Side effects (in addition to pain)	44 (70%)	19 (30%)	NS

Data is reported as mean ± SD, or median [interquartile range], or number (percentage). Row percentages are reported.

BMI = body mass index. NS = not significant.

Women who withdrew for seeking pregnancy (*n*=4) were excluded.

Women who withdrew before the 12-month follow-up were considered as not satisfied (n=24).

[a]A total of 100/101 of the women who underwent previous surgery had stage III-IV endometriosis according to the revised American Society for Reproductive Medicine classification[55].

[b]The sum does not add to the total as some women had both lesion types.

[c]Eleven women did not have sexual intercourses either at baseline and/or at 12-month evaluation.

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Supplemental Table 2. Comparison of baseline clinical assessment of women who were satisfied and women who were not satisfied after 12 months of treatment with norethisterone acetate (*n* = 149).

Symptoms / Questionnaires	Satisfied *n* = 105	Not satisfied *n* = 44	*P*
Dysmenorrhea			
NRS	8 [6-9]	7 [5-8]	NS
MCRS ≥ 2	80 (76%)	31 (70%)	NS
Deep dyspareunia [a]			
NRS	7 [0-8]	8 [4-9]	NS
MCRS ≥ 2	46 (45%)	25 (61%)	NS
Non-menstrual pelvic pain			
NRS	5 [0-7]	7 [5-8]	0.002
MCRS ≥ 2	37 (35%)	25 (57%)	0.015
Dyschezia			
NRS	4 [0-7]	6 [0-8]	NS
MCRS ≥ 2	44 (42%)	23 (52%)	NS
SF-12			
Physical component	30.1 ± 10.3	31.3 ± 12.8	NS
Mental component	45.4 ± 9.6	44.2 ± 9.9	NS
HADS			
Anxiety	6.0 ± 3.2	6.2 ± 3.3	NS
Depression	6.0 ± 3.5	6.5 ± 4.0	NS
Total	12.0 ± 6.4	12.7 ± 7.0	NS
FSFI total score [a]	21.5 ± 6.2	21.2 ± 6.4	NS
Tolerability[b]			
NRS	5.4 ± 2.5	5.9 ± 2.9	NS
Well tolerated (NRS ≥ 7)	35 (33%)	18 (41%)	NS

Data is reported as mean ± SD, or median [interquartile range], or number (percentage).

NRS = 0-10-point Numerical rating scale. MCRS = 0-3-point multidimensional categorical rating scale modified from

that devised by Biberoglu and Behrman[46]. SF-12 = Short Form-12[50]. HADS = Hospital Anxiety and Depression Scale[51]. FSFI = Female Sexual Function Index[52,53]. NS = not significant.

Women who withdrew for seeking pregnancy (n=4) were excluded.

Women who withdrew before the 12-month evaluation were considered as not satisfied (n=24).

[a]Refers to 99 satisfied women and 41 not satisfied women.

[b]Assessed using a 0 to 10-point numeric scale and a 5-category scale: very well tolerated, well tolerated, moderately tolerated, poorly tolerated, not tolerated.

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