Original Article

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest
DOI: 10.1159/000486335

Received: August 28, 2017
Accepted after revision: December 14, 2017
Published online: February 27, 2018

Shifting from Oral Contraceptives to Norethisterone Acetate, or Vice Versa, because of Drug Intolerance: Does the Change Benefit Women with Endometriosis?

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Keywords
Endometriosis · Medical treatment · Estrogen-progestin combinations · Progestins · Norethisterone acetate · Pelvic pain

Abstract
Background/Aims: Oral contraceptives (OC) and norethisterone acetate (NETA) are among first-line medical therapies for symptomatic endometriosis, but their use is sometimes associated with intolerable side effects. We investigated whether shifting from low-dose OC to NETA (2.5 mg/day), or vice versa, improved tolerability. ***Methods:*** Sixty-seven women willing to discontinue their treatment because of intolerable side effects despite good pain relief, were enrolled in a self-controlled study, and shifted from OC to NETA (n = 35) or from NETA to OC (n = 32). The main study outcome was satisfaction with treatment 12 months after the change. Tolerability, pain symptoms, health-related quality of life, psychological status, and sexual functioning were also evaluated. ***Results:*** After treatment change, good tolerability was reported by 37% of participants who shifted to NETA, and by 52% of those who shifted to OC. At 12-month assessment, 51% of women intolerant to OC were satisfied with NETA, and 65% of those intolerant to NETA were satisfied with OC (intention-to-treat analysis). Other study variables did not vary substantially. ***Conclusions:*** In selected endometriosis patients, shifting from OC to NETA, or vice versa, because of side effects, improved tolerability. Better results were observed when substituting NETA with OC rather than the other way round.

Introduction

Combined oral contraceptives (OC) and progestins are indicated by major international guidelines as the first-line medical treatment options for women not seeking conception and with endometriosis-associated pelvic pain [1–4]. Overall, about two thirds of patients appear to benefit from these therapies [5–16]. The main reason of treatment failure in the remaining third, in addition to inefficacy, is drug intolerance. As untoward effects of OCs and progestins partly differ, a shift from the former to the latter compounds, or vice versa, could allow continuing treatment with a safe, effective, and inexpensive medication without the need for stepping up

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to a drug with a less favorable therapeutic profile or resorting to surgery. However, very limited information is available on what should a patient expect from these changes [17, 18]. The answers to these questions seem important, as the clinical issue is not rare and may interfere with health-related quality of life and disease management. Given this background, we sought to investigate whether shifting from an OC to a progestin, or vice versa, specifically because of drug intolerance, is of benefit in terms of relief from side effects and, in case these measures are effective, whether they imply reduced efficacy on pain symptoms.

Materials and Methods

The main objective of the present study was to assess the proportion of patients satisfied with their therapy 12 months after a change from a low-dose, monophasic OC to norethisterone acetate (NETA), or vice versa, because of side effects intolerable to the point of requesting treatment discontinuation. Therefore, in the present study population, patient dissatisfaction was not caused by inefficacy on pain symptoms. 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, or vice versa.

A prospective, self-controlled study design was adopted because it allows within-person comparisons avoiding the potential confounding caused by differences between patients [19]. The investigation was performed in an academic department specializing in the management of endometriosis, and the competent Institutional Review Board approved the study. Patients signed an informed consent form before enrollment. Women who denied their consensus were excluded.

Patients

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, and using an OC or NETA for pelvic pain, but unwilling to continue the current treatment because of dissatisfaction due to intolerable side effects. Non-surgical diagnoses were based on previously published criteria [20–22]. Participants were recruited during the period August 2014 and July 2015.

Women were given the following information: (i) OC or NETA may, in some women, cause side effects, frequently because of the estrogen component in the former case, and of residual androgenic activity in the latter case; (ii) switching to, respectively, a progestin monotherapy or an OC containing another type of progestin could result in subjective improvement; (iii) also the alternative drug was associated with side effects, and the efficacy of the proposed change of therapy was uncertain; (iv) OCs and progestins are indicated by major international guidelines as the first-line treatment for endometriosis-associated pelvic pain [1–4], but that other medical therapies exist, although characterized by a less favorable balance between benefits, harms and costs [23–27]; and (v) laparoscopic surgery was a reasonable alternative in case they declined a change in pharmacological treatment, but that pain and lesion recurrence was about 10% a year without long-term postoperative medical therapy [28, 29].

Treatments

Switch from OC to NETA

NETA, a 19-nortestosterone derivative progestin, has been repeatedly evaluated in women with endometriosis [6, 9–11, 30–32], and has been routinely used in our referral center for several years [7, 14–16]. NETA 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. NETA 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.

Switch from NETA to OC

The OCs used in our center 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 those who smoked and in those with a BMI ≥30, a combination of ethinyl-estradiol 0.02 mg and levonorgestrel 100 mg was prescribed. We informed women who smoked during NETA use about the risk of combining OC and smoking, and request them to quit smoking before shifting to OC. The same approach was adopted with overweight women who were invited to decrease caloric intake and increase physical activity. Participants were allowed to choose between cyclic and continuous OC use based on their preference because the reason for the change of medication was intolerance, not inefficacy on pain. A pause without treatment was not suggested before starting OC.

NETA and OC were 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 during NETA or continuous OC use, the patients were advised to discontinue treatment for 1 week in the former case and for 4–7 days in the latter case.

Measurements

All patients assisted in our center systematically undergo clinical and ultrasonographic evaluation every 6 months. On these occasions, women are routinely asked to complete 5 questionnaires, 2 on pain (a numeric rating scale [NRS]; and a multidimensional 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 an NRS and to rate the degree of satisfaction with their treatment.

The above scales and questionnaires have been described previously in detail [7, 13–16]. 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 presence of 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 [33]. 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 dysmenorrhea.

The SF-12 health survey developed from the original SF-36 questionnaire [34, 35] is a well-known, 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 Physical Component Summary (PCS-12) and Mental Component Summary (MCS-12) measures [36, 37], with higher scores indicating better health perception.

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 questions, 7 for the anxiety subscale and 7 for the depression subscale. Lower scores indicate better psychological status [38].

The FSFI questionnaire is a 19-item, multidimensional, self-report instrument for evaluating the main categories of female sexual dysfunction and sexual satisfaction [39–41]. The transformed maximum score for each domain is 6 and the maximum (best) transformed full-scale score is 36, with a minimum full-scale score of 2.0.

Occurrence of side effects associated with medical treatments is actively investigated in our endometriosis outpatient clinic, and the overall tolerability of hormonal therapies is measured using a 0- to10-point NRS, with 0 indicating absolutely intolerable untoward effects and 10 indicating the absence of adverse effects. Scores are then categorized, with 9–10 indicating that a drug is very well tolerated; 7–8, well tolerated; 5–6, moderately tolerated; 3–4, poorly tolerated; 0–2, not tolerated [16].

Patients rated the degree of satisfaction before and after the modification of their treatment according to a five-category scale (very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied) by answering the following question: "Taking into consideration the variations occurred in side effects and overall tolerability of treatment, pain symptoms, physical and psychological well-being, health-related quality of life, and sexual functioning, how would you define the level of satisfaction with your current treatment?" In order to limit the potential effect of confounding, satisfaction with treatment at 12-month follow-up, the main study outcome, was dichotomized into "satisfied" (very satisfied plus satisfied) and "dissatisfied" (neither satisfied nor dissatisfied plus dissatisfied plus 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 a change in treatment 12 months after OC or NETA discontinuation because of intolerance. No study is available to define the potential benefits of shifting from OC to NETA or vice versa in this clinical condition. Therefore, a preplanned power calculation was not performed, and we decided to include all the eligible patients evaluated in a 12-month period.

Data were archived using Excel 2003 (Microsoft Corporation, Redmond, Washington, DC, USA) and exported in SPSS 18.0 (SPSS, Inc., Chicago, IL, USA) or SAS software 9.4 (SF-12 data; SAS Institute Inc., Cary, NC, USA) for statistical analysis. Patient satisfaction rate was estimated according to the intention-to-treat principle, considering that all patients who dropped out of the study for any reason except conception seeking were dissatisfied, thus including request for surgery and lost to follow-up. Variations in drug tolerability, pelvic pain symptoms, health-related quality of life, psychological status, and sexual functioning 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-square test for categorical variables). All statistical tests were 2-sided. A p value <5% was considered statistically significant. When appropriate, 95% CIs were calculated for the observed differences by applying a binomial distribution model.

Results

A total of 35 women shifted from OC to NETA, and 32 from NETA to OC. The distribution of demographic and clinical characteristics of the patients in the 2 study groups is shown in Table 1.

Switch from OC to NETA

The median duration (interquartile range) of OC use was 6 months [3–14]. Nineteen women (54%) were using OC cyclically and 16 (46%) continuously. The most frequent untoward effects that determined the request for OC discontinuation despite an appreciable effect on pain symptoms were headache (49%), breakthrough bleeding (14%), and weight gain (11%). At baseline, that is, before switching to NETA, 3 women (8%) were very dissatisfied, 22 women (63%) were dissatisfied, and 10 women (29%) were neither satisfied nor dissatisfied. By definition, none of the women was very satisfied or satisfied (Table 1).

Eight women (23%) dropped out from the study between the 6- and 12-month evaluation owing to persistence of (headache, $n = 3$) or onset of different (mood changes, $n = 1$; urticarial rash, $n = 1$; breakthrough bleeding, $n = 1$) side effects, onset of non-menstrual pelvic pain ($n = 1$), and unwillingness to undertake any further treatment ($n = 1$). Variation of frequency of side effects associated with the shift from OC to NETA in the 27 women who completed the 12-month study period is reported in Table 2. None of the differences were statistically significant. A trend was observed toward a decrease in frequency of headache (from 56 to 30%) and an increase in that of weight gain (from 30 to 44%). However, the severity of untoward effects decreased significantly, as the mean ± SD tolerability NRS score increased from 3.0 ± 1.6 to 5.7 ± 2.4 ($p < 0.001$). Ten women (37%) reported good or very good (NRS ≥7) drug tolerability, compared with none at baseline.

Table 1. Distribution of baseline demographic and clinical characteristics of women who shifted to NETA for intolerance to low-dose OC, and of women who shifted to OC for intolerance to NETA

Characteristic	From OC to NETA study group (n = 35)	From NETA to OC study group (n = 32)
Age, years	35.5±4.7	34.2±5.3
BMI, kg/m^2	23.6±4.0	20.5±2.6
Smoking	6 (17)	9 (28)
Previous deliveries	15 (43)	6 (19)
Previous surgical procedures for endometriosis		
None	9 (26)	14 (44)
1	18 (51)	11 (34)
2	7 (20)	5 (16)
≥3	1 (3)	2 (6)
Endometriotic lesion type[a]		
Deep infiltrating endometriosis	17 (49)	24 (75)
Ovarian endometriomas	28 (80)	18 (56)
Pain symptoms[b]		
Dysmenorrhea	15 (42)	8 (25)
Deep dyspareunia	5 (15)[c]	15 (30)[d]
Non-menstrual pelvic pain	5 (14)	12 (37)
Dyschezia	2 (6)	7 (22)
Duration of previous treatment, months	6 (3–14)	12 (5–22)
Degree of satisfaction with treatment[e]		
Very satisfied	0 (0)	0 (0)
Satisfied	0 (0)	0 (0)
Neither satisfied nor dissatisfied	10 (29)	9 (28)
Dissatisfied	22 (63)	18 (56)
Very dissatisfied	3 (8)	5 (16)

Data is reported as mean ± SD, or number (percentage), or median (interquartile range). NETA, norethisterone acetate; OC, oral contraceptives; BMI, body mass index.

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

[b] Numeric rating scale >0. Mild pain symptoms are also included.

[c] One woman did not have sexual intercourses at basal and/or at 12-month evaluation.

[d] Two women did not have sexual intercourses at basal and/or at 12-month evaluation.

[e] Patients rated the baseline degree of satisfaction with their treatment according to a five-category scale (very satisfied, satisfied, neither satisfied, nor dissatisfied, dissatisfied, very dissatisfied).

The severity of pain symptoms did not vary significantly except for dysmenorrhea that decreased at evaluation by medians of the NRS (Table 3). Overall, the frequency of moderate or severe complaints was marginal at both baseline and 12-month assessment. No substantial variations were observed also in psychological status and sexual functioning. With regard to health-related quality of life, a significant improvement was reported only in the physical component of the SF-12 questionnaire (Table 3). At the end of the study period, 18 out of 35 (51%; 95% CI 36–67) women were satisfied or very satisfied with the treatment change, whereas 17 out of 35 (49%; 95% CI 33–64%) were neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied. All the patients who dropped out from the study were included as dissatisfied in this intention-to-treat analysis.

Switch from NETA to OC

The median duration (interquartile range) of NETA use was 12 months [5–22]. The most frequent untoward effects that determined the request for NETA discontinuation despite an appreciable effect on pain symptoms were weight gain (19%), headache (16%), breakthrough bleeding (16%), decreased libido (16%), spotting (12%), and mood changes (12%).

At baseline, that is, before switching to OC, five women (16%) were very dissatisfied, 18 women (56%) were

Table 2. Per-protocol analysis[a] of frequency of side effects reported at baseline and at 12-month evaluation by patients (n = 27) shifting from OC to NETA

Side effect[b]	Baseline evaluation	12-Month evaluation	p value
Headache	15 (56)	8 (30)	ns
Spotting	5 (18)	6 (22)	ns
Breakthrough bleeding	1 (4)	0 (0)	ns
Weight gain	8 (30)	12 (44)	ns
Nausea	2 (7)	1 (4)	ns
Decreased libido	7 (26)	5 (18)	ns
Vaginal dryness	4 (15)	6 (22)	ns
Bloating or swelling	5 (18)	6 (22)	ns
Breast tenderness	0 (0)	4 (15)	ns
Acne	0 (0)	3 (11)	ns
Alopecia	0 (0)	0 (0)	ns
Mood changes	5 (18)	5 (18)	ns
Others	11 (41)	9 (33)	ns

Data are number (percentage).
NETA, norethisterone acetate; OC, oral contraceptives; ns, not significant.
[a] Women who withdrew before 12-month follow-up assessment (n = 8) were excluded.
[b] Some women reported more than one side effect.

Table 3. 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 = 27) shifting from OC to NETA

Symptoms/questionnaires	Baseline evaluation	12-Month evaluation	p value
Dysmenorrhea			
NRS	0 (0–4)	0 (0–0)	0.01
MCRS ≥2	2 (7)	0 (0)	ns
Deep dyspareunia[b]			
NRS	0 (0–0)	0 (0–0)	ns
MCRS ≥2	1 (4)	2 (8)	ns
Non-menstrual pelvic pain			
NRS	0 (0–0)	0 (0–0)	ns
MCRS ≥2	1 (4)	0 (0)	ns
Dyschezia			
NRS	0 (0–0)	0 (0–0)	ns
MCRS ≥2	1 (4)	0 (0)	ns
SF-12			
Physical component	50.0±11.1	55.4±4.5	0.03
Mental component	40.0±11.7	42.6±13.2	ns
HADS			
Anxiety	6.6±4.3	5.9±4.6	ns
Depression	5.8±4.3	5.4±5.1	ns
Total	12.4±8.1	11.3±9.1	ns
FSFI total score[b]	26.2±5.7	26.2±6.7	ns

Data is reported as mean ± SD, or number (percentage), or median (interquartile range).
[a] Women who withdrew before 12-month follow-up assessment (n = 8) were excluded.
[b] One woman did not have sexual intercourses either at baseline and/or at 12-month evaluation.
NRS, 0 to 10-point numeric rating scale; MCRS, 0 to 3-point multidimensional categorical rating scale modified from that devised by Biberoglu and Behrman [33]; SF-12, Short Form-12 [36, 37]; HADS, Hospital Anxiety and Depression Scale [38]; FSFI, Female Sexual Function Index [39, 40]; ns, not significant; NETA, norethisterone acetate; OC, oral contraceptives.

Table 4. Per-protocol analysis[a] of frequency of side effects reported at baseline and at 12-month evaluation by patients ($n = 25$) shifting from NETA to OC

Side effect[b]	Baseline evaluation	12-Month evaluation	p value
Headache	5 (20)	10 (40)	ns
Spotting	4 (16)	7 (28)	ns
Breakthrough bleeding	3 (12)	0 (0)	ns
Weight gain	9 (36)	4 (16)	ns
Nausea	2 (8)	0 (0)	ns
Decreased libido	11 (44)	8 (32)	ns
Vaginal dryness	9 (36)	6 (24)	ns
Bloating or swelling	4 (16)	2 (8)	ns
Breast tenderness	0 (0)	0 (0)	ns
Acne	2 (8)	0 (0)	ns
Alopecia	0 (0	0 (0)	ns
Mood changes	5 (20)	1 (4)	ns
Others	5 (20)	1 (4)	ns

Data are number (percentage).
NETA, norethisterone acetate; OC, oral contraceptives; ns, not significant.
[a] Women who withdrew before 12-month follow-up assessment ($n = 7$) were excluded.
[b] Some women reported more than one side effect.

dissatisfied, and 9 women (28%) were neither satisfied nor dissatisfied. By definition, none of the women was very satisfied or satisfied (Table 1).

Seven women (22%) dropped out from the study between the 6- and 12-month evaluation owing to persistence of (acne, $n = 1$) or onset of different (headache, $n = 4$) side effects, onset of non-menstrual pelvic pain ($n = 1$), and pregnancy desire ($n = 1$). Variation of frequency of side effects associated with the shift from NETA to OC in the 25 women who completed the 12-month study period is reported in Table 4. Again, none of the differences were statistically significant. A trend was observed toward a decrease in frequency of weight gain (from 36 to 16%), decreased libido (from 44 to 32%), and vaginal dryness (from 36 to 24%), and an increase in that of headache (from 20 to 40%). However, the severity of untoward effects decreased significantly, as the mean ± SD tolerability NRS score increased from 3.5 ± 1.7 to 6.9 ± 2.5 ($p < 0.001$). Thirteen women (52%) reported good or very good (NRS ≥7) drug tolerability, compared with none at baseline.

Based on NRS assessment, the severity of deep dyspareunia and non-menstrual pelvic pain decreased significantly (Table 5). A trend was observed toward a decrease in the frequency of moderate to severe deep dyspareunia (8 women at baseline vs. 3 at 12 months) and dyschezia (4 and 2 women, respectively) at MCRS evaluation (Table 5). Significant improvements were observed in both the anxiety and depression HADS subscales scores, as well as in the FSFI scores. No significant variations were reported in both the physical and the mental components of the SF-12 questionnaire (Table 5). One woman who dropped out of the study because of her desire to become pregnant was not considered in the intention-to-treat analysis of satisfaction with treatment. At the end of the study period, 20 out of 31 (65%; 95% CI 47–79) patients were satisfied or very satisfied with the treatment change, whereas 11 out of 31 (35%; 95% CI 20–52) were neither satisfied nor dissatisfied, dissatisfied, or very dissatisfied.

Discussion

Overall, the main finding of the present study was that, when OC or NETA are not tolerated, shifting to the other compound allows the majority of patients with endometriosis to improve tolerability and to continue medical treatment with a safe, effective, and inexpensive drug. The benefit seems larger when the shift is from NETA to OC rather than the other way round, as the proportion of satisfied patients at the end of the study period was, respectively, 65 and 51%. Moreover, in the latter case, the 95% CIs of the rates of satisfied and dissatisfied women amply overlapped, whereas in the former case, the 95% CI overlapping was marginal.

Table 5. 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 = 25) shifting from NETA to OC

Symptoms/questionnaires	Baseline evaluation	12-Month evaluation	p value
Dysmenorrhea			
NRS	0 (0–1.5)	0 (0–3)	ns
MCRS ≥2	0 (0)	1 (4)	ns
Deep dyspareunia[b]			
NRS	5 (0–8)	0 (0–5.5)	0.02
MCRS ≥2	8 (35)	3 (13)	ns
Non-menstrual pelvic pain			
NRS	0 (0–4.5)	0 (0–0)	0.02
MCRS ≥2	2 (8)	1 (4)	ns
Dyschezia			
NRS	0 (0–1.5)	0 (0–0)	ns
MCRS ≥2	4 (16)	2 (8)	ns
HADS			
Anxiety	4.7±3.5	3.6±3.2	0.02
Depression	5.4±4.0	3.8±3.4	0.03
Total	10.1±7.3	7.4±6.3	0.02
SF-12			
Physical component	52.8±9.1	54.8±4.4	ns
Mental component	42.1±11.7	46.1±10.0	ns
FSFI total score[b]	21.9±8.6	25.4±7.9	0.01

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

[a] Women who withdrew before 12-month follow-up assessment (n = 7) were excluded.

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

NRS, 0 to 10-point numeric rating scale; MCRS, 0 to 3-point multidimensional categorical rating scale modified from that devised by Biberoglu and Behrman [33]; SF-12, Short Form-12 [36, 37]; HADS, Hospital Anxiety and Depression Scale [38]; FSFI, Female Sexual Function Index [39, 40]; ns, not significant; NETA, norethisterone acetate; OC, oral contraceptives.

Considering a shift from OC to NETA may be beneficial especially in women experiencing headache, as previously suggested by Morotti et al. [17]. The frequency of the other untoward effects associated with OC use were not reduced, but their severity was, as demonstrated by the increase in 12-month follow-up NRS tolerability score compared with baseline values.

Considering a shift from NETA to OC may be beneficial especially in women experiencing side effects typically associated with this type of progestin, such as weight gain, acne, bloating, and decreased libido. On the other hand, this change may lead to an increase in the frequency of headache, likely associated with the estrogen component. This confirms that OCs with the lowest possible estrogen dose should be chosen also in women with endometriosis in order to improve both safety and tolerability [42–45]. In particular, the risk of venous and arterial thrombosis should be adequately taken into consideration when prescribing OC to women over 35 years of age who smoke and are overweight. In our series, none of the women over 35 years of age who shifted from NETA to OC also smoked or was overweight. Patient decision aids may be of benefit in these situations and, as an example, we now systematically use the patient decision aids on thrombosis and breast cancer risk in OC users developed by the National Institute for Health and Care Excellence that issued guideline NG73 for the diagnosis and management of endometriosis [46, 47].

The larger effect observed when the shift was from NETA to OC confirms that low-dose, monophasic estrogen-progestin combinations should retain their role in the management of endometriosis, provided pain symptoms are adequately relieved. In this regard, it should be highlighted that at baseline, pain was generally well controlled in both study groups, and that the focus here was on tolerability, not efficacy on symptoms. This also explains the limited significant variations in pain symptoms' severity independently of the direction of the

change between the 2 medications, demonstrating that the observed amelioration of tolerability was not at detriment of efficacy on pain. Conversely, marginal improvements in the severity of dysmenorrhea when shifting from OC to NETA, and of deep dyspareunia and nonmenstrual pain when shifting from NETA to OC were reported, although of questionable clinical importance.

Our study has limitations. The combination of the observational design with the limited sample size increases the risk of confounding. Noteworthy, it would have been of interest adjusting separately the incidence of the different side effects associated with the shift from OC to NETA and vice versa (such as headache, spotting, and vaginal dryness), for confounders such as age, BMI or smoking. A further issue of interest would have been conducting separate sub-analyses according to different endometriosis forms and cyclic vs. continuous OC use. However, the number of cases per subgroup would be so scarce as to impede any meaningful conclusion.

Moreover, the population was highly selected, and this precludes the generalization of the results to endometriosis patients with different complaint types. However, the self-controlled design was chosen purposely because the objective of the study was to assess variations in tolerability when shifting to NETA or OC not in a general population using the other drug but specifically in those patients who were dissatisfied because of intolerable side effects and that would have otherwise discontinued medical therapy. In a self-control study, recruited patients act as their own control, thus limiting the effect of confounding. In fact, study outcomes may be influenced by relevant characteristics that may differ between patients [19]. In addition, overoptimistic results should have been avoided, as patient satisfaction was assessed including all dropouts as dissatisfied.

The period of use of OC and NETA before changing medication was fairly long. Thus, the phenomenon of regression toward the mean seems unlikely, given that the clinical condition was chronic and that all study variables were measured repeatedly before enrollment. Also, a carry-over effect should be ruled out, as the baseline patients' conditions were the worst possible in terms of tolerability. Therefore, if a carry-over effect was in play, this was detrimental, not beneficial, again potentially leading to conservative estimates. Also, a placebo effect cannot be excluded. However, given the long study period, this seems little probable, as the placebo effect may not last for one year when drug tolerability is unacceptable.

The proportion of dropouts was high and above the usually indicated 20% cutoff over which the study findings are considered of questionable validity [48]. However, this cutoff may not be appropriate when all patients at recruitment are considering abandonment of medical treatment owing to dissatisfaction. In these conditions, a 22–23% dropout rate may even appear fairly low.

Owing to the limited number of participants, the analysis of determinants of success was deemed unreasonable. More in general, the small sample size could have led to some type II errors, thus impeding the identification of potential factors predictive of satisfaction with treatment change. On the other hand, in our experience, it is not easy for endometriosis patients to decide to discontinue a medical therapy that is effective on pain, solely because of side effects. In this regard, it may not be excluded that women referred or self-referred to our center are more motivated to choose medical rather than surgical treatment. If this was true, such selection bias would render generalization of the study results more problematic.

However, when discussing generalization, we also believe that our findings provide a realistic picture of what happens in everyday practice, and our data may help clinicians when counselling patients experiencing upsetting untoward effects with OC or NETA. Observational studies may be very helpful in assessing the real-world effectiveness of treatments that have already been demonstrated to work in highly controlled research settings [49], as OCs and NETA in women with symptomatic endometriosis [5, 7, 8, 12].

It could also be argued that, in women who were intolerant to NETA, instead of suggesting OC, we could have suggested shifting to dienogest, which has been proven to be better tolerated than NETA [16]. However, many women assisted in our center cannot afford the cost of dienogest (€730 – $860 – £670 per year in Italy, not reimbursed by the Italian NHS) and prefer NETA (€18 – $21 – £17 per year in Italy, €4 per year when reimbursed by the Italian NHS) specifically for economic reasons. Indeed, we previously demonstrated that the cost of dienogest limited its effectiveness despite its good tolerability [16]. Moreover, here the issue was not poor pain control, but drug intolerance, and indeed the larger benefit was observed precisely when shifting from NETA to OC. Thus, changing for dienogest would have led to waste of money in a majority of patients.

In conclusion, when endometriosis-associated pain was relieved by OC or NETA, but the medications could no longer be used because of intolerable side effects, shifting to the other compound resulted in substantial improvement of tolerability in a majority of women. The

change of therapy was particularly beneficial in patients using NETA who shifted to OC. Women should be informed about this further therapeutic option in order to be enabled to choose a treatment modification that is aligned with their preferences and priorities.

Disclosure Statement

P.V., F.O., M.P.F., L.B., and A.R. declare that they have no conflicts of interest. E.S. received grants from Ferring and Serono.

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