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Norethindrone acetate versus extended-cycle oral contraceptive (Seasonique®) in the treatment of endometriosis symptoms: A prospective open-label comparative study

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ABSTRACT

Introduction: This patient preference prospective study was designed to compare patients' satisfaction in women with endometriosis treated either by an extended-cycle oral contraception (OC) or by norethindrone acetate (NETA).

Methods: This patient preference prospective study included women of reproductive age with endometriosis. Patients were submitted to one of the following 12 months' treatments: Group A, continuous oral treatment with NETA (2.5 mg/day) and Group B, a 91-day extended-cycle OC (LNG/EE 150/30 mcg for 84 days and EE 10 mcg for 7 days). Patient satisfaction was the primary endpoint.

Results: There was no statistically significant difference in the rate of satisfied patients at 12-month follow up between the two study groups, 82.2% and 68.4% in Group A and Group B respectively (p = 0.143). At 6 and 12-months, there was a significant amelioration in the intensity of all pain in both groups. The median number of days of unscheduled bleeding during the first cycle was significantly higher in Group B compared to Group A.

Conclusion: Both NETA and extended-cycle OC are effective in treating pain symptoms related to endometriosis. Extended-cycle OC may cause more unscheduled bleeding, but the rate of satisfaction for those who completed the treatment was similar in the two groups.

Introduction

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial-like tissue outside the uterine cavity with a reported prevalence of 2%–10% in the general population, up to 50% among infertile patients [1,2]. It usually causes a wide spectrum of symptoms, in particular pelvic pain, dysmenorrhea and infertility. Although several aspects of endometriosis remain still unclear, the management of the disease has been changed progressively during the last decades, focusing progressively from the disease to the symptoms, the desires and women expectations [3]. Thus, the management of patients with endometriosis depends on their age, reproductive plans and quality of life, the reported symptoms, the extent of the disease, the treatment risks, side effects, and cost considerations [4].

Hormonal therapies are an established therapeutic option to treat endometriosis [5,6]. A Cochrane review showed that suppression of menstrual cycles with oral contraceptive (OC), GnRH analogues, LNG-IUD and danazol was beneficial to improve pain symptoms [7]. However, progestogens are one of the therapies most commonly used to treat endometriosis and these drugs are particularly advantageous for patients suffering primarily from dysmenorrhea [8–12].

A 91-day extended-cycle OC consisting of levonorgestrel (LNG)/ethinylestradiol (EE) 150/30 lg for 84 days and ethinylestradiol 10 lg for 7 days (Seasonique) has recently been approved for the prevention of pregnancy in adult women in the European Union [13]. This regimen allows a reduction in the scheduled bleeding to four episodes per year and has been shown to be effective, safe and generally well tolerated [14]. However, no study investigated the efficacy of extended-cycle OC in the treatment of endometriosis.

This patient preference prospective study was designed to compare patients' satisfaction in women with endometriosis treated either by an extended-cycle OC or by NETA.

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Material and methods

Study population

This patient preference prospective study included women with endometriosis. Patients eligible for the study were recruited among women referred to our centre because of pelvic pain or known diagnosis of endometriosis. Criteria for inclusion in the study were: histological diagnosis of endometriosis during previous surgery, ultrasonographic diagnosis of deep endometriosis and/or endometriomas. All patients underwent transvaginal ultrasonography by using a Voluson E6 or Voluson S8 machine (GE Healthcare, Milwaukee, WI, USA), as previously described; standardized ultrasound criteria were used for the diagnosis of deep endometriosis and endometriomas [15,16]. All the procedures were performed by the same experienced ultrasonographer.

Participation in the study was offered only to women unwilling to undergo surgery and who did not desire pregnancy in the year after inclusion in the study. Exclusion criteria were: typical contraindications for estrogens and progestogens; uropathy or symptomatic bowel stenosis; use of drugs that interfere with contraceptive steroid metabolism; abnormal findings at breast examination and mammary ultrasound scan; psychotic disturbances; history of drug or alcohol abuse.

The study protocol was approved by the Regional Ethic Committee (372REG2017). Participants to the study signed a written consent form. Women were informed that there is no evidence on the effects of 91-day extended-cycle OC on the symptoms caused endometriosis.

Study design

Patients accepting to participate in the study were submitted to one of the following 12 months' treatments: **Group A**, continuous oral treatment with NETA (2.5 mg/day, Primolut-Nor®; Bayer Pharma AG, Berlin, Germany) and **Group B**, a 91-day extended-cycle OC (LNG/EE 150/30 mcg for 84 days and EE 10 mcg for 7 days, Seasonique®, Teva, Assago, Italy). The choice of the treatment was decided on the basis of the preference of the patient.

Patient satisfaction with the treatment was the primary endpoint. Secondary endpoints were: changes in pain symptoms, changes in the volume of the endometriomas and the rectovaginal nodules, changes in quality of life assessed with the EH*P*-30, and bleeding assessment.

Assessment of symptoms

An electronic database was used to record the demographic and clinical characteristics of the patients.

Firstly, an intention-to-treat analysis has been performed at 12 months to evaluate the overall degree of satisfaction of the 100 patients included in the study. The patients who withdraw the treatment before the 12 months were asked to rate the satisfaction at the time of the withdrawal. The women rated the overall degree of satisfaction with their treatment by answering 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 [17]. Answers were based on a 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied). Furthermore, a second analysis was performed to evaluate the overall degree of satisfaction in both groups taking into account only the patients who completed the 12 month's treatment using the same 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied).

All patients recorded in their diaries the information regarding pain changes (every 3 months) throughout a 10-cm visual analogue scale (VAS); the left extreme of the scale indicating the absence of pain and the right indicating the worst pain possible.

The volume of the endometrioma and the rectovaginal endometriotic nodules was estimated by ultrasonography at baseline, after 6 and 12 months of hormonal therapy. The volume of the endometrioma and the rectovaginal endometriotic nodule was estimated by virtual organ computer-aided analysis (VOCAL, GE Healthcare), [18].

The validated language version of the Endometriosis Health Profile-30 (EH*P*-30) core questionnaire was administered to the

Table 1
Demographic and clinical characteristics of the patients included in the study.

	Group A (n = 50)	Group B (n = 50)	*P value*
Age (years, mean ± SD)	32.5 ± 5.3	33.1 ± 4.4	0.579
Smokers, *n (%)*	7 (14)	5 (10)	0.538
Nulliparous *n (%)*	42 (84)	41 (82)	0.790
Race *n (%)*			
• Caucasian	40 (80)	38 (76)	0.856
• Afro-Caribbean	8 (16)	9 (18)	
• Asian	2 (4)	3 (6)	
• Others	0 (0)	0 (0)	
BMI (Median, IQR)	23 (21.25–26)	24 (22–26.75)	0.410
Ovarian endometrioma, *n (%)*[a]	25 (50)	27 (54)	0.689
Rectovaginal endometriosis, *n (%)*[a]	18 (36)	25 (50)	0.157
Colorectal endometriosis, *n (%)*[a]	15 (30)	11 (22)	0.362
Uterosacral endometriotic nodule, *n (%)*[a]	8 (16)	11 (22)	0.444
Vaginal endometriosis, *n (%)*[a]	3 (6)	2 (4)	0.646
Bladder endometriosis, *n (%)*[a]	0 (0)	2 (4)	0.153
Previous hormonal treatments, *n (%)*	32 (64)	31 (62)	0.836
Withdraw treatment before 12 months, *n (%)*	5 (10)	12 (24)	0.062

SD: standard deviation; BMI: Body Mass Index; IQR: interquartile range.
[a] Each patient might have more than one endometriosis lesions.

patients at baseline and after 12 months of therapy to measure the changes in quality of life [19].

Cycle control was evaluated by analysing duration and intensity of withdrawal bleeding and the incidence of breakthrough bleeding and/or spotting. Patients enrolled in Group A were asked to report the number of "unscheduled" bleeding and/or spotting days during the continuous treatment with NETA. Patients enrolled in Group B were asked to report the number of "scheduled" bleeding and/or spotting days (during the 7-day EE monotherapy interval), and the number of "unscheduled" bleeding and/or spotting days (during the 84-day continuous OC pill interval).

Statistical analysis

In calculating the sample size required, the primary objective was the rate of satisfied patients (very satisfied and satisfied) at 12-month follow up. Based on previous data investigating the effects of progestins on pain symptoms of patients with endometriosis [17], we hypothesized that about 60% of the patients treated with NETA would be satisfied. We considered a difference of 25% in satisfaction rate between the study groups as clinically relevant. To have an 80% change of detecting such a difference at an overall statistical significance level of 5%, it was estimated that about 50 patients per group were required. Considering that treatment allocation was based on patient preference, the recruitment continued until the planned sample-size was reached in the least numerous group. Categorical variables were compared by using the chi-squared test and the Fisher exact test. Changes in severity of symptoms during treatment in each study group were analysed by using the paired *t*-test and the signed rank test according to data distribution. The comparisons in the changes of intensity of the symptoms and volume of the nodules during treatment between the two study groups were performed by using the *t*-test or Mann–Whitney *U* test according to data distribution. Data were analysed using the SPSS software version 20.0 (SPSS Science, Chicago, IL, USA).

Results

One hundred and twenty-two patients were invited to participate to the study and 100 agreed. Table 1 shows the characteristics of the women enrolled in the study. A trend towards a higher number of patients who withdrew from the study before 12-month treatment was reported in group B ($p = 0.062$, Table 1).

At 12-month follow up the first intention-to-treat analysis including all the 100 patients showed that, in group A, 30% of women were very satisfied, 44% were satisfied, 12% were uncertain and 14% were dissatisfied. In group B, 10% of women were very satisfied, 42% were satisfied, 22% were uncertain and 26% were dissatisfied. Therefore, the rate of satisfied patients (very satisfied and satisfied) at 12-month follow up was higher in group A (74%) than group B (52%; $p < 0.005$). The second analysis at 12 months performed excluding the women who withdraw before the end of the treatment showed that, in group A, 33.3% of women were very satisfied, 48.9% were satisfied, 13.3% were uncertain and 4.4% were dissatisfied. In group B, 15.8% of women were very satisfied, 57.9% were satisfied, 18.4% were uncertain and 7.9% were dissatisfied. Therefore, there was no statistically significant difference in the rate of satisfied patients (very satisfied and satisfied) at 12-month follow up between the two study groups, 82.2% and 68.4% in group A and group B respectively ($p = 0.143$).

Table 2 shows the changes in pain scores during treatment. Obviously, in group A, symptoms associated with menstruation (such as dysmenorrhea) disappeared during treatment. At 6 months and 12-month follow up, there was a significant amelioration in the intensity of all pain compared with baseline in both groups. (Table 2).

Tables 3 and 4, respectively, provide a summary of "scheduled" bleeding and/or spotting days in the study group B and "unscheduled" bleeding and/or spotting days alone in both the study groups, A and B. The median number of days of unscheduled bleeding and/or spotting and bleeding alone during the first cycle was significantly higher in group B compared to group A

Table 2
Comparison of the intensity of pain during treatment in Group A and Group B.

Symptom	Baseline	6 months	12 months
Dysmenorrea			
• Group A	6.0 (±0.8)	NA	NA
• Group B	6.1 (±0.8)	4.1 (±1.0) $p < 0.05$[a]	2.2 (±0.8) $p < 0.05$[a]
P value	0.591	NA	NA
Deep dyspareunia			
Group A	5.8 (±0.7)	3.6 (±0.9) $p < 0.05$[a]	2.1 (±0.8) $p < 0.05$[a]; $p < 0.05$[b]
Group B	5.7 (±0.8)	3.7(±0.9) $p < 0.05$[a]	2.4 (±0.6) $p < 0.05$[a]; $p < 0.05$[b]
P value	0.757	0.805	0.218
Non menstrual pelvic pain			
• Group A	5.7 (±0.7)	3.0 (±0.8) $p < 0.05$[a]	1.9 (±0.5) $p < 0.05$[a]; $p < 0.05$[b]
• Group B	5.5 (±0.6)	3.4(±0.6) $p < 0.05$[a]	1.6 (±0.5)$p < 0.05$[a]; $p < 0.05$[b]
P value	0.373	0.109	0.148
Dyschezia			
• Group A	5.6 (±0.6)	4.8 (±0.6) $p < 0.05$[a]	4.0 (±0.7) $p < 0.05$[a]; $p < 0.05$[b]
• Group B	5.5 (±0.8)	4.6 (±0.8) $p < 0.05$[a]	3.7 (±0.8) $p < 0.05$[a]; $p < 0.05$[b]
P value	0.758	0.350	0.199

NA: not available.
[a] Intensity of symptoms compared with baseline.
[b] Intensity of symptoms compared with 6-month follow-up.

Table 3
Summary of diary reports of scheduled bleeding and/or spotting days (Group B).

Cycle	Scheduled bleeding/spotting days	
	Mean (SD)	Median
1	3.37 (1.33)	3
2	3.18 (1.10)	3
3	2.64 (1.04)	3
4	2.46 (1.23)	3

SD: standard deviation.

($p < 0.005$), however the number of days decreased sharply in subsequent cycles and no statistically significant difference has been found between the study groups.

There was no significant difference in the volume of the endometrioma and rectovaginal endometriotic nodules between patients included in group A and group B (Tables 5 and Table 6). The mean volume of the endometriotic cysts and rectovaginal endometriotic nodules significantly decreased at 6 and 12 months of treatment compared with baseline in both study groups. Furthermore, a significant reduction in the mean volume of the cysts and the endometriotic nodules was also observed between the 6- and 12-month treatment in both study groups (Table 5 and Table 6).

The EH*P*-30 score variation during the study period is shown in Fig. 1. At 12 months' evaluation, the women enrolled in group A scored significantly better in pain and control and powerlessness domains (Fig. 1A and B). However, no significant difference was found for what concern social support, emotional well-being and self-image between the study groups at the end of the treatment (Fig. 1C, D and E).

Discussion

Progestogens and estrogen–progestogen combinations have been reported to be safe, well tolerated, and effective in the treatment of women with symptomatic endometriosis [20,21–27]. In the last few years, several studies have shown that medical treatments (such as NETA, low-dose oral contraceptive pill, triptorelin and letrozole) improve pain symptoms and reduce the size of the endometriotic nodules [12,28,29].

In this study, two hormonal therapies (extended-cycle OC and NETA) were compared in the treatment of endometriosis related pain symptoms. We choose these therapies because low-dose oral contraceptive pill and NETA have been previously shown to be effective in treating pain symptoms caused by pelvic endometriosis [30].

Our findings suggest that overall both therapies are effective in improving pain symptoms, reducing the volume of the endometriotic lesions, psychological well-being and health-related quality of life in women with endometriosis.

The number of patients who withdraw the treatment before the completion of the study was higher, but not significant, in the group of patients treated with extended-cycle OC than in those with NETA. This seems to be due to the significantly higher prevalence of adverse events, in particular the number of unscheduled bleeding/spotting days in the first 6 months of treatment with extended-cycle OC. Reasonably for this reason, the rate of satisfaction was higher in patients treated with NETA than in those with extended-cycle OC; however when we analysed the rate of satisfaction including only women who managed to complete the 12 months treatment, no significantly difference has been found in the rate of satisfaction (82.2% and 68.4% respectively, $p = 0.143$).

The intensity of all endometriosis related pain symptoms ameliorated in both groups at 6 months and 12 months' evaluation compared to baseline, and no difference has been found in the severity of deep dyspareunia, dyschezia, non-menstrual pelvic pain, between the two study groups.

As previously demonstrated, the administration of hormonal therapies is effective to reduce the volume of the endometriotic lesions [12,28,29]. The current study confirms that the administration of NETA and extended-cycle OC for 12 months significantly decrease the volume of both endometrioma cysts and rectovaginal endometriotic nodules. However, this results might be limited by the small number of patients included in each study group and by the relatively short length of treatment.

Endometriosis is well known to be associated with debilitating pelvic pain who may cause impairment of psychological as well as social functioning and reduction in quality of life as well as sexual satisfaction [31]. It has been repeatedly highlight the importance of using a disease-specific instrument to assess the health-related quality of life burden of endometriosis [32,33], and it is well accepted that the EH*P*-30 questionnaire is a user-friendly self-report tool suitable for use in endometriosis-related clinical research [32]. In our study, variations of the EH*P*-30 questionnaire

Table 4
Summary of diary reports of scheduled bleeding and/or spotting days (Group A and B).

Cycle	Unscheduled bleeding/spotting days (Group A)		Unscheduled bleeding/spotting days (Group B)		P value
	Mean (SD)	Median	Mean (SD)	Median	
1	9.6 (2.5)	10	11.7 (2.9)	12	<0.005
2	7.8 (2.1)	8	7.9 (2.2)	8	0.747
3	5.2 (2.2)	5	5.4 (2.2)	5	0.643
4	2.4 (1.5)	2	2.5 (1.5)	2.5	0.548

SD: standard deviation.

Table 5
Volume of the endometriotic cyst at baseline, after 6 months and 12 months of treatment.

	Group A	Group B	*P value*
Baseline	128.1 ± 9.2 (n = 25)	124.6 ± 9.1 (n = 27)	0.178
6 months treatment	68.9 ± 8.4 (n = 23) $p < 0.05$[a]	69.2 ± 10.1 (n = 25) $p < 0.05$[a]	0.943
12 months treatment	55.7 ± 7.7 (n = 23) $p < 0.05$[a]; $p < 0.05$[b]	55.2 ± 6.9 (n = 20) $p < 0.05$[a]; $p < 0.05$[b]	0.795

Intensity of pain symptoms was measured on a VAS scale, data are presented as mean ± SEM. The number of patients is shown in parenthesis.
[a] Change of the volume compared with baseline.
[b] Change of the volume compared with 6-month follow-up.

Table 6
Volume of the rectovaginal endometriotic nodules at baseline, after 6 months and 12 months of treatment.

	Group A	Group B	*P value*
Baseline	2.7 ± 0.9 (n = 18)	2.6 ± 1.0 (n = 25)	0.805
6 months treatment	2.2 ± 0.7 (n = 18) $p < 0.05$[a]	2.1 ± 0.9 (n = 22) $p < 0.05$[a]	0.789
12 months treatment	1.8 ± 0.8 (n = 17) $p < 0.05$[a]; $p < 0.05$[b]	1.9 ± 0.8 (n = 19) $p < 0.05$[a]; $p < 0.05$[b]	0.746

Intensity of pain symptoms was measured on a VAS scale, data are presented as mean ± SEM. The number of patients is shown in parenthesis.
[a] Change of the volume compared with baseline.
[b] Change of the volume compared with 6-month follow-up.

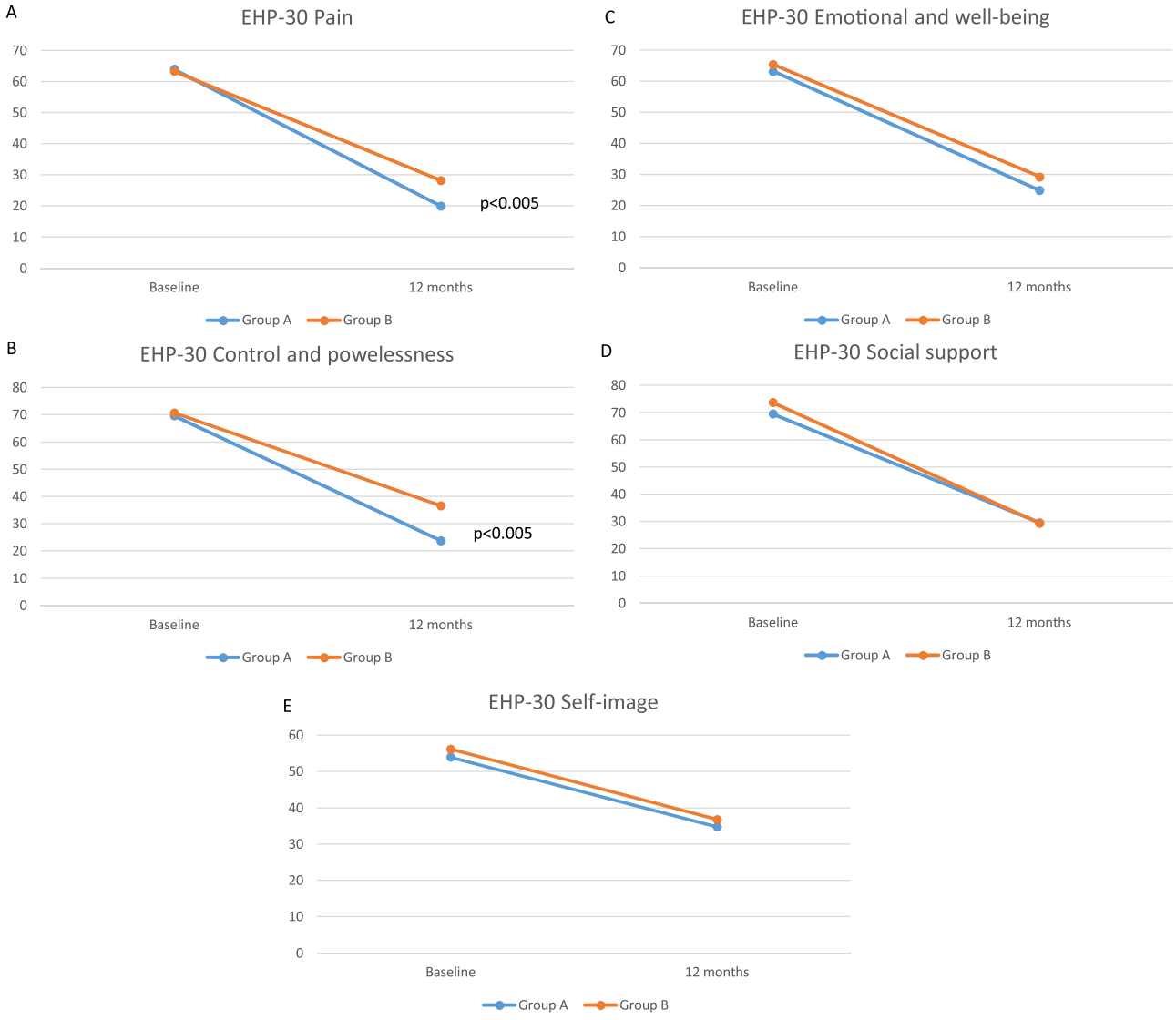

Fig. 1. Variation of EHP-30 scores in the two treatment groups during the study period. Values are mean ± standard deviation (SD) shown by vertical bars. EHP subdomains scores range from 0 to 100. Lower score indicates fewer negative symptoms. Blue line Group A (NETA); orange line Group B (91-day extended-cycle OC). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
(1A) Pain domain scores. (1B) Control and powerlessness domain scores. (1C) Emotional well-being domain scores. (1D) Social support domain scores. (1E) Self-image domain scores.

scores in both study groups followed a substantially similar temporal pattern. We observed only a significant better score in the pain and control and powerlessness domains in patients treated with NETA than in those treated with extended-cycle OC. These differences could be explained by the persistence of dysmenorrhea in patients treated with the extended-cycle OC, since every 3 months they suffered breakthrough bleeding, while patients treated with NETA were in amenorrhea thought all treatment and did not experienced menstrual-related symptoms.

This study has some limitations. The most relevant limitation of this study is that it was not randomised. A patient preference trial was chosen because the two hormonal therapies cause different bleeding patterns and some women may not accept amenorrhea due to the continuous progestin treatment. Furthermore, because of the lack of data on the extended-cycle oral contraceptive in patients with endometriosis, results of this study may pave the way for future randomised studies with larger sample size. Although the input of the clinician in the discussion of the two

treatment may have some influence on the patient's choice, we tried to objectively explain the characteristics of the treatments without influencing the decision, which was mainly based on the desire of having or avoiding menstruation. Furthermore, it is possible that the final choice might be influenced by the characteristics and the intensity of symptoms; in fact, women with severe dysmenorrhea or dyschezia during the menstrual cycle might have preferred the continuous progestin therapy. However, no significant difference was observed in the baseline characteristics of symptoms of the two study groups. The observed similarity in baseline clinical characteristics of subjects in the two study groups may reduce, but not eliminate this potential bias. In addition, lack of statistically significant differences in the considered demographic aspects may be due to lack of power relative to the small sample size. Finally, in our investigation, women had to pay for the chosen treatment. Patients were informed that the 12 months' treatment cost of NETA is slightly lower compared to the cost of extended-cycle OC, and this could be a potential bias in patients' final choice.

In conclusion, this study, demonstrates that both NETA and extended-cycle OC are effective in treating pain symptoms related to the presence of endometriosis. Extended-cycle OC may cause more unscheduled bleeding during the first 3 months of treatment, but the rate of satisfaction for those who manage to complete the treatment was similar in the two groups. On the basis of these findings we believe that extended-cycle OC is a valid alternative for the treatment of endometriosis related symptoms and might be a first option for patients who desire having menstrual cycle.

Conflict of interest

The Authors report no conflict of interest.

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