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# Norethisterone acetate versus norethisterone acetate combined with letrozole for the treatment of ovarian endometriotic cysts: a patient preference study

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ABSTRACT

*Objective:* To compare the efficacy of norethisterone acetate (NETA; group N) or letrozole combined with NETA (group L) in treating endometriotic ovarian cysts.
*Study design:* This patient-preference study included 20 patients in group N and 20 patients in group L. The primary aim of the study was to compare the volume of the endometriomas during and after treatment. The secondary outcome was the evaluation of the changes in pain symptoms during and after treatment.
*Results:* After six months of treatment, the volume of the endometriomas significantly decreased compared with baseline in both study groups; it was smaller in group L than in group N ($p = 0.026$). The rate of satisfied patients at six months of treatment was similar between the study groups ($p = 0.451$). No significant difference was reported between the two study groups in the amelioration of pain symptoms and in the incidence of adverse events.
*Conclusions:* Letrozole combined with NETA is more efficacious than NETA alone in reducing the volume of endometriotic cysts but in none of the 40 patients included in the study did the endometriomas disappear. The efficacy of aromatase inhibitors, however, should be balanced with the need to administer long-term treatment.



## 1. Introduction

Endometriosis affects at least 4% of reproductive age women [1], and endometriotic ovarian cysts are present in 17–44% of women with endometriosis [2]. The volume of endometriomas decreases during the administration of hormonal therapies including gonadotropin-releasing hormone analogs [3,4], danazol [4] and progestins [5]. These therapies, however, do not lead to complete regression of ovarian endometriotic cysts: in some cases, their volume may increase during treatment and they commonly grow after its discontinuation. Alternatively, endometriotic ovarian cyst may be treated by laparoscopy, but post-operative recurrence of endometriomas is observed in up to 30% of patients at 2–5 years from surgery [6–9]. Furthermore, surgical excision of endometriomas may decrease ovarian reserve [10,11].

Third generation non-steroidal aromatase inhibitors (anastrozole or letrozole) combined with ovarian suppressing agents (oral contraceptive pill, progestins or gonadotrophin-releasing hormone analogs) decrease the intensity of endometriosis-related pain symptoms [12,13]. A case series including five premenopausal women reported that 6-months' treatment with letrozole (2.5 mg/day) and an oral contraceptive pill (0.15 mg desogestrel and 0.03 mg ethinyl estradiol) caused the disappearance of ovarian endometriomas in all the cases [14].

This prospective patient-preference trial assessed whether letrozole combined with norethisterone acetate (NETA) is superior to NETA alone in decreasing the size of endometriotic ovarian cysts. Furthermore, the effects of the two hormonal therapies on pain symptoms were investigated.

## 2. Materials and methods

### 2.1. Study design

This prospective, non-randomized, open-label trial study included women of reproductive age with unilateral single

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endometrioma. Patients were recruited between February 2010 and November 2011. The study protocol was approved by the Hospital Research Review Committee and patients signed a written informed consent.

The primary end-point of the study was to compare the changes in the volume of endometriomas after six months' treatment with the two study protocols. The secondary objective of the study was to evaluate the changes in pain symptoms between baseline and six months of therapy. Further objectives of the study were to investigate the incidence of adverse effects of treatment, to assess the changes in pain symptoms after the discontinuation of treatment and to compare the volume of the endometriomas six months after the discontinuation of treatment.

### 2.2. Study population

The diagnosis of endometriomas was based on transvaginal ultrasonography, which was performed by using a Voluson E6 machine (General Electric Medical Systems, Milwaukee, WI, USA). The criteria for the diagnosis of endometriomas were: round cystic mass with thick walls, regular margins, homogeneous low echogenic fluid content with scattered internal echoes, and without papillary projections with no or poor vascularization of capsule [15,16].

Patients with a diagnosis of unilateral single endometrioma agreeing to participate in the study underwent, after two months, a second transvaginal ultrasonography. If the diagnosis of unilateral single endometrioma was confirmed, the volume of the cyst was measured (baseline assessment) and hormonal therapy was started on the first day of the subsequent menstrual cycle.

Exclusion criteria for the study were: previous surgery for endometriomas, presence of bilateral ovarian endometriomas; use of hormonal therapies in the six months prior to inclusion in the study; previous use of aromatase inhibitors; unwillingness to tolerate menstrual changes; undiagnosed vaginal bleeding; immediate desire to conceive; osteopenia or osteoporosis; current or past history of seizure disorders; pulmonary, cardiac, hepatic or renal diseases; thromboembolic or cerebrovascular events; pregnancy; psychiatric disturbances and history of drug or alcohol abuse.

### 2.3. Study protocol

Patients received one of the following therapies for six months: oral norethisterone acetate (2.5 mg/day, Primolut-Nor; Schering, Milan, Italy; group N) or a combination of oral letrozole (2.5 mg/day, Femara; Novartis Farma, Varese, Italy), norethisterone acetate (2.5 mg/day), elemental calcium (1000 mg/day) and vitamin D3 (880 IU/day, Cacit-Vitamina D3; Procter & Gamble, Rome, Italy; group L). In addition, after the completion of the 6-month treatment, patients underwent a follow-up (at 3 and 6 months) if they did not use hormonal therapy, did not undergo surgery or IVF, and did not conceive.

Patients were informed of the potential benefits and adverse effects of treatment. They were told that NETA is approved by the Italian Ministry of Health for the treatment of endometriosis while aromatase inhibitors are not approved for the treatment of endometriosis by the Italian Ministry of Health and, therefore, the use of these drugs should be considered experimental. Patients were informed that aromatase inhibitors have previously been used to treat endometriosis-related pain symptoms [5,13] but only one study with small sample size suggested that these agents could cause the disappearance of endometriotic ovarian cysts [14]. A detailed list of potential adverse effects of the hormonal therapies was given to the patients [5,13,17]. The costs of the two treatment protocols were provided. Treatment allocation was decided on the basis of the preference of the patients. In order to obtain the desired same sample size in each study group, patients were recruited in each study arm until the desired sample size was achieved. When the sample size of the more numerous group was achieved (group N), patients choosing to be treated with that treatment (NETA alone) were excluded from the study.

The volume of the endometrioma was estimated by using virtual organ computer-aided analysis (VOCAL, GE Healthcare, Milwaukee, WI, USA) as previously described [18]. Briefly, the VOCAL technique was used to obtain a sequence of 20 sections of each endometrioma around a fixed axis, each after 9° rotation from the previous section. The contour of each endometrioma was drawn manually using the roller ball cursor of the 3D-ultrasound machine to obtain a 3D volume measurement. Each measurement was performed offline after scanning by a single trained operator who was not aware of the type of hormonal therapy administered to the patients.

### 2.4. Assessment of symptoms

The intensity of pain symptoms (dysmenorrhea, non-menstrual pelvic pain and deep dyspareunia) was measured using a 10 cm visual analog scale (VAS). Study subjects had monthly consultation during the 6-month treatment and consultations at 3 and 6 months after the completion of treatment. The volume of the endometrioma and the intensity of pain symptoms were evaluated before starting the treatment, after 3 and 6 months of treatment, and at 3 and 6 months after interruption of treatment.

After the completion of treatment, the women rated the overall degree of satisfaction with their treatment by answering to the following question: "Taking into consideration the variations in pain symptoms, in overall well-being and quality of life, as well as the adverse effects experienced, if any, how would you define the level of satisfaction with your treatment?" as previously described by other authors [17] and by us [19]. Answers were based on a 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied).

Complete blood count, serum electrolytes, kidney and liver function tests, and lipids were checked before the onset of therapy, monthly during treatment, and at the completion of treatment. A bone densitometry determination of the hip and lumbar spine (by dual-energy X-ray absorptiometry or DEXA scan) was performed within one month before the onset of the study and was repeated within one month after completion of the treatment in group L. Adverse effects experienced during the 6-month treatment were recorded.

### 2.5. Statistical analysis

The sample size calculation was based on the primary objective of the study (to assess the changes in the volume of endometriomas after six months of treatment with the two study protocols). For this purpose, we retrospectively analyzed the prospectively collected database of premenopausal patients with endometriomas who were treated with NETA for 6 months at our institution in the two years before designing in the study. In the 85 patients with a single endometrioma included in the analysis, the 6-month treatment with NETA caused a mean (±SD) 30.6% reduction (±25.4%) in the volume of the cyst. A difference of 30% in the percentage reduction of the volume of the cyst between the study groups was considered clinically relevant. To have an 85% chance of detecting such a difference at an overall statistical significance level of 5%, 18 patients per group were required.

Categorical variables were compared by using the chi-square test and the Fisher exact test. Changes in the severity of symptoms and in the volume of the cysts during treatment in each study