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Is dienogest the best medical treatment for ovarian endometriomas? Results of a multicentric case control study

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ABSTRACT

Ovarian endometriomas are common manifestations of endometriosis. Surgical excision has been shown to potentially decrease ovarian reserves. In this prospective study, we included 81 patients with ovarian endometriosis. 40 were treated with 2 mg of dienogest daily (DNG) and 41 were treated with cyclic oral estro-progestins (ethinyl estradiol 30 mcg [EE] plus dienogest 2 mg) (DNG + EE). Aim of the study was the effect of the treatment on the size of the endometriotic cysts. Further, in the symptomatic patients, follow-up included an evaluation of chronic pain before and during treatment. Both treatments were able to significantly decrease the pain in symptomatic patients with no statistical differences. The mean visual analog scale score at enrollment was 65 ± 14 and 70 ± 18, and there was significant improvement (19 ± 15, $p < .001$, DNG; 18 ± 12, $p < .001$, DNG + EE). The size of the endometrioma cysts were significantly reduced in the DNG group. The mean cyst diameter was 52 ± 22 mm at baseline and 32 ± 12 mm after six months of treatment ($p < .001$), yielding a 75% volume reduction in DNG group. The decrease in the size of endometrioma cysts observed in the women treated with only progestin could be noteworthy, as it may reduce the negative impacts on the affected ovary and avoid surgery.

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Introduction

Endometriosis is a benign, chronic inflammatory condition characterized by the presence and growth of endometrial implants outside the uterine cavity [1]. It often causes pain, dysmenorrhea, dyspareunia, non-cyclical pelvic pain, infertility and bleeding disorders. The etiology of endometriosis is not precisely understood, and it is probably multifactorial [1,2]. An endometrioma is the formation of a cyst with ectopic endometrial tissue lining within the ovary. This is one of the most common manifestations of endometriosis. Endometriomas are found in 17%–44% of patients with endometriosis. The prevalence of endometriomas is much easier to determine, as the diagnosis is based on ultrasound results [3]. Alcazar et al. reported that the B-mode ultrasound with the use of mean gray value has an 80% sensitivity rate and a 91% specificity rate in discriminating endometriomas from unilocular cysts in premenopausal women [4]. Medication and surgery have been used to treat endometriosis, but these methods do not result in long-term cures or symptom elimination [5,6]. The prevalence of recurrence at 5 years is 36%–57%. About 50% of patients who undergo surgery to cure endometriosis fail to conceive. Pharmacological treatment can improve the prevalence of remission after surgery and reduce the prevalence of recurrence, but its impact on conception is unknown [7]. Conflicting reports exist regarding the impact of an endometrioma on ovarian reserves, particularly when its growth compresses healthy ovarian tissue [8,9]. Conversely, multiple studies show the detrimental effect of surgery on ovarian reserves and the role of surgical technique in reducing this complication [10–12]. The medical approach is suggested for many women who suffer with symptomatic endometriosis and have no desire to become pregnant. An ideal hormonal therapy for endometriosis should be able to decrease pain while avoiding a hypoestrogenic state and have limited side effects, as it should be administered for a prolonged period of time [13,14]. Estroprogestins and progestins are prescribed in most cases as a first-line therapy. Moreover, recent data suggest that the use of progestin-only pills could have some advantages in endometriosis treatment, as supraphysiologic concentrations of estrogens often present in estro-progestin pills could rescue endometrial cell clusters deposited in the pelvis during retrograde menses [15,16]. The aim of our study was to compare the effect of a single progestin with estroprogestin pills in the treatment of patients with ovarian endometriomas.

Materials and methods

Our prospective study (without randomization) was conducted in five tertiary University Centers (Cagliari, Padova, Pisa, Milano and Foggia) from June 2013 to April 2015. The inclusion criteria consisted of endometriosis patients who signed written consent with the following characteristics: unilateral or bilateral

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Table 1. Clinical and ultrasound characteristics of patients.

	AGE (years)	BMI	Baseline VAS in symptomatic patients	Cyst diameter (mm)	Cyst volume (ml)
DNG (n°40)	34.4 ± 4.1	24.4 ± 5	65 ± 14 (27 pts)	54 ± 22	65 ± 10
DNG + EE (n°41)	32.6 ± 8	23.2 ± 3.5	70 ± 18 (22 pts)	49 ± 18	76 ± 20
p	ns	ns	ns	ns	ns

All values are mean ± SD, except if otherwise stated.
BMI: body mass index; VAS: visual analog scale.

endometrioma cysts, with the larger diameter cysts measuring between three and eight cm via a transvaginal ultrasound; age between 18 and 45; regularly menstruating; not previously submitted to surgery involving the ovaries or to medical treatment for endometriosis in the previous three months. Exclusion criteria were as follows: desire to conceive, positive human chorionic gonadotropin test, suspicious Pap smear, uterine or adnexal anomalies other than endometriosis (e.g. leiomyomas, genital malformations, chronic pelvic inflammatory disease and endometrial polyps), endometriomas larger than eight cm or smaller than three cm, any kind of malignancy, hysterectomy, contraindications to hormonal treatment, use of an oral contraceptive pill/progestins injectable hormonal treatments (e.g. GnRH agonists) within the three months prior to the study and the absence of written informed consent.

The study was approved by the institutions' ethics committees and review boards. Before inclusion, patients underwent a pelvic transvaginal ultrasound and endometrioma volumes were calculated using the formula for a prolate ellipsoid: $(\pi/6 \times (D1 \times D2 \times D3)$, where D represented the maximum diameter in the transverse, anteroposterior and longitudinal axes). Moreover, women were requested to grade the severity of non-menstrual pelvic pain on a 100-mm visual analog scale (VAS). The left extreme indicated the absence of pain, and the right extreme indicated maximum pain.

We enrolled 81 women aged 20–42 years (mean = 32.2 years; SD = 6.7). Eligible subjects were either assigned to receive dienogest 2 mg/die (DNG) or dienogest 2 mg plus ethinyl estradiol 30 mcg (DNG + EE), depending on patient preference or choice. The intended follow-up period was 6 months. The primary outcome measure was the change in endometrioma volume after 3 and 6 months, measured by transvaginal ultrasound. Patients with a mean VAS score higher than 50 over a period of 30 days before entering the study were requested to complete the VAS for evaluation of maximum pain symptom intensity once daily for 14 consecutive days before the respective follow-up visit. Pain diaries were checked and collected at every visit, and women were asked about side effects (e.g. unintentional weight gain, headache, loss of libido, acne, alopecia and breast tenderness) and intake of analgesics.

Statistical analysis

Statistical analysis was done with SPSS 15.0 software (SPSS Inc, Chicago, IL, USA). Values for continuous variables are mean ± standard deviation. Statistical analysis was performed before and at the end of the 6-month treatment using the paired *t* test or the Wilcoxon signed test (as appropriate) for the comparison of cyst size, and VAS was used to analyze associated pain. The χ^2 and Fischer's exact tests were used to compare proportions in different groups. A *p* values of $<.05$ was considered statistically significant.

Results

All 81 patients were evaluated at enrollment and at the 6-month follow-up. Patients' characteristics are presented in Table 1. The two groups of patients did not show statistically differences at baseline. Chronic pain was recorded at baseline in 27 patients in the DNG group and in 22 patients in the DNG + EE treatment group. The other patients were either asymptomatic or under the VAS cutoff chosen in this study. The symptomatic patients were evaluated with the VAS at three and 6 months. Significant improvement was observed in both treatments. The mean visual analog scale score at enrollment was 65 ± 14 and 70 ± 18, with a significant improvement at 3 and 6 months (19 ± 15, $p < .001$, DNG; 18 ± 12, $p < .001$, DNG + EE; Table 2). The size of the endometrioma were significantly reduced in the DNG group after 3 and 6 months of treatment. Endometrioma cyst volume decreased significantly in the group taking the progestin-only pill. The mean cyst diameter was 54 ± 22 mm at baseline and 32 ± 12 mm after 6 months of treatment ($p < .001$), yielding a 75% volume reduction in DNG group (Table 2). Despite the improvement in symptoms in the estroprogestin group, we did not observe any significant reduction in the volume of the cysts. No side effects were reported in the estroprogestin group. One case of transient alopecia and one case of headache were reported in the DNG group, but these side effects did not cause therapy discontinuation. No patients needed surgery for cyst enlargement or for pain not responding to medical treatment.

Discussion

The role of surgical treatment for endometriosis cysts with and without symptoms has been debated, and the possible negative effects to the reproductive potential of the treated ovary have decreased the number of patients with endometriomas electing to receive surgical treatment, particularly repeated surgeries [17]. Roman et al. [18] found that an increase in cyst diameter increased the volume of ovarian tissue removed. In contrast, Romualdi et al. [19] observed that more follicles were lost in women who had surgery to remove smaller cysts. Moreover, it seems that anti-mullerian hormone (AMH) values before surgery do not influence the fertility results after the endometriosis treatment [20]. The available guidelines suggest that only endometriomas with a mean diameter below 4 cm should not be systematically removed before *in vitro* fertilization procedures [13]. Nevertheless, the endometrioma, particularly its growth, could be detrimental for the reproductive potential of the affected ovary. Consequently, the request for medical treatment for such patients is increasing; the goal is to avoid, and possibly reduce, cyst growth. Another issue regarding the medical treatment of patients with endometriomas concerns symptom control. Indeed, many patients suffer chronic pain and the concomitant presence of deep endometriosis is associated with an impaired quality of life [21,22]. Our results support that medical treatment could be an option, as both progestin and estroprogestin treatments are able to improve symptoms in patients with

Table 2. Results of medical treatment of endometriomas.

	DNG	DNG + EE	*p*
Cyst volume (ml)			
Time			
0	65 ± 10	76 ± 20	ns
3	45 ± 15	65 ± 18	<.05
6	16 ± 5	65 ± 25	<.001
p	<.001	ns	
VAS			
Time			
0	65 ± 14	70 ± 18	ns
3	25 ± 10	28 ± 12	ns
6	19 ± 15	18 ± 12	ns
p	<.001	<.001	

All values are mean ± SD, except if otherwise stated.

endometriomas and pain. Further, it seems that use of dienogest without estrogens could have a more beneficial effect on endometriomas. In fact, we only saw evidence of a significant decrease in endometrioma cyst volume in the group under DNG. This effect was not observed in patients treated with DNG and EE. Dienogest is a well-tolerated new progestin that seems very effective in the treatment of painful endometriosis and even in reducing endometriosis nodules [23,24]. It is possible that with the addition of a potent estrogen (ethinyl estradiol), this progestin could induce supraphysiological concentrations of estrogens that might act on progesterone-resistant endometriosis cells with increased estrogen activity [16]. Our study presents some limits, as it is a non-randomized study. Moreover, a great variability of endometrioma diameters and other possible unknown factors (e.g. other localizations or the concomitance of adhesions on the ovaries) could have altered our results. However, even if further randomized controlled trials are needed, our results suggest that medical treatment of patients with endometriomas could be suggested. It is effective on symptoms and does not allow the growth of the cyst. Moreover, progestin-only pills could have greater advantages, as they appear to be able to decrease the size of endometrioma cysts.

Disclosure statement

The authors report no conflict of interests.

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