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Dienogest or Norethindrone acetate for the treatment of ovarian endometriomas: Can we avoid surgery?

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ABSTRACT

Objective: To compare the effects of Dienogest (D) and Norethindrone acetate (N) in symptomatic women with ovarian endometriomas, analyzing the efficacy in reducing endometrioma size and symptom relief and drug tolerability.

Study design: Retrospective study including 135 symptomatic women with ultrasonographic diagnosis of ovarian endometrioma. Women were divided into two groups: 1) women who received D 2 mg/day (group D); 2) women who received N 2.5 mg/day (group N). Women were evaluated at therapy prescription and after 6 and 12 months of treatment: transvaginal ultrasound was performed to assess the mean diameter of endometriomas, a Visual Analogue Scale was used to rank endometriosis related symptoms (dysmenorrhea, dyspareunia, chronic pelvic pain). The main outcome measure was the comparison between the 2 groups in terms of variations in endometrioma size and endometriosis related symptoms during the follow-up. Drug tolerability was also analyzed in terms of side effects.

Results: A reduction in ovarian endometrioma size was observed during treatment in both groups, with no significant differences between groups D and N. Endometriosis related symptoms decreased in both groups, but the decrease was significantly higher in group D than in group N for all symptoms, both at 6 and 12 months of treatment. Regarding drug tolerability, uterine bleeding/spotting and weight gain were reported more frequently by women in the group N than women in the group D, both at 6 and 12 months of treatment.

Conclusion: Progestin therapy with D or N appears to be effective in reducing the size of endometriomas and related symptoms, with a greater effect on symptoms relief and higher tolerability in women treated with D.

Introduction

Endometriosis is an inflammatory disease, characterized by the growth of endometrial-like tissue outside the uterine cavity [1]. It affects 5–10% of women of reproductive age and is characterized by pain and infertility symptoms [2]. The ovary is the most frequently affected site, with potential unilateral or bilateral involvement [3]. Laparoscopic excision of ovarian endometrioma with stripping technique used to be considered the treatment of choice in symptomatic patients with ovarian endometriosis [4]. The main risks after surgery are the high rate of disease recurrence [5] and the accidental removal of healthy ovarian tissue, which can potentially reduce the ovarian reserve and fertility [6]. Consequently, there is an important concern about the usefulness of surgical management of ovarian endometriomas.

To date, the main professional bodies [1,7–9] recommend the use of progestins, with or without estrogens, as first line medical treatment for symptomatic ovarian endometriosis. This is due to their favorable safety, efficacy and tolerability and limited costs, especially in the perspective of a long-term therapy. In some studies these drugs have also proved useful in the reduction of ovarian endometrioma size in addition to the improvement of endometriosis related pain [10,11].

Dienogest (D), a semisynthetic 19-nortestosterone derivative progestin, has recently introduced as a medical treatment for endometriosis. Some studies demonstrated a promising ability of this drug in reducing the size of endometriotic lesions and associated pain symptoms, with a favorable tolerability profile [12–14], and also a reduction in the size of recurrent endometriomas [15]. Norethindrone acetate (N), a 19-nortestosterone

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derivative progestin, has also been widely used in women with endometriosis [16–18], although there are few studies that investigated its efficacy in the treatment of ovarian endometriomas, mainly recurrent endometriomas [10,19]. Ferrero et al. [11] compared the efficacy of N alone or in combination with letrozole in the treatment of endometriomas and observed a reduction in their volume after six months of therapy. Morotti et al. [20] studied the efficacy of D in the treatment of a subpopulation of women with rectovaginal endometriosis and pain resistant to N, but only one study [21] compared the effectiveness of these two progestins in symptomatic endometriosis.

In the present study, we aimed to compare the effects of D and N in symptomatic patients with ovarian endometriomas, analyzing their efficacy in reducing endometrioma size and in relieving symptoms and tolerability of the drug.

Materials and methods

Subjects

This retrospective study included 141 women of reproductive age, who were referred to our Center from February 2015 to February 2017 for endometriosis. Inclusion criteria were: a) age between 20 and 45 years, b) ultrasonographic diagnosis of the "typical" mono or bilateral ovarian endometrioma, with a mean diameter of 40 mm or less, c) the presence of at least one of the following pain symptoms: dysmenorrhea, chronic pelvic pain, dyspareunia, d) progestin therapy with D or N for at least 12 months. Exclusion criteria were: a) suspicion or diagnosis of deep infiltrating endometriosis on clinical and/or ultrasound examination, b) any hormonal therapy undertaken within three months before enrollment.

Study design

We retrospectively reviewed data from the clinical records. As we do in our daily practice, women were evaluated at baseline visit (V0), when the therapy was prescribed, and after 6 and 12 months of therapy (follow-up visits V1 and V2, respectively). According to the therapy prescribed at V0, women were divided into two groups: 1) the first group received Dienogest 2 mg/day (group D); 2) the second group received Norethindrone acetate 2.5 mg/day (group N), starting both from the first day of menstruation following the visit. At each visit medical history, semiological analysis, detailed gynecological examination, transvaginal and transabdominal ultrasound were recorded in all women. Data on demographic and clinical characteristics of the participants were collected: age, body mass index and parity. During visits the women were asked to rank endometriosis related symptoms (dysmenorrhea, chronic pelvic pain, dyspareunia) using a numerical Visual Analogue Scale (VAS) from 0 (absence of pain) to 10 ("the maximum pain you could imagine") [22]. At each follow-up visits (V1 and V2), women were also asked to report the presence of side effects related to the treatment (weight gain, mood disorders, loss of libido, headache, nausea, swelling, acne, hair loss, breast tenderness, vaginal dryness, uterine bleeding including spotting). All women gave written informed consent and the study was approved by our local ethics committee. All procedures were in accordance with the Helsinki declaration of 1975.

Table 1
Demographic and clinical characteristics in the study groups (135 women).

	Group D (69)	Group N (66)	P
Age[a]	37 (29-42)	36 (28-44)	0.75
Body mass index[a]	24 (10-25)	25 (20-26)	0.37
Previous deliveries[b]	14 (20.3%)	13 (18.8%)	0.93
Previous surgery for endometriosis[b]	12	11	0.91
Patients with Cyst side monolateral[b]	46 (66.7%)	50 (75.8%)	0.24
Patients with Cysts side bilateral[b]	23 (33.3%)	16 (24.2%)	0.24

[a] Data are presented as median and interquartile range.
[b] Data are presented as number and percentage.

Ultrasound examination was performed by sonographers experienced in endometriosis, making a subjective evaluation of gray-scale and Doppler ultrasound "pattern recognition": a "typical" ovarian endometrioma was diagnosed when a unilocular cyst with ultrasound features of regular wall, 'ground glass' echogenicity of the cyst content and poor capsular vascularization at Power Doppler was observed [23,24]. To assess the size of ovarian endometriomas, the main diameters (longitudinal, transverse, and antero-posterior) were measured and the mean diameter was then calculated.

Statistics

Statistical analysis was performed using the Statistical Program for Social Sciences (IBM SPSS, version 24.0, IBM Co., Armonk, NY). Changes in clinical symptoms and size of ovarian cysts between V0, V1 and V2 visits were evaluated by one way analysis of variance. The results were expressed as median and interquartile range and as number and percentage. Categorical variables were expressed as numbers and percentages and evaluated with Chi-Square test. The

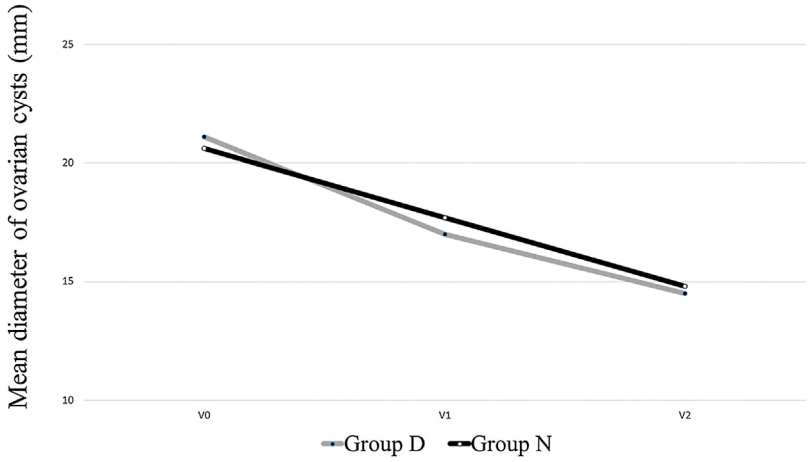

Fig. 1. Mean diameter of ovarian endometriomas at baseline visit (V0), after 6 months (V1) and 12 months of treatment (V2) in the study groups.

Student *t*-test was used to compare continuous parametric variables. A P-value of <.05 was considered significant for all tests.

Results

According to the inclusion criteria, of the 141 women enrolled in the study, 6 women were lost during follow-up (3 were submitted to surgery for pain resistant to medical therapy, 4 did not complete the V2 visit), therefore 135 women completed the study: 69 (51.1%) in the group D and 66 (48.9%) in the group N. All three women submitted to surgery belonged to group N. The demographic and clinical characteristics of the 135 women who completed the study are reported in Table 1. Thirty-nine (28.9%) had bilateral endometriomas for a total of 174 endometriomas, of which 92 endometriomas belonged to the group D and 82 to the group N. No new endometriomas occurred during the follow-up period in both groups. At V0 the mean diameter of the endometriomas was 21.07 ± 10.23 mm in group D and 20.62 ± 10.61 mm in group N. The differences in mean diameters of the endometriomas between the two groups during follow-up are shown in Fig. 1. The mean diameter of endometriomas reduced during follow-up in both group D (−2.51 mm at V1 and −6.54 mm at V2) and group N (−2.94 mm at V1 and −5.80 mm at V2), with no significant differences between the two groups (P = NS at V1 and V2).

Endometriosis associated symptoms in the two groups are reported in Fig. 2. A marked decrease in pain were detected in both groups but the decrease was significantly higher in group D than in group N for all symptoms, both at V1 (chronic pelvic pain P = 0.002, dysmenorrhea P = 0.001, dyspareunia P < 0.001) and at V2 (chronic pelvic pain, P < 0.001, dysmenorrhea P < 0.001, dyspareunia P < 0.001).

Regarding tolerability, side effects during treatment are reported in Table 2. At V1 38 women (57.6%) in N group reported side effects, compared with 32 women (46.4%) in group D. The most frequent side effects at V1 were: uterine bleeding/spotting, weight gain, vaginal dryness and loss of libido. In particular, both uterine bleeding/spotting and weight gain were significantly more frequent in group N (P = 0.03 and P = 0.01, respectively).

At V2 31 women (47.0%) in group N reported side effects, compared with 26 women (37.7%) in group D. The most frequent side effects at V2 were: uterine bleeding/spotting, weight gain, vaginal dryness and loss of libido. In particular, also at this control, both uterine bleeding/spotting and weight gain were significantly more frequent in group N (P = 0.04 and P = 0.03, respectively). No significant differences (P = NS) were found in the other side effects between the two groups both at V1 and V2. No patients discontinued therapy due to side effects.

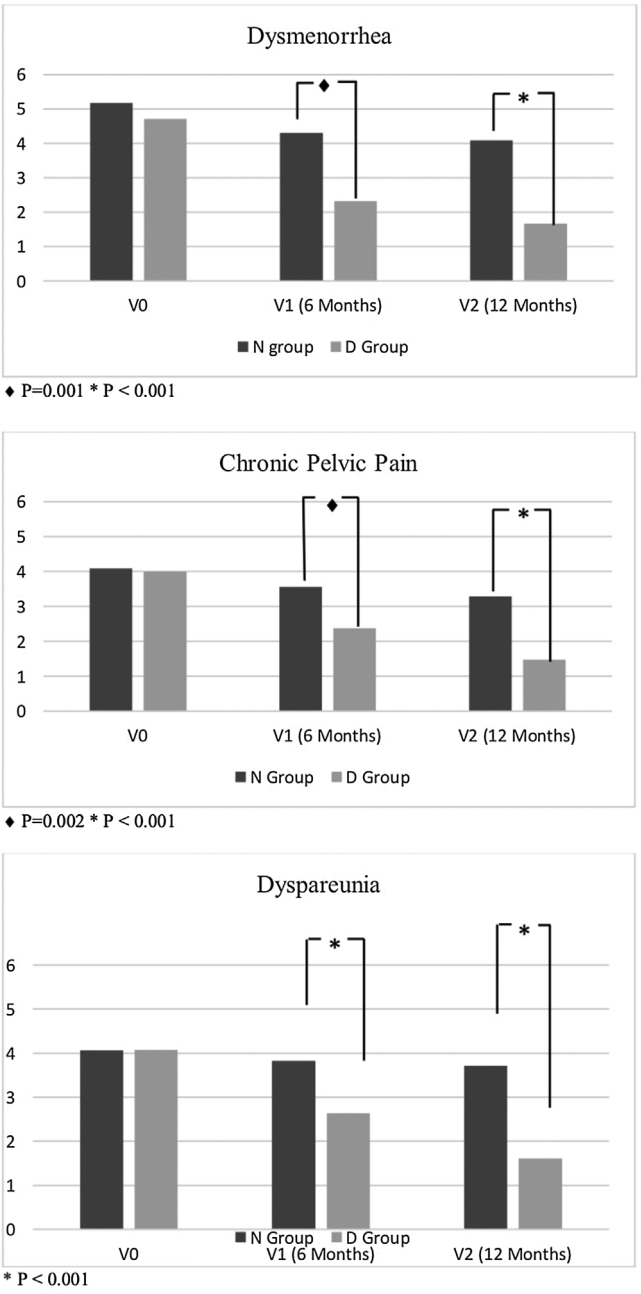

Fig. 2. Endometriosis related symptoms VAS scores at baseline visit (VO), after 6 months (V1) and 12 months of treatment (V2) in the study groups.

Comment

In this retrospective study we analyzed the efficacy of D and N in terms of endometrioma size reduction, relief from endometriosis related symptoms and tolerability. Our data showed that both oral administration of D and N can reduce the size of ovarian endometriomas. In comparison to N, D was more effective in reducing endometriosis related symptoms both after 6 and 12 months of treatment and was better tolerated. These findings suggest that both drugs, but in particular D, may represent valid therapeutic options for the management of endometriomas, in order to avoid or delay surgery even in short-term administration.

Despite D and N are the most used progestins for the treatment of endometriosis, only one study compared the effectiveness of the two progestins in symptomatic patients after 6 months of treatment [21], finding comparable effects in terms of pain relief, improvement of sexual function, health related quality of life and psychological status, with a greater tolerability profile in women treated with D.

Dienogest acts on endometriotic lesions by inducing a hypoestrogenic environment with initial decidualization and subsequent atrophy of endometriotic implants [25]. Moreover, recent studies on the analysis of endometriotic tissue taken from women with ovarian endometriomas treated with D showed interesting histological features, such as reduced proliferation, aromatase expression, angiogenesis and increased apoptosis [26], as well as higher decidualization rate compared to controls [27]. Similarly, N produces a hypoestrogenic hormonal environment by suppressing gonadotropins, inhibiting ovulation, and developing amenorrhea with subsequent decidualization and atrophy of endometrial tissue [10]. These effects may explain the reduction in endometrioma size observed in both groups, as well

Table 2
Side effects during treatment in the study groups (135 women).

	V1 (after 6 months of treatment)			V2 (after 12 months of treatment)		
	D group (69)	N group (66)	P	D group (69)	N group (66)	P
Weight gain	11 (15.9)	23 (34.8)	0.01*	10 (14.5)	20 (30.3)	0.03*
Uterine Bleeding/Spotting	7 (10.1)	16 (24.2)	0.03*	6 (8.7)	14 (21.2)	0.04*
Loss of libido	6 (8.7)	11 (16.7)	0.16	5 (7.2)	12 (18.2)	0.06
Vaginal dryness	5 (7.2)	7 (10.6)	0.49	5 (7.2)	7 (10.6)	0.49
Mood disorders	2 (2.9)	5 (7.6)	0.22	1 (1.4)	5 (7.6)	0.08
Breast tenderness	2 (2.9)	5 (7.6)	0.22	1 (1.4)	3 (4.5)	0.29
Bloating or swelling	4 (5.8)	4 (6.1)	0.95	3 (4.3)	4 (6.1)	0.65
Acne	1 (1.4)	1 (1.5)	0.97	1 (1.4)	1 (1.5)	0.97
Headache	3 (4.3)	2 (3.0)	0.69	2 (2.9)	2 (3.0)	0.96
Hair loss	2 (2.9)	1 (1.5)	0.59	2 (2.9)	0 (0.0)	N/A
Nausea	1 (1.4)	0 (0.0)	N/A	0 (0.0)	0 (0.0)	N/A

as the reduction of endometriosis related symptoms. The improvement in symptoms was more significant in group D after 6 and 12 months of treatment. Other studies showed similar results of D in reducing endometriosis symptoms such as dyspareunia, dysmenorrhea, premenstrual pain and diffuse pelvic pain [28,29]. The greater improvement in VAS scores symptoms during treatment in group D may be related to the anti-proliferative and anti-inflammatory effects of D on endometriotic cells [30]. Our outcomes are different from the results of Vercellini et al [21] which found comparable effects of N and D in terms of pain relief after 6 months of treatment. Regarding the drug tolerability, uterine bleeding/spotting and weight gain were reported more frequently by women in the group N than women in the group D, both at 6 and 12 months of treatment. The data agree with those of Vercellini et al. [21], which found a greater tolerability profile in women treated with D compared to women treated with N.

Considering the negative effect of surgical removal of endometriomas on ovarian reserve [6], the reduction of the endometrioma size and related symptoms with medical therapy may consent to avoid or delay surgery. The comparison of the two drugs showed that D may be more effective in reducing endometriosis related symptoms, even in the short term administration, and better tolerated. However, comparing D with N, we must consider the higher cost of D, which may represent a limit for the use of the drug, especially in the perspective of a long term treatment, as already reported by others [21,25].

The main limitations of the study are the retrospective design and the limited number of women. Another drawback is the absence of a histological diagnosis of endometriomas. However, we included only women with 'typical endometriomas', which can be safely and correctly diagnosed with transvaginal ultrasound [23,24].

Progestin therapy with D or N appears to be effective in reducing the size of endometriomas and endometriosis related symptom, suggesting a potential role of both drugs in avoiding or delaying surgery. Effectiveness on symptoms relief, as well as tolerability profile, was higher in women treated with D. However, our outcomes cannot be generalized and should be confirmed by randomized controlled trials, comparing effectiveness, safety and tolerability of D and N in the long-term treatment of women with ovarian endometriomas.

Conflict of interest

The authors have no conflicts of interest to disclose.

Acknowledgment

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