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ORIGINAL ARTICLE

Estradiol/nomegestrol acetate as a first-line and rescue therapy for the treatment of ovarian and deep infiltrating endometriosis

Luca Liban Mariani, Lorenzo Novara, Matteo Mancarella, Luca Fuso, Elisa Casula and Nicoletta Biglia

Obstetrics and Gynecology University Department, Azienda Ospedaliera Ordine Mauriziano di Torino, Torino, Italy

ABSTRACT

Purpose: Estradiol valerate/nomegestrol acetate (E2V/NOMAC) is a new combined oral contraceptive with a good tolerability profile and low drop-out rates, which was shown to improve menstrual-related symptoms. This study aims to evaluate its effectiveness in the control of symptoms and progression of disease in women with ovarian endomestriomas and deep infiltrating endometriosis (DIE).

Methods: This was a retrospective cohort study on 39 women with pelvic endometriosis treated with E2V/NOMAC. We assessed for each patient, at the beginning of treatment and after 6 months, the painful symptoms, through a global VAS (Visual Analogue Scale) index and the size of the greatest ovarian and/or deep infiltrating endometriotic lesions.

Results: After 6 months of treatment, a significant reduction was observed for the global VAS score for pain symptoms and for the mean size of ovarian endometriomas, whereas DIE lesions did not present significant changes in mean size.

Conclusions: E2/NOMAC was effective in reducing pain symptoms associated with pelvic endometriosis and the size of ovarian endometriomas, whereas DIE lesions remained stable. This therapy could provide good results in the control of symptoms and disease progression in women with pelvic endometriosis.

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Introduction

Women with endometriosis are widely prescribed with Combined oral contraceptives (COCs) since they are usually effective in controlling symptoms, well-tolerated and relatively inexpensive, allowing long-term use [1,2]. However, the limiting factors include the necessity for a prolonged duration of the therapy, the high rates of recurrence after discontinuation, the increased risk of thromboembolism and the occurrence of side effects which can reduce compliance to treatment [3,4].

Since current therapeutic options present several limitations, it is essential to focus on new treatments with better efficacy and tolerability. In this setting, COCs containing estradiol valerate and nomegestrol acetate (E2V/NOMAC) may represent a new effective therapeutic option, with few withdrawal symptoms and a better profile of safety in terms of thrombotic and cardiovascular risk in comparison with other COCs containing ethinylestradiol [4–8].

This regimen has been recently shown to reduce chronic pelvic pain in women with endometriosis, with a better symptom control when compared to nonsteroidal antinflammatory drugs [9]; however, no research has focused so far on its potential efficacy in controlling the progression of the disease.

The present study aims at investigating the efficacy of E2V/NOMAC in women affected by ovarian and deep infiltrating endometriosis, in terms of control of symptoms and progression of the lesions, including both patients treated with this regimen as a first line and cases where it was used as a rescue therapy after discontinuation of other drugs.

Materials and methods

This was a retrospective cohort study on women with symptomatic endometriosis undergoing E2V/NOMAC treatment at the Endometriosis Clinic of the Obstetrics and Gynecology Unit, Mauriziano Umberto I Hospital, in Turin, between January 2018 and June 2020.

The inclusion criteria were: women with symptomatic endometriosis, presenting with ovarian endometrioma or DIE, undergoing therapy with E2V/NOMAC during a minimum six months follow-up period.

Treatment consisted of a combined oral therapy with estradiol valerate 1.5 mg plus nomegestrol acetate 2.5 mg, either in a continuous or cyclic administration according to the type of symptoms and preferences of the patient. We included in our study population both women prescribed with E2V/NOMAC at first diagnosis of endometriosis, and patients previously submitted to other medical treatments, for whom it represented a "rescue therapy". In all women, medical eligibility criteria for the use of COCs where assessed before starting treatment.

The exclusion criteria were: women who were asymptomatic at diagnosis; patients submitted to surgical treatment for endometriosis during the follow-up period.

In our study we reviewed the medical charts of our patients, to collect relevant anamnestic data, including previous surgical interventions and medical treatment for endometriosis, and information about the symptomatic burden and the extension of the disease, like localization, appearance and size of the lesions.

At each visit, a patient interview was carried out to describe subjective pain symptoms associated with the disease and

CONTACT Nicoletta Biglia nicoletta.biglia@unito.it Obstetrics and Gynecology University Department, Azienda Ospedaliera Ordine Mauriziano di Torino, Largo Turati 62, Torino, 10128, Italy

measure their intensity and frequency through the use of a global VAS (Visual Analogue Scale) score, ranging from 0 to 10, as the sum of the VAS scores for each one of these symptoms, at the beginning of treatment with E2V/NOMAC and and after six months of therapy [10]; we used this variable as an outcome measure, quantifying the burden of pain symptoms due to endometriosis and their variation through the period of medical treatment.

During each visit, an ultrasound transvaginal and transabdominal examination was carried out according to available evidence-based consensus guidelines [11–13]. We calculated for each patient the mean diameter of the greatest ovarian and/or deep infiltrating lesion, which we used as target lesions; we then evaluated these measures at the beginning of the therapy with E2V/NOMAC and after six months of treatment.

Statistical analysis

We compared the global VAS score and the mean diameter of the greatest ovarian and/or deep infiltrating endometriotic lesion in each patient at the beginning and after six months of treatment. Univariate analysis was performed for each comparison with a two-tailed *t*-test for paired samples. A difference was considered statistically significant when it was associated with a two-tailed $p < .05$. Statistical analysis was carried out by SPSS 11.0 software (SPSS Inc., Chicago, Illinois, USA).

Results

During the study interval, 39 women diagnosed with ovarian or deep infiltrating endometriosis were treated with E2V/NOMAC and followed up in our Hospital for a minimum period of 6 months.

Table 1 describes the main characteristics of our population; Table 2 summarizes the characteristics of previous medical treatments. Table 3 summarizes the sonographic features of endometriosis affecting the women included in the study.gVAS scores and the mean size of the greatest ovarian and deep infiltrating lesions were measured at the beginning and after six months of the E2V/NOMAC therapy. The comparison was carried out with a two-tailed t Student's test for paired samples; the choice of this parametric statistic was made after checking with Kolmogorov-Smirnov test that the distribution of our sample did not differ from the normal one.

Table 4 shows the results of our analysis. During the period of treatment with E2V/NOMAC, a reduction in perceived pain symptoms was reported by our patients: the mean global VAS score was significantly reduced from 8.1 points at the beginning to 2.5 points at six months ($p = .0038$). Among women with ovarian endometriosis, we observed a reduction in the size of endometriomas in 22 out of 24 patients (91.7%), whereas in 2 cases the target lesion increased in dimensions; the mean diameter of the greatest lesion was significantly reduced from 30.6 mm at the beginning to 13.3 mm at six months ($p = .021$). As for DIE, we did not observe a significant difference between the size of the target lesion from the initial evaluation to the control at six months (mean diameter 18.2 mm vs 16.9 mm, $p = .12$).

In 2 out 39 women (5.1%), after 6 months of treatment with E2V/NOMAC the therapy was discontinued due to an increase in the size of ovarian endometriomas observed at ultrasound examination.

Table 1. Characteristic of the study population.

Variables	$n = 39$
Age (years)*	34.9 ± 1.8 [22.0; 48.0]
BMI (kg/m2)*	21.8 ± 0.9 [16.1; 27.9]
Parity (%)	
- nulliparous	28 (71.8%)
- parous	11 (20.2%)
Previous surgery for endometriosis	17 (43. 6%)
Previous medical treatment for endometriosis	31 (79.5%)

BMI: body mass index.
*Data reported as mean ± standard error [range].

Discussion

In the present study E2V/NOMAC was shown to be effective in relieving pain, with a significant overall improvement in the gVAS evaluation after six months of treatment.

Our result is consistent with data available in literature where, up to 80–90% of women treated with COC experience control of painful symptoms [14]. In a recent study by Caruso et al. [9], treatment with E2V/NOMAC was evaluated in women affected by endometriosis-associated pelvic pain, demonstrating a significant improvement in VAS scores for painful symptoms, quality of life and sexual function, and a low rate of drop-out by patients.

Women with ovarian and deep infiltrating endometriosis may be likely to report a greater burden of painful symptoms [15,16]; moreover, they require a dedicated ultrasound monitoring in follow up, to check for signs of progressing disease such as growth of the lesions or changes in their sonographic features. So far, our study was the first to investigate the potential effect of E2V/NOMAC treatment in controlling the progression of these types of endometriosis.

As for ovarian endometriomas, in our population, after six months of treatment, a significant reduction in the size of the lesion was observed at ultrasound examination.

Current evidence suggests that approach to ovarian endometriomas should be tailored according to symptoms and patients' desire for offspring, even if a first-line pharmacological approach is recommended [17,18]. Surgical treatment might in fact cause a

Table 2. Previous medical treatment for endometriosis.

Medical treatment for endometriosis	$n = 31$
Type of treatment (%)	
- Progestins as single-therapy	7 (22.6%)
- Combined oral contraceptives	24 (77.4%)
Main reason for treatment discontinuation (%)	
- Intolerance to side effects of medical treatment	13 (42%)
- Ineffective control of pain symptoms	9 (29%)
- Progression of disease evaluated at ultrasonography	9 (29%)

Table 3. Sonographic features of endometriotic lesions.

Sonographic features	$n = 39$
Ovarian endometriosis (%)	24 (61.5%)
Mean diameter of greatest ovarian lesion (mm)*	30.6 ± 6.7
Deep infiltrating endometriosis	26 (66.7%)
- Utero-sacral ligaments	16
- Sigmoid colon and rectum	10
- Recto-vaginal septum	5
- Bladder	2
Mean diameter of greatest DIE lesion (mm)*	18.2 ± 3.0
Absent/reduced posterior sliding sign	15 (38.5%)
Uterine adenomyosis	29 (74.4%)

*Data reported as mean ± standard error.

Table 4. Outcomes of medical treatment.

Outcomes	Beginning of treatment	Evaluation at 6 months	p^*
gVAS score (points)	8.1	2.5	.0038
Mean diameter of greatest ovarian lesion (mm)	30.6 ± 6.7	13.3 ± 4.3	.021
Mean diameter of greatest DIE lesion (mm)	18.2 ± 3.0	16.9 ± 3.3	.12

Data are reported as mean ± standard error.
*Comparison was carried out with a two-tailed *t*-test for paired samples.

decrease in ovarian reserve due to damage to residual parenchyma, appearing as a postoperative fall in circulating anti-Mullerian hormone (AMH) [19]. On the other hand, an expectant management might as well be related to a reduction in AMH levels [20,21]; this is thought to be due to damage to ovarian parenchima caused by the endometrioma itself. A reduction in size of ovarian lesions might therefore be likely to decrease this detrimental effect, with crucial benefits in terms of preservation of ovarian function, offering an alternative option to surgery or offering the chance of an easier excision of the lesion before the intervention.

At the moment, dienogest is the most important progestin used for the treatment of endometriomas, allowing in several cases a reduction in the size of the cysts [22,23] and benefits in terms of quality of life and sexual function even in the setting of long-term treatment, with fairly good tolerability [24,25]. However, as progestin-only treatments do, it might be associated with variable and unpredictable changes in bleeding patterns, which is the most common adverse effect, reported by about a woman out of seven[23]; this may lead to discomfort and in several cases to discontinuation of the therapy [26]. Moreover, up to one third of patients treated with dienogest may report an inadequate response [27].

For these reasons, the use of COCs represents an adequate alternative in the treatment of endometriosis, especially after the recent introduction of regimens containing 17β-estradiol as an estrogenic component, combined with NOMAC or dienogest.

The presence of 17β-estradiol as an estrogenic component has been associated to a better safety profile in terms of hemostasic parameters, lipid and glucose metabolism, in comparison with conventional COCs regimens containing ethinylestradiol [6–8]. On the other hand, NOMAC is a highly selective 19-nor progestogen derivative with specific binding to progesterone receptors, anti-estrogenic activity and no androgenic, mineralocorticoid nor glucocorticoid effects; moreover, its long half-life allows it to cover hormone-free interval even when used in cyclic regimens [28]. Altogether, this may allow a better cardiovascular, hemostatic and metabolic profile of E2V/NOMAC compared with other COCs [5,6].

In our study, we also evaluated the effect of treatment with E2V/NOMAC on DIE lesions. In this case, we did not observe any significant differences in the size of the lesions after six months of treatment. This result is consistent with data available in Literature, suggesting that hormone therapies for DIE are effective in controlling symptoms even if they do not appear to reduce the size of infiltrating lesions [29]. This might be explained by the fact that since DIE nodules are mainly constituted of fibrous scar tissue, they have a low probability of regression with medical treatment [29].

However, pain associated with endometriosis is not only due to the presence of the lesion itself and its growth, but also to a mechanism of peripheral and central nerve sensitization induced by the release of pro-inflammatory cytokines and growth factors in the surrounding environment. Hormone treatments for endometriosis have been shown to counteract this phenomena, reducing inflammation and nerve fiber density in peritoneal endometriotic lesions [30]. This allows medical treatments to provide an effective control of pain in DIE, without a cytoreductive effect on infiltrating lesions [29].

During treatment with E2V/NOMAC, the therapy was well tolerated in all patients and no cases of spontaneous interruption were reported. At six months visit, in 94.9% of patients the indication to treatment with E2V/NOMAC was confirmed due to the evidence of efficacy in symptom and disease control, without significant side effects.

It is noteworthy that our population had a high prevalence of sonographic signs of uterine adenomyosis; this condition has been reported to increase the burden painful symptoms, reducing the efficacy of endometriosis treatment in controlling pain [28,29] nevertheless most of our patients experienced a good response to E2V/NOMAC.

This exploratory study has several limitations, such as its retrospective nature, the small size of our population and the absence of a control arm; moreover, a longer period of follow up might be necessary to better define the rate of possible discontinuation of this therapy. However, our research provides significant information in the field of medical treatments for endometriosis, with preliminary data suggesting a potential efficacy of E2V/NOMAC in symptomatic improvement even in patients with ovarian or deep infiltrating lesions and possible benefits in reducing the size of endometriomas in a pre-operative setting or even as an alternative to surgery.

Ethics approval

The study was conducted in accordance with the 1964 Declaration of Helsinki. Since this was a retrospective study on a treatment with estrogen-progestins which are considered first-line treatment for endometriosis and being therefore all the procedures performed as part of the routine care, no ethical committee approval was needed.

Consent to participate and to publish

Informed consent was obtained from all individual participants included in the study. All patients gave their consent to the anonymous use and publication of their data for scientific purposes.

Disclosure statement

All Authors declare that there is no conflict of interests regarding the publication of this article.

ORCID

Nicoletta Biglia http://orcid.org/0000-0003-1009-5309

Data availability statement

Due to their sensitive nature, the data that support the findings of this study are available on request from the corresponding author (N.B.).

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