Title: Pelvic pain and quality of life of women with endometriosis during quadriphasic estradiol valerate/dienogest oral contraceptive. A patient-preference prospective 24-week pilot study.

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Abstract

Objective: The progestin dienogest (DNG) given alone effectively reduces pelvic pain of women with endometriosis. *It is not clear whether the same occurs when DNG is associated with estradiol (E2).*

Design: Patient preference prospective observational study.

Setting: Outpatient centre of university hospital.

Patients: 40 patients with endometriosis and menstrual pain.

Interventions: 24-week treatment with a quadriphasic association of estradiol valerate (E2V) and DNG or a non-steroidal anti-inflammatory drug (NSAID) to be used only in case of pain (ketoprofene 200 mg tablets).

Main Outcome Measures: Menstrual pain and, when present, inter-menstrual pain and dyspareunia were investigated by means of a 10 cm visual analogic scale (VAS). Quality of life was investigated by the short form-36 of the health related quality of life (SF-36) questionnaire.

Results: Final study group consists of 34 patients, 19 in *the* E2V/DNG group and 15 in *the* NSAID-group. After 24 weeks no significant modification of menstrual *pain*, inter-menstrual pain, dyspareunia or SF 36-score was observed in the NSAID-group. Treatment with E2V/DNG reduced *the* VAS score of menstrual pain by 61% ($p<0.0001$). In the subgroups of women with inter-menstrual pain or dyspareunia, E2V/DNG reduced these complaints by 65% ($p=0.013$) and 52% ($p=0.016$), respectively. The reduction of menstrual ($p=0.0001$) and inter-menstrual pain ($p=0.03$) was significantly greater during E2V/DNG than NSAID. Quality of life improved during E2V/DNG ($p=0.0002$), both in physical ($p=0.0003$) and mental domains ($p=0.0065$). Only few minor adverse effects were described during E2V/DNG, and none caused withdrawal from treatment.

Conclusion: In patients with endometriosis and pelvic pain, the 24-week administration of the quadriphasic association of E2V/DNG decreases pelvic pain and improves quality of life.

Keywords (n=11): Endometriosis, Dysmenorrhea, Chronic Pelvic Pain, Dyspareunia, Quality Of Life, Hormonal Contraception, Combined Oral Contraceptive, Dienogest, Estradiol Valerate, NSAID, Ketoprofene

Introduction

Endometriosis is a chronic disease that affects about 10% of women in reproductive age. It is associated with recurrent episodes of menstrual or inter-menstrual pain and deep dyspareunia[1, 2]. These may have a negative impact on the woman's quality of life [3]. Combined oral contraceptives (COCs) are an accepted and effective medical therapy for menstrual pain related to endometriosis [4-7]. Among different types of progestins used in COCs, a particular role belongs to dienogest (DNG). In women with endometriosis, DNG given alone at a dose of 2 mg/day reduces pain [8], in a way similar to that obtained with a GnRH analogue [9,10]. The effect over-lasts its use [11] and is associated with improved quality of life [9,12]. Direct effects of DNG on growth, neo-angiogenesis and cell proliferation of endometriotic lesions have been also reported [13-15]. In addition to the cost, two aspects may limit the widespread and prolonged use of DNG alone. DNG alone is not licensed as a method for contraception, and sexually active women should use additional non-hormonal contraceptive method. Furthermore, the use of DNG alone is associated with a high incidence of irregular uterine bleedings, with values ranging from 13.3% [11] to 71.9% [16]. This may lead to a low acceptance and an early discontinuation of DNG treatment [9-11]. Both contraception and cycle control can be achieved with the addition of an estrogenic component to DNG. Indeed, DNG is marketed in two COC formulations, one containing estradiol valerate (E2V) and the other ethinyl-estradiol (EE). At the moment, it is not clear whether the efficacy of DNG in the treatment of pain associated with endometriosis could be eliminated by the addition of an estrogenic component.

In this study we evaluated the efficacy of DNG associated with E2V in reducing pelvic pain and in improving quality of life of women with endometriosis.

The present study is reported according to the STROBE statement for improving the quality of observational studies (http://www.strobe-statement.org).

Material and methods

A patient preference, observational, prospective cohort mono-centric study, was performed at the University Hospital of Modena (Italy) in the outpatient service for endometriosis and chronic pelvic pain. The study was performed between January 2011 and June 2013, and it was conducted in full accordance with the World Medical Association Declaration of Helsinki. The institutional review board (IRB) of our institution approved this observetional study. Each patient was enrolled into the study after having signed a specific informed consent for the use of her sensitive data. Exclusion criteria were: women with contraindications to the use of COC (category 3 and 4 of WHO guidelines) [17], women having undergone surgical treatment or having used hormonal contraceptives, progestins, GnRHa or other treatments for pain or endometriosis in the previous 3 months.

Inclusion criteria were: subjects of normal weight (BMI < 25), 18 to 50 years of age, with regular menstrual cycles, suffering from menstrual pain from more than 6 months. All women suffered from symptomatic endometriosis (diagnosed by previous laparoscopy or laparotomy or the presence of an ovarian endometrioma diagnosed by trans-vaginal ultrasound) and were not scheduled for first or repeated surgery. Women were informed about the different pharmacologic options available for the treatment of their pain. Those women who spontaneously chose either the COC under investigation or a non-steroidal anti-inflammatory drug (NSAID) were enrolled into the study [18]. The COC under investigation was a quadriphasic oral contraceptive containing E2V/DNG (days 1-2: 3mg E2V, days3-7: 2 mg E2V+2 mg DNG, days 8-24: 2 mg E2V+3 mg DNG, days 25-26: 1 mg E2V, days 27-28: placebo) (Klaira®, Bayer Schering Pharma, Milan, Italy). The NSAID was ketoprofene 200 mg tablets (Orudis®, Sanofi Aventis SpA, Milan, Italy) to be taken only when needed, not exceeding three times a day. Both treatments were prescribed for 24 weeks. At the time of study start-up, DNG alone was not available in Italy, and E2V/DNG was the only COC containing DNG available in our country. Women interested to participate were enrolled after having signed an informed consent. Subjects paid for their medicines as in real life condition.

Patients were evaluated prior to treatment, on days 2-5 of menstrual phase and on days 2-5 of the 4th and 7th cycle of treatment. Side effects, tolerability, pain and quality of life were evaluated prior to and at the end of the six cycles, while adverse events and tolerability were evaluated also at the end of the first 12 weeks of treatment.

Height and weight were measured barefoot with the subject wearing light clothes. BMI (Kg/m2) was calculated. A 10-cm visual analogue scale (VAS) was used to measure intensity of menstrual pain, inter-menstrual pain and dyspareunia [19]. A validated Italian version of the SF-36 questionnaire [20] was used to quantify health-related quality of life.

Data analysis

Statistical analysis was performed using the statistical package StatView (version 5.01.98, SAS Institute Inc, Cary, NC, USA). Intra-group analysis was performed with the t-test for paired data and by the Wilcoxon signed-rank test for normal and non-normal data distribution, respectively. Between groups comparison was performed by two factors analysis of variance (ANOVA) for repeated measures, with treatment and time as factor 1 and factor 2 and subjects as replicates.

For all analyses the null hypothesis was rejected at a two-tailed p value <0.05. Results are expressed as the mean ± standard deviation (SD).

Potency of the study

Sample dimension was calculated on possible modification of menstrual pain VAS score. Based on a previous study performed with an EE based COC [7], during E2V/DNG we assumed a VAS score decrease of about 3.1 with a SD of about 2.0. Similarly, we assumed a non-significant effect of NSAID with a maximum VAS score decline of 1 and a SD of 2.0. The number of participants required to detect a significant difference at a p-value of 0.05 was 14 participants for each arm. Assuming a patient withdrawal of about 20% we set our sample size to 18 subjects for group.

The final group of enrolled women was 22 subjects in the E2V/DNG group and 18 subjects in the NSAID-only group.

Results

A total of 40 women were included into the study, 22 in the E2V/DNG group and 18 in the NSAID-only group. One woman discontinued E2V/DNG during the second cycle of treatment for desire of pregnancy. Two women in the E2V/DNG group and 3 in the control group did not want to repeat scheduled controls. Accordingly, analyses were performed in the 34 women who finished the study (19 in the E2V/DNG group and 15 in the NSAID-only group). Treatment continuation was similar in the E2V/DNG and the NSAID-only group (86.4% vs. 83.3%). Features of patients analyzed in the two groups did not differ at baseline (Table 1).

E2V/DNG group

Pelvic pain and quality of life

Among enrolled women, all suffering from menstrual pain, 11 (57.9%) also suffered from inter-menstrual pelvic pain and 13 (68.4%) from deep dyspareunia.

During the 24-week treatment mean VAS score of menstrual pain decreased by 61% (p=0.0001). Furthermore, in the subgroups of women with inter-menstrual pain and dyspareunia, these complaints decreased by 65% (p=0.013) and 52% (p=0.016), respectively (**Figure 1** ~~Table 2~~).

In a post-hoc analysis, we considered how many subjects exceeded a VAS score of 4 for each type of pain. For menstrual pain, the number was14 at baseline and 4 after 6 cycles of treatment (73.7% vs. 21.0%; p<0.001). In these women the mean VAS score declined from 7.99±1.68 to 3.02±2.19 (-59.9%±29.95; p<0.0001). For inter-menstrual pain, the number was 7 at baseline and 1 after 6 cycles of treatment (63.6% vs. 9.1%; p<0.01). In these women the mean VAS score declined from 7.57±2.03 to 1.87±3.06 (-80.2%±28.8%; p=0.008). For deep dyspareunia, the number was 9 at baseline and 3 at the end of treatment (69.2% vs. 23.1%; p=0.018). In these women the mean VAS score declined from 7.30±1.95 to 2.66±2.92 (-65.7%±36.5%; p=0.001).

During treatment we observed a significant increase in total SF-36 score **(from 58.41±21.75 to 69.82±16.88;** p=0.0002) and in its physical **(from 55.85±24.05 to 70.53±18.80;** p=0.0004) and

mental **(from 57.17±26.31 to 67.72±19.47;** p=0.007) general domains (**Figure 2** ~~Table 3~~). In particular, a significant increase in bodily pain **(from 43.68±28.63 to 67.89±23.53;** p=0.0004), physical functioning **(from 67.63±30.34 to 80.53±23.39;** p=0.007) and role-physical **(from 61.84±43.60 to 77.63±32.16;** p=0.048) was observed for the physical domains, and in vitality **(from 48.42±24.21 to 56.84±19.45;** p=0.022) and social functioning **(from 49.87±34.44to 70.39±28.21;** p=0.007) for the mental domains (**Figure 2** ~~Table 3~~).

Adverse effects

During the first cycle of therapy spotting was experienced by 2/19 (10.5%) of patients. It was spontaneously resolved within the second cycle of treatment. No major adverse effects were reported. Regarding the minor effects, headache was reported by 4/19 (21.1%), bloating by 2/19 (10.5%), irritability and fatigue by 1/19 (5.2%) of cases. None of these symptoms lead to treatment withdrawal.

NSAID-only group

Pelvic pain and quality of life

All enrolled women were suffering from menstrual pain, and among these 12 (80%) also suffered from inter-menstrual pain and 8 (53.3%) from deep dyspareunia.

In this group of patients we did not observe any modifications of any pelvic pain score (**Figure 1** ~~Table 2~~).

Similarly the SF-36 score and its domains did not vary, with the exception of an isolated improvement in the vitality score **(from 42.08±14.99 to 56.94±22.76;** p=0.014) (**Figure 2** ~~Table 3~~).

Adverse effect

No particular adverse effect was reported by women of this group.

Discussion

Main results

Effect on pelvic pain

This 24-week preliminary pilot study shows that a COC containing DNG associated in a quadriphasic fashion to E2V significantly reduces pelvic pain and improves quality of life of women with endometriosis. By contrast, and in accordance with a recent meta-analysis [21], NSAIDs are ineffective in reducing pain and improving quality of life.

The effect of E2V/DNG is not exerted only on menstrual pain but also on inter-menstrual pain and deep dyspareunia. These effects are rather impressive, particularly in women with intense pain, where E2V/DNG is capable of reducing by about 60% menstrual pain, by 80% inter-menstrual pain and by 65% deep dyspareunia. These improvements are associated with an amelioration of quality of life. Obviously, menstrual pain can be improved by avoiding menstrual bleeding. Accordingly, continuous regimens of combined hormonal contraceptives are capable to markedly affect menstrual pain [22,23] with a maximal reduction up to 87.5%, which was obtained with the non-contraceptive association of EE 10 mcg and cyproterone acetate 3 mg [24]. The effect on menstrual pain is less evident when combined hormonal contraceptives are administered in a cyclic fashion, with studies reporting either no effect [25], or a decrease of menstrual pain not superior to 55% [7,23,26-28]. In our study, E2V/DNG given cyclically induced a decline of the menstrual pain VAS score of about 60%, which is similar to the one observed with other combined hormonal contraceptives cyclically administered. What is interesting with the E2V/DNG administration, it is the amelioration of inter-menstrual pain. Inter-menstrual pain decreased by about 60%, but in very symptomatic women the score declined by about 80%. In the literature, several studies did not evaluate the effect of hormone administration on inter-menstrual pelvic pain [22,29,30]. Among those that performed this evaluation, inter-menstrual pain was either not improved [23,25,28] or only slightly improved. Improvements did not exceed a 30% VAS score reduction [7,24,26,27].

Only in one study inter-menstrual pain decreased by 52%, but this result was obtained with the administration of a non-contraceptive association containing 10 mcg EE and 3 mg cyproterone acetate [23]. Deep dyspareunia was also not investigated in some studies [7,29,30], in others it was unaffected [23,25], and in others again it was improved by therapy [22,26-28]. The reductions of the VAS score for dyspareunia was reported in the range of about 35%, with the exception of one study, where the non-contraceptive association of EE (10 mcg) and cyproterone acetate (3 mg) decreased it by 78.3% [24]. In our study the decline of the VAS score for dyspaurenia was 52% reaching about 70% in very symptomatic women.

Accordingly, present data indicate that E2V/DNG is highly effective in reducing all types of pelvic pain of women with endometriosis. In agreement with our results, a retrospective study reported a high efficacy of quadriphasic E2V/DNG in the treatment of pelvic pain of patients who had undergone surgery for endometriosis [31].

The possible explanation for this “triple” action on menstrual, inter-menstrual pain and dyspareunia may depend on several factors.

In comparison to the traditional 7 days hormone-free interval the reduction of the hormone-free interval, with an almost continuous regimen (2 days of hormone-free interval), is associated with a decrease of hormone-withdrawal-associated symptoms [32-34].

DNG has a strong endometrial affinity and it may directly decrease growth, neoangiogenesis and proliferation of endometriotic lesions [7-14]. In our study DNG was used at doses sufficient to perform this clinical effect. The cumulative exposure per cycle to DNG was about 2.2 mg/day, which is comparable to that approved for the treatment of endometriosis (2 mg/day) [8-12].

It is likely that the circulating levels of E2 induced by E2V/DNG, with values ranging between 60-90 pg/ml [32], were not capable to counteract the potent effect of DNG on endometriotic lesions. Large randomized clinical comparative trials on this topic are mandatory.

On the other hand, the presence of the step-down estrogen component (E2V) could represent an advantage in terms of bleeding control and therapy adherence [32-35]. In the present study 10.5%

of patients experienced irregular bleedings, which were confined to the first cycle of treatment, and less frequent than those reported for DNG alone [8-12,16].

Effect on quality of life

Pelvic pain, in particular inter-menstrual pain and, in lesser extent, menstrual pain, is associated with a reduced quality of life [19]. Accordingly, improvements in pelvic pain in women with endometriosis are expected to improve quality of life, as herein shown. A comparable (≈10 points SF- 36) increase in quality of life was already observed with the administration of DNG alone in women with endometriosis [9,12]. To our knowledge there is no previous prospective evidence that any hormonal combined contraceptive can increase, per se, quality of life of women with endometriosis [25].

Limitations

The non-random allocation to treatments constitutes a drawback of the present study. About this we shared the approach proposed by Vercellini et al. [22], using a research environment more similar to the "real world" conditions. Even the small sample size undoubtedly limits the strength of our results. However, in view of the lack of prospective data on the use of E2V/DNG for endometriosis-related pain, we decided first to conduct a small pilot study.

In conclusion, in patients with endometriosis it is still unknown if the administration of estrogens should be completely avoided or could be permitted in low dosages. Waiting for large randomized trials, in this study we demonstrated that the 24-week administration of quadriphasic E2V/DNG combination is associated with a reduction of pelvic pain and an improvement of quality of life of patients with symptomatic endometriosis.

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Interest notification page

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Legend for Figures

Figure 1

Mean (±SD) visual-analogic scale (VAS) score of menstrual pain, inter-menstrual pain and deep dyspareunia evaluated prior to and after 6 cycles of treatment with E2V/DNG or NSAID-only.

** $p < 0.025$ vs. Basal; *** $p < 0.01$ vs. Basal; § $p < 0.05$ vs. NSAID-only group; §§§ $p < 0.01$ vs. NSAID-only group

Figure 2

Mean (±SD) SF-36 scores and its domains sub-scores (physical and mental) evaluated prior to and after 6 cycles of treatment with E2V/DNG or NSAID-only.

* $p < 0.05$ vs. Basal; ** $p < 0.025$ vs. Basal; *** $p < 0.01$ vs. Basal