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Dienogest and deep infiltrating endometriosis: The remission of symptoms is not related to endometriosis nodule remission

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ABSTRACT

Objective: To evaluate the effectiveness of dienogest in controlling pain caused by deep infiltrating endometriosis (DIE), its influence on the quality of live (QoL) of women affected by the disease, and the effect of the drug on the volume of endometriotic lesions.
Study design: A prospective cohort study including 30 women with a sonographic diagnosis of DIE (intestinal and posterior fornix) treated with dienogest 2 mg per day for 12 months. We evaluated the pain symptoms and the volume of the intestinal and posterior fornix lesions before and after 12 months of use of dienogest. To perform the statistical analysis, we used the Wilcoxon signed-rank test, and the relationship between the data was tested using the Spearman correlation coefficient.
Results: Women were on average 36.13 ± 6.24 years old. Pain symptoms most commonly reported were dyspareunia (83.3%), dysmenorrhea (73.3%), and pelvic pain (66.7%). After 12 months of treatment with dienogest, there was significant improvement of various symptoms (dyspareunia $p = 0.0093$, dysmenorrhea $p < 0.0001$; pelvic pain $p = 0.0007$; and bowel pain $p < 0.0001$), without a reduction in the volume of endometriotic nodules. There were significant improvements in the parameters that comprise the QoL (physical $p < 0.0001$; $p = 0.0007$ psychological) and the self-assessment of QoL ($p = 0.0069$) and health ($p = 0.0001$).
Conclusion: Dienogest is an effective medication to control symptoms of pain related to DIE, even without reducing the volume of DIE nodules.

Introduction

Endometriosis is an estrogen-dependent inflammatory disease defined as the presence of endometrial-like tissue outside the uterus. In its severe form, deep infiltrating endometriosis (DIE), which is marked by endometrial implants below the peritoneum, can affect the rectosigmoid colon, rectovaginal septum, uterosacral ligament, bladder, and ureters [1].

On average, 10% of women of reproductive age are affected by endometriosis. It is estimated that 20% of these are stricken by DIE [2,3] and may experience symptoms such as dysmenorrhea, chronic pelvic pain, dyspareunia, cyclic changes in bowel habits as well as infertility [4].

DIE can have a negative influence on quality of life (QOL), affecting physical and psychological health as well as jeopardizing social relationships [5,6]. Studies have reported a reduction of approximately 38% in the productivity of women with DIE, mainly due to chronic pelvic pain [7]. In addition, about 88% of them have anxiety disorders and depression [8] and 50% have some disorder of fertility [9].

Although the gold standard for diagnosis is histological, various types of imaging, such as rectal endoscopic sonography, transvaginal sonography (TVS), and magnetic resonance imaging, are acquiring an important role to diagnose DIE, allowing the mapping of pelvic injuries and the monitoring of clinical treatment [10]. Currently, in association with bowel preparation, TVS is considered a first-line test in the assessment of DIE with 91% sensitivity and 95% specificity [2,11,12].

There is no definitive treatment for endometriosis, which implies the need for long-term therapeutics to control and reduce pain symptoms and, if possible, postpone or even avoid recurrent surgical procedures [13–15]. Dienogest is a therapeutic option in the treatment of pain complaints of endometriosis acting through the inhibition of gonadotropin secretion, inducing estrogen deprivation and causing decidualization of endometrial tissue

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followed by the atrophy of endometriotic lesions [16–18]. Several authors have reported its effectiveness in controlling the symptoms with few side effects; however, there are still scarce specific studies for DIE showing the action of the drug on the regression of the endometriotic nodules [19–21].

Materials and methods

This longitudinal study, approved by the Research Ethics Committee of the institution (REC n° 302817/2013), involved 30 women diagnosed with DIE (intestinal and posterior fornix) at the Endometriosis Clinic of the Department of obstetrics and gynecology at University of Campinas (UNICAMP), between April 2013 and October 2015.

Inclusion criteria were between 18 and 45 years of age, a diagnosis of deep endometriosis, and the presence of at least one of the pain symptoms of endometriosis: chronic pelvic pain, dysmenorrhea, dyspareunia, and urinary and/or intestinal pain. Women who had undergone a therapeutic surgical procedure in the past 6 months, abnormal menstrual bleeding that was undiagnosed, chronic diseases such as cancer, liver, heart, and/or kidney disease, as well as pregnant women or those with a desire for immediate pregnancy were excluded.

All women included had been referred to our clinic for the evaluation of surgical treatment for expressing persistent pain complaints despite medical treatment with other progestin for at least 6 months. Treatment with dienogest was proposed to them prior to surgery. The inclusion was sequential, according to standard attendance until the statistically determined sample size was achieved.

The diagnosis of deep endometriosis, as well as control after 12 months of treatment, was established by transvaginal sonography with bowel preparation performed always by the same expert on such diagnosis.

Participating patients were instructed to take a daily dose of 2 mg dienogest in tablet form. All of the women underwent outpatient visits at the beginning, and after 3, 6, 9, and 12 months of treatment. In all inquiries, adherence to treatment, side effects, and symptoms of the disease, such as chronic pelvic pain, dysmenorrhea, dyspareunia, and urinary and intestinal pain, were evaluated according to the visual analog scale (VAS) of pain on a scale of 0–10, where 0 represented the absence of pain and 10 maximum pain. We applied a QoL questionnaire at the beginning, 6 months and after 12 months of treatment.

There was also a daily evaluation of the intensity of nonspecific pelvic pain according to the VAS of pain on a scale of 0–10. Every 3 months these daily reports were added and, considering the number of days, the mean ± standard deviation was calculated. Women also wrote down the presence of bleeding and side effects on a daily basis. For this, specific calendar-type cards were provided, which had been filled out at home with pain intensity (values 0–10) and the amount of vaginal bleeding per day, assigning the following values: 0–no bleeding; 1–2 spotting or 3–4 bleeding average large amount.

DIE was diagnosed and monitored by transvaginal sonography performed after bowel preparation using Toshiba X (Aryan, Spain) or Voluson E8 (GE Healthcare, Austria) appliances, providing a description of the injuries in millimeters, allowing the calculation of the lesion volume by multiplying 3 measurements (depth, length, extension) and then multiplying the result by a correction factor (0.52). An anatomical description of the location of the injury was also provided.

The instrument used to assess QoL was the brief version of the World Health Organization QoL measure (WHOQOL-BREF) [22], developed by the WHOQOL Group and validated in Brazil [23]. It contains 26 questions, of which 2 are general, regarding the woman's impression of her QoL and health, and the other 24 represent each of the facets that make up the original instrument (the WHOQOL-100), which includes 4 domains: physical, psychological, social relationships, and environment. The assessment of the domains is carried out through the attribution of scores to each question, which are converted into a score from 0 to 100, with the highest score indicating improvement in the different aspects of QoL [24].

Statistical analysis

The sample size calculation was based on previous studies with dienogest in the treatment of endometriosis [19–21], taking into account improvements in complaints of pain assessed by the VAS and calculated using a sample size of at least 24 subjects.

Quantitative data analysis was performed with the Wilcoxon signed-rank test, and the relationship between the data was tested using the Spearman correlation coefficient Wilcoxon test. The relationship between the variables pelvic pain, dysmenorrhea, dyspareunia, urinary and intestinal pain, and the volume of the lesions was tested using the Spearman correlation index. A significance level of 5% was assumed. The software used for analysis was SAS version 9.4.

Results

The 30 women diagnosed with DIE were on average of 36.13 ± 6.24 years, and reported an onset of symptoms at 29.24 ± 7.82 years. Of these, 60% were nulliparous. The average volumes of the posterior fornix and intestinal injury were, respectively, 2.21 ± 1.46 and 2.18 ± 2.99 cm3. No woman had endometriotic lesions involving the urinary tract.

The symptoms reported included dysmenorrhea in 73.3% (initial AVS 5.07 ± 3.8), pelvic pain in 66.7% (initial AVS 4.0 ± 3.6), dyspareunia in 83.3% (initial AVS 5.3 ± 3.1), bowel movement pain in 63.3% (initial AVS 3.8 ± 3.4), and dysuria in 13.3% (initial AVS 0.6 ± 1.9).

The use of dienogest for 12 months was found to significantly reduce the pain symptoms of dysmenorrhea ($p < 0.0001$), pelvic pain ($p = 0.0007$), dyspareunia ($p = 0.0093$), and intestinal pain ($p < 0.0001$) (Table 1). At baseline, the women reported pain on average 6 days of the month, with moderate pain (VAS 4–6) or severe (VAS 7–10) in 4.59 ± 5.42 days. At the end of 12 months, there was a reduction in the number of days of intense pain to 0.73 ± 1.17 ($p < 0.0001$) (Table 1).

In the present literature, spotting is a very frequent side effect related by women during the use of dienogest; however, in our study, this side effect was infrequently observed and at the very first month of dienogest use, women showed 24.9 ± −5.6 days without bleeding and with continuous administration of the drug, consistent with previous studies, we obtained a significant improvement in this side effect: 29.4 ± 2.1 days without abnormal bleeding at the end of 12 months of treatment ($p = 0.0003$).

Table 1
Evaluation of pain symptoms in women with DIE treated with dienogest for 12 months (n = 30).

	beginning Mean ± sd	6 months Mean ± sd	12 months Mean ± sd	0–12 months *p*-value*
AVS – Dysmenorrhea	5,7 ± 3,8	1,2 ± 2,3	0,7 ± 1,6	<0,0001
AVS – pelvic pain	4,0 ± 3,6	1,7 ± 2,5	1,2 ± 2,1	<0,0001
AVS – Dyspareunia	5,3 ± 3,1	3,0 ± 3,2	3,7 ± 3,3	0,0093
AVS – intestinal pain	3,8 ± 3,4	2,2 ± 3,2	1,4 ± 2,4	<0,0001
AVS – urinary pain	0,6 ± 1,9	0,4 ± 1,5	0,4 ± 1,3	0,250

AVS – analogic visual pain scale; sd – standat deviation.
* Wilcoxon signed-rank test.

Side effects, such as headaches 63.3%, breast pain 43,3%, reduced desire 43.3% and nausea/vomiting 23.3%, presented by our patients do not motivate the discontinuation of treatment and during the 12 months of treatment there was no need of surgical procedure in any case.

Treatment with dienogest for 12 months positively affected several domains of QoL, with significant improvement in the physical (53.58 ± 8.47, 60.00 ± 8.04, $p < 0.0001$), psychological (49.25 ± 7.71, 53.75 ± 12.03; $p = 0.0007$), as well as a self-assessment of QoL (73.33 ± 27.65 87.50 ± 23.44, $p = 0.0069$) and health (61.67 ± 27.65, 85.83 ± 22.44, $p < 0.0001$) (Table 2).

There was no significant change in the volume of endometrotic lesions in bowel (before = $2.18 \pm 2.99\,cm^3$; after = $2.21 \pm 4.06\,cm^3$ $p = 0.23$) or posterior fornix (before = $2.21 \pm 1.46\,cm^3$ and after = $2.34 \pm 1.90\,cm^3$, $p = 0.77$) after treatment for 12 months with dienogest. There was no relation between remission of pain symptoms and reduction of the volume of DIE nodules (Table 3).

Comments

DIE is a chronic and serious disease that often requires surgical treatment, which is not free of complications, and recurrence rates can reach 25%.

The use of dienogest for 12 months in women with DIE with intestinal involvement proved to be an effective therapeutic alternative in significantly reducing pain symptoms, preventing a surgical procedure with high morbidity. Several studies in the literature evaluating the clinical treatment of endometriosis in all its stages also show similar results regarding pain control in women who used dienogest; however, there are no specific studies investigating exclusively treatment of DIE [19–21,25]. One study involving only patients with deep endometriosis with intestinal involvement treated with dienogest for 6 months showed satisfactory control of pain symptoms, such as dyspareunia, dysmenorrhea, pelvic pain, and intestinal pain [26].

A systematic review with 9 randomized trials of the use of dienogest versus placebo or GnRH analogue in the period of 2002–2011 showed that, regardless of the dose, dienogest is an effective drug for controlling pain in women with DIE with no major side effects, such as bone mass reduction, as happens with GnRH analogue, a fact that contraindicates long-term treatment [27].

In the present study, all the participating women had to have pain symptoms; however, it is important to note that most of them had a combination of different types of pain complaints. The most frequent association was dysmenorrhea, dyspareunia, and bowel pain, similar to other studies; a single pain symptom complaint is not typical in the presence of DIE [28]. As we observed, although there was a significant reduction in the intensity of different types of pain, these symptoms remained present in lower frequency after 12 months of treatment.

Spotting is a very common side effect during the use of progestagens, including dienogest, and it is highly associated with discontinuation of treatment [29,30]. In our study, this adverse effect was rare. Most women had little irregular bleeding since the beginning of the administration of the medication, and at the end of 12 months of treatment we observed a significant decrease in the frequency of this adverse event. There was no discontinuation in the use of dienogest due to spotting [31]. The complete adherence to treatment with dienogest was probably due to significant pain symptoms' control with fewer side effects and low intensity when present.

As in prior literature, there was a significant improvement in the QoL of women with DIE, which can be explained by the reduction of pain symptomatology. The control of pain symptomatology was reflected in the improvement of physical and psychological domains and the self-assessment of quality of life and health [32].

We found no significant reduction in the volume of endometriotic lesions. In the literature, there are few studies showing the reduction of endometriosis lesions with clinical treatment, and all these studies are case reports [33]. Cohort studies that indicates reduction of endometriotic lesions make this assessment inferring that there was a decrease in lesion volume due to decreased score according to ASRM without carrying out specific measures of injuries in bowel and posterior fornix as we did in our study [27].

The non-response of the lesions after treatment may be due to the structural feature of the DIE lesions that are described as being composed of large fiber components and a lower percentage of endometrial tissue [34]. We believe that is possible to assume that the improvement of pain symptoms may be related not only to the atrophy of ectopic endometrium, but mainly to the anti-inflammatory action or regulatory immune attributed to dienogest [30,35].

A limitation of our study is the fact that we did not use the specific questionnaire for women with endometriosis (The Endometriosis Health Profile – 30), as this study was designed and started before the validation of this instrument in Portuguese [36]. In addition, there was no comparison with a control group with the gold standard already established as an effective treatment. However, there was long-term monitoring for 12 months, and it included only women with DIE affecting the rectosigmoid and also held the volume calculation of intestinal endometriosis lesions by transvaginal sonography.

Our results indicate that dienogest is a good alternative to the clinical management of pain symptoms in women with deep endometriosis, regardless of the change in volume of the lesions, thus avoiding surgical procedures of high complexity in all women studied.

Dienogest is effective for the treatment of the pain symptomatology of deep endometriosis regardless of cause size reduction of the lesions.

Table 2
Quality of life (QoL) of women with DIE treated with dienogest for 12 months (n = 30).

	Beginning Mean ± sd	6 months Mean ± sd	12 months Mean ± sd	0–12 months *p*-value*
QoL_physical	53,58 ± 8,48	57,00 ± 8,79	60,00 ± 8,04	<0,0001
QoL_psycho	49,25 ± 7,72	50,58 ± 8,27	53,75 ± 1,20	0,0007
QoL_relationship	25,17 ± 4,10	24,17 ± 4,48	27,08 ± 4,16	0,0547
QoL_environment	68,08 ± 9,69	68,34 ± 6,34	68,08 ± 7,51	0,9061
QoL_life	73,30 ± 2,36	73,30 ± 21,7	87,50 ± 23,4	0,0069
QoL_health	61,70 ± 2,77	65,8 ± 22,3	85,80 ± 22,4	0,0001

* Wilcoxon signed-rank test.

Table 3
Correlation between volume of endometriotic nodule and pian symptoms after 12 months of treatment with dienogest (n = 30).

	Posterior fornix	Rectosigmoid
Dysmenorrhea	R – 0,25551 p = 0,1730	R – 0,16982 p = 0,3696
Pelvic pain	R – 0,03216 P = 0,8660	R – 0,4807 P = 0,8009
Dyspareunia	R 0,18286 P = 0,3334	R 0,24095 P = 0,2744
Intestinal pain	R 0,05045 P = 0,7912	R 0,20616 P = 0,2744
Urinary pain	R – 0,13232 P = 0,4858	R – 0,49953 P = 0,0049

Spearman correlation index.

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None declared.

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