



Evaluation of endometrial thickness and pain symptoms in women with deep endometriosis using dienogest: retrospective cohort

Avaliação da espessura endometrial e sintomas de dor em mulheres com endometriose profunda usando dienogeste: coorte retrospectiva

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ABSTRACT

BACKGROUND AND OBJECTIVES: Endometriosis is a chronic, inflammatory and estrogen-dependent disease. The most common symptoms include dysmenorrhea, dyspareunia, chronic pelvic pain and infertility. The study's objective is to evaluate the effect of dienogest on endometrial thickness and correlate it with pain symptoms in women with deep endometriosis.

METHODS: Retrospective cohort study with 104 women diagnosed with deep endometriosis from a tertiary hospital from 2018 to 2022. The variables of sociodemographic characteristics of women, pain symptoms at the beginning of treatment with dienogest and after one year, in addition to the endometrial thickness measured by ultrasound were evaluated at the beginning of treatment and after one year of using dienogest.

RESULTS: The average age of the women was 36.0±6.3 years, the majority were white (81.7%), nulliparous (44.2%), with a partner (68.2%) and with a body mass index of 27.6±5.4 kg/m². Among the study participants, 41.3% had undergone previous surgeries and only 15.3% had another comorbidity. There was better control of dysmenorrhea (p<0.001) and dysuria (p=0.031) with the use of dienogest. The greater the endometrial thickness, the greater the dysmenorrhea (p=0.04). There was no correlation between endometrial thickness and other pain symptoms.

CONCLUSION: The use of dienogest for 12 months reduced dysmenorrhea and dysuria but did not reduce other pain complaints. Endometrial thickness is directly related to dysmenorrhea.

KEYWORDS: Dysmenorrhea, Pelvic pain, Endometriosis.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A endometriose é uma doença crônica, inflamatória e dependente de estrogênio. Os sintomas mais comuns incluem dismenorreia, dispareunia, dor pélvica crônica e infertilidade. O objetivo do estudo foi avaliar o efeito do dienogeste na espessura endometrial e correlacioná-lo com os sintomas de dor em mulheres com endometriose profunda.

MÉTODOS: Estudo de coorte retrospectivo com 104 mulheres diagnosticadas com endometriose profunda de um hospital terciário de 2018 a 2022. Foram avaliadas as variáveis características sociodemográficas das mulheres, sintomas de dor no início do tratamento com dienogeste e após um ano, além da avaliação da espessura endometrial medida por ultrassonografia no início do tratamento e após um ano de uso do dienogeste.

RESULTADOS: A média de idade das mulheres foi de 36,0±6,3 anos, a maioria era branca (81,7%), nulípara (44,2%), com companheiro (68,2%) e apresentava índice de massa corporal de 27,6±5,4 kg/m². Entre as participantes, 41,3% haviam passado por cirurgias prévias e apenas 15,3% apresentavam outra comorbidade. Houve melhor controle da dismenorreia (p<0,001) e da disúria (p=0,031) com o uso do dienogeste. Quanto maior a espessura endometrial, maior a dismenorreia (p=0,04). Não houve correlação entre a espessura endometrial e outros sintomas de dor.

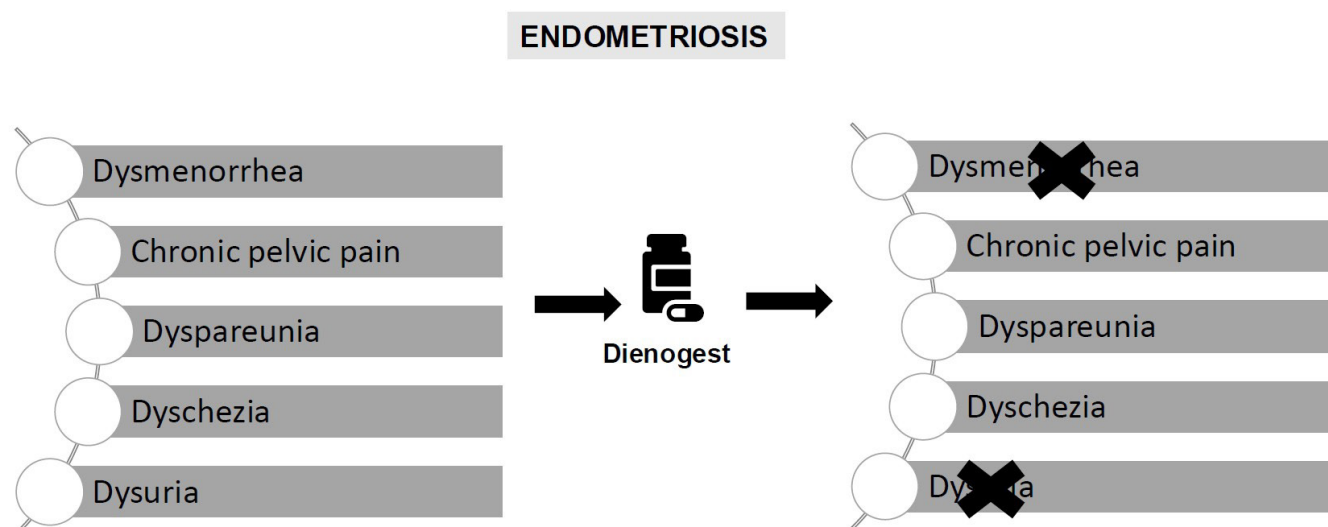
CONCLUSÃO: O uso do dienogeste por 12 meses reduziu a dismenorreia e a disúria, mas não reduziu outras queixas de dor. A espessura endometrial está diretamente relacionada à dismenorreia.

DESCRIPTORES: Dismenorreia, Dor pélvica, Endometriose.

HIGHLIGHTS

- The effectiveness of dienogest in the treatment of pain of deep endometriosis
- Endometrial thickness is directly related to dysmenorrhea
- There was no correlation between endometrial thickness and other pain symptoms

GRAPHICAL ABSTRACT



INTRODUCTION

Endometriosis is a chronic, inflammatory and estrogen-dependent disease. It is defined by the presence of endometrial tissue, gland and/or stroma outside the uterine cavity, mainly in places such as the pelvis, ovaries and rectovaginal septum. It affects around 200 million women worldwide. The most common symptoms include dysmenorrhea, dyspareunia, chronic pelvic pain and infertility, being a debilitating condition that can affect the quality of life of affected women¹. Studies report a reduction of approximately 38% in the productivity of these women, attributed mainly to pelvic pain. Furthermore, around 88% of them have anxiety or depression disorders¹⁻⁵.

Considered a chronic disease, endometriosis requires long-term treatment that is effective and presents few adverse effects to postpone and/or avoid surgical procedures, either due to the high morbidity or the high recurrence rate of endometriosis, which is approximately 40%-50% in five years⁶.

The modern treatment of endometriosis must be individualized and patient-centered, with a multidisciplinary approach. Pharmacological treatment is often the choice to begin treatment. Clinical treatment has been shown to be effective in controlling pelvic pain and should be the treatment of choice in the absence of absolute indications for surgery. It is done using combined oral contraceptives, danazol, GnRH agonists and progestins^{7,8}. A good response to drug treatment improves women's quality of life and reduces surgical treatment, which can lead to several complications for them.

Among the progestins, there is dienogest, which is a fourth-generation selective progesterone that combines the pharmacological properties of 19-nortestosterone and progesterone derivatives, acting on endometriosis lesions with minimal metabolic impact and little hormonal action. It has strong action on progesterone receptors and transforms a proliferative endometrium, induced by estrogen, into a secretory endometrium, causing, in the long term, endometrial atrophy. The mechanism of action of dienogest in endometriosis involves a moderate inhibition of gonadotropin

secretion, which reduces endogenous estradiol production. This induction into a state of hypoenestrogenism leads to decidualization and subsequent atrophy of the endometrial implants. Some exploratory models also demonstrate that dienogest has antiproliferative, anti-inflammatory and antiangiogenic effects. In vitro and animal studies show that dienogest has a direct inhibitory effect on the proliferation of endometrial-like tissue independent of the progesterone receptor⁹⁻¹¹.

Endometrial thickness, measured on transvaginal ultrasound, reflects the overall effect of estrogen stimulation on the endometrial glands and stroma, therefore, it could theoretically be used to evaluate the efficacy of hormonal therapy in inhibiting estrogenic stimulation, suppressing proliferation, and inflammatory changes in the ectopic endometrium. A thin endometrium reflects atrophy of the endometrial gland and stroma, while a thick endometrium may be the sign of an incomplete suppression of hormonal stimulation and is therefore responsible for a greater risk of disease progression and symptoms. Thus, the assessment of endometrial thickness can evaluate the response to the use of progestogen hormone therapy by reducing pain symptoms¹². It is not known whether a reduction in endometrial thickness would be correlated with an improvement in pain symptoms in women with endometriosis. Therefore, the objective of this study was to evaluate the effect of dienogest on endometrial thickness and correlate it with pain symptoms in women with deep endometriosis.

METHODS

Retrospective cohort study with 104 women with deep endometriosis followed at the endometriosis outpatient clinic of a tertiary hospital from 2018 to 2022. Women of reproductive age, with an ultrasound diagnosis of deep endometriosis and using dienogest 2 mg per day for at least one year, who had an ultrasound assessing endometrial thickness and who had pain scores assessed by the VAS were included. Women were excluded if they did not

present data in the medical record necessary to adequately fill out the study information, who suspended or replaced the medication before the proposed period or who underwent hysterectomy surgery before completing 12 months of treatment.

All variables were evaluated from the medical records. The variables analyzed were age, color (white and non-white), marital status (with and without a partner), parity, BMI, pain symptoms (dysmenorrhea, dyspareunia, chronic pelvic pain, dyschezia and dysuria), previous surgeries, comorbidities (systemic arterial hypertension, diabetes mellitus, hypothyroidism) and ultrasound description (uterine volume, ovarian volume), presence of endometriosis lesions (anterior cul-de-sac, posterior cul-de-sac, intestine, bladder, ovarian endometrioma, adenomyosis), endometrial thickness, number of endometriosis lesions.

Pain symptoms were assessed using VAS, where zero is the absence of pain and 10 is the most intense pain. The pain scale was applied at the beginning of the woman's follow-up in the service before starting to use dienogest and after one year of follow-up using dienogest. The scale was applied by the doctor who treated the woman. Pain symptoms and ultrasound results were assessed at baseline and after 12 months of dienogest use. All other variables were assessed only at baseline.

Endometrial thickness was assessed by transvaginal pelvic ultrasonography after adequate bowel preparation, performed by the same radiologist who has more than ten years of experience. Toshiba X or Voluson E8 devices were used. For this examination, bowel preparation (home use) was performed with four bisacodyl tablets one day before the examination. Endometrial thickness was described in millimeters. Ultrasounds were performed at the beginning of the women's follow-up and after one year of follow-up using the medication dienogest.

This research was approved by the institution's Research Ethics Committee under number: 53195521.3.0000.5404. STROBE guidelines were followed.

Statistical analysis

To describe the sample profile according to the variables under study, frequency tables were created for the categorical variables with absolute frequency (n) and percentage (%), and descriptive statistics for the numerical variables with mean, standard deviation, minimum and maximum, median and quartiles. To compare categorical variables, the McNemar test was used for related samples. To compare numerical variables, the Wilcoxon test was used. To analyze the relationship between pain symptoms and ultrasound results, Spearman's correlation coefficient was used, due to the lack of normal distribution of the variables. The level of significance adopted for the statistical tests was 5%. The software used for statistical analysis was Statistical Analysis System – 9.2. (SAS Institute Inc, 2002-2008, Cary, NC, USA).

The calculation of the sample size for the purpose of comparing the average pain delta (using the VAS) between the endometrial thickness groups (smaller thickness and greater thickness) of women with endometriosis, with estimates obtained from the literature, setting the level of significance at 5% and sample power

at 80%. Based on the results, a minimum sample of $n=104$ women were estimated¹².

RESULTS

The women's average age was 36.0 ± 6.3 years, the majority were white (81.7%), nulliparous (44.2%), with a partner (68.2%) and had a body mass index of 27.6 ± 5.4 kg/m². Among the participants, 41.3% had undergone previous surgeries and only 15.3% had another comorbidity (Table 1).

There was better control of dysmenorrhea ($p<0.001$) and dysuria ($p=0.031$) with the use of dienogest. There was no significant difference in uterine volume and endometrial thickness after using dienogest for 12 months ($p=0.097$ and 0.154 respectively). There was a reduction in left ovarian volume ($p=0.002$) and an increase in right ovarian volume ($p=0.044$) (Table 2).

Endometrial thickness was directly proportional to dysmenorrhea ($p=0.04$). There was no correlation between endometrial thickness and other pain symptoms such as chronic pelvic pain, dyspareunia and dyschezia (Table 3).

DISCUSSION

In the present study, there was no reduction in endometrial thickness. Endometrial thickness was directly proportional to dysmenorrhea and there was no correlation between endometrial thickness and other pain symptoms. The study evaluated 510 medical records of women with endometriosis who were followed up at the endometriosis outpatient clinic of the tertiary hospital in order to select 104 medical records of women with endometriosis using dienogest for 12 months.

Women were on average 36 years old and presented a reduction in some pain symptoms. In the literature, another Brazilian study showed equal mean age and a reduction in all pain symptoms with the use of dienogest for 12 months¹³. Other studies also present women in the same age group and with a reduction in some or all pain symptoms with the use of dienogest for 6 months^{14,15}. A Taiwanese study also showed that the use of dienogest for 12 months was effective in controlling pain and reducing ovarian endometrioma¹⁶.

Table 1. Clinical and sociodemographic characteristics of women with deep endometriosis (n=104).

Variables	Mean $\pm$ SD/n(%)
Age (years)	36.0 $\pm$ 6.3
Nulliparous	51 (44.2)
White	85 (81.7)
With partner	71 (68.2)
BMI (kg/m ²)	27.6 $\pm$ 5.4
Previous surgeries	43 (41.3)
Comorbidities	16 (15.3)

SD = standard deviation; BMI = body mass index.

Table 2. Assessment of pain symptoms and ultrasound results of women with deep endometriosis using dienogest for 12 months (n=104).

	Initial	12 months	p-value
	Mean± SD	Mean± SD	
Dysmenorrhea	4.0±4.1	2.1±3.5	<0.001
Chronic pelvic pain	3.7±3.9	2.9±3.6	0.074
Dyspareunia	2.6±3.3	2.5±3.2	0.746
Dyschezia	2.1±3.3	1.7±3.2	0.200
Dysuria	0.8±2.3	0.3±1.4	0.031
Uterine volume (mm ³)	95.6±52.2	98.6±99.6	0.097
Left ovarian volume (mm ³)	32.1±80.4	20.0±44.5	0.002
Right ovarian volume (mm ³)	19.7±44.6	29.9±159.8	0.044
Endometrial thickness (mm)	4.5±2.3	4.2±2.2	0.154

SD = standard deviation; Wilcoxon test.

Table 3. Correlation of pain symptoms with endometrial thickness in women with deep endometriosis before and after treatment with dienogest (n=104).

	Dysmenorrhea	Chronic pelvic pain	Dyspareunia	Dyschezia	Dysuria
Endometrial thickness initial					
R	0.20	-0.10	-0.05	-0.19453	0.02
P	0.041	0.326	0.617	0.0549	0.041
Endometrial thickness final					
R	0.18	0.15	0.11	0.09	0.02
P	0.068	0.138	0.252	0.372	0.821

R = Spearman correlation coefficient; P = p-value.

A trial that evaluated women using dienogest alone and dienogest in combination with estrogen showed that these medications are effective for pain control, with two-thirds of women not needing other medications to control symptoms¹⁷. Another trial that also evaluated women using dienogest alone and dienogest in combination with estrogen for 12 months showed that dienogest was effective in controlling pain and reducing ovarian endometriomas, reducing the need for surgery in 30% of cases¹⁸.

In the present study, there was a reduction in pain symptoms, but significantly in the symptoms of dysmenorrhea and dysuria. An Italian study that followed women using dienogest for a long term (36 months) also showed similar results, with a reduction in pain symptoms, but a significant reduction only in the symptoms of dysmenorrhea and dysuria¹⁹.

Pain is defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. The definition should be valid for acute and chronic pain and apply to all pain conditions, regardless of their pathophysiology (e.g., nociceptive, neuropathic, and nociplastic). Secondly, the definition of pain should be applicable to humans and non-human animals. Thirdly, pain was to be defined whenever possible from the perspective of the one experiencing the pain, rather than an external observer²⁰. Thus, pain has a multidimensional aspect that depends on several aspects for its assessment.

There was no reduction in endometrial thickness in the present study. This is due to the fact that women were already using other treatments before being included in the study. In the literature, a measurable reduction in endometrial thickness has previously

been described in women undergoing medical treatment for endometriosis with GnRH (gonadotropin-releasing hormone) analogues or levonorgestrel-releasing intrauterine devices and this change reflects both the absence of estrogenic stimulation in therapies that induce hypoestrogenism, regarding the effect of progestins causing glandular atrophy and reduction in vascular density²¹.

As this study is retrospective, there are limitations such as: lack of information in medical records, discontinuation of treatment by some women after only a few months of the pharmacological treatment, lack of imaging tests before or after treatment, the study site being a tertiary health care service where many women begin follow-up already undergoing treatment and the evaluation period encompassed the years of the Covid-19 pandemic, which reduced the number of visits to the service as a safety measure for women.

The result of this study is consistent with the existing literature, despite corresponding to only one study that evaluates endometrial thickness, in which there is control of dysmenorrhea with the continuous use of dienogest and the correlation of the smaller the endometrial thickness, the better the control of dysmenorrhea²².

CONCLUSION

Use of dienogest reduced dysmenorrhea and dysuria, but did not reduce other pain complaints and also did not reduce endometrial thickness. Endometrial thickness is directly related to dysmenorrhea. Endometriosis represents a significant global health challenge due to its high incidence in women of reproductive age.

In addition, this condition is a major cause of impaired quality of life due to pain symptoms. Given this context, it is imperative that more research be conducted into this disease to ensure adequate treatment for pain control.

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Cristina Laguna Benetti-Pinto: Writing - Review and Editing
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