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Evaluation of the efficacy and safety of drospirenone in women with endometriosis

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Abstract
Introduction: Endometriosis is an inflammatory, chronic, debilitating, high-incidence condition with serious consequences for women's reproductive, quality of life and sexual health.
Objective: To determine the efficacy and safety of drospirenone when compared to Dienogest / Estradiol Valerate, in the treatment of endometriosis pain, and its influence on sexual function.
Materials and Methods: A randomized, controlled, triple-blind, multicenter clinical trial. We included 185 women, aged 18 to 39, diagnosed with endometriosis. In fifteen institutions of medium and high complexity, in the Eje Cafetero, Colombia. 94 were administered drospirenone (DRSP) (experimental group), and 91 received Dienogest / Estradiol Valerate (VE/DNG) (control group); between 2020 and 2025. They were followed up three times, every 8 weeks. Descriptive statistics were performed.
Outcomes: At 24 weeks, pain relief was observed in both groups: 75.53% (DRSP) and 71.42% (VE/DNG) ($p>0.05$). The decrease in pain was accompanied by an improvement in sexual function, with increased sexual desire, excitation/lubrication in both groups ($p>0.05$). Regarding adverse effects, no significant differences were observed between groups (24.46% versus 20.87%; p = 0.81), whose intensity was considered “mild” by the patients. There was no superiority or inferiority of DRSP versus the combination of VE/DNG in efficacy, safety, tolerability, and satisfaction ($p>0.05$).
Conclusions: DRSP is effective for the treatment of endometriosis pain, and it is similar to the combination of VE/DNG, with no significant difference in incidence of adverse effects. More randomized clinical trials evaluating the positive influence of drospirenone are required.

Keywords: Hormonal contraception, sexual behavior, dyspareunia, endometriosis, efficacy, progestins

Introduction

Endometriosis is defined as a benign inflammatory, estrogen-dependent disease characterized by the presence of functioning ectopic endometrial glands and stroma; insidious in onset, surgical diagnosis, and usually progressive and debilitating in nature [1]. It usually affects women in the reproductive stage [1, 2].

The prevalence of endometriosis varies according to the way the diagnosis is made, ranging from 1.5% to 15% [3].

The pathogenesis of endometriosis is unknown; however, it points to retrograde menstruation (implantation theory), metaplasia of the germinal epithelium (celomic metaplasia theory), metastatic dissemination (lymphocytic and hematogenous metastasis theory), altered immunity, stem cells, and genetic origins; but none of the theories alone could explain the enigmatic behavior of the disease, yet the theory of retrograde menstruation is the most widely accepted world-wide [2, 4].

The clinical manifestations of endometriosis are both unpredictable and different; being the main cause of chronic pelvic pain, there is no correlation between the degree of endometriosis and the symptoms [5]. In some women, symptoms may develop early in adolescence and persist after menopause [6]. The most common symptoms associated with chronic pelvic pain are dysmenorrhea (80%) and deep dyspareunia (30%) [2, 6, 7].

Clinical history allows suspicion, although clinical examination does not provide a definitive diagnosis of endometriosis, but pain in vaginal examination, painful nodules in the back of the sac, adnexal masses, and immobility of the uterus, particularly in fixed retroversion, are diagnostic indicators [8]. The gold standard in definitive diagnosis is direct visualization by laparoscopy or laparotomy [9, 10], with biopsy and histological confirmation [10].

Suppression of ovarian function may reduce disease and pain activity [11]. Medical treatment is aimed at suppressing estrogen synthesis, inducing atrophy of the ectopic endometrium, or interrupting the stimulation cycle and bleeding; Combined hormonal contraceptives (cyclically or continuously) and continuous progestogens (medroxyprogesterone acetate, norethisterone, cyproterone acetate, dienogest or levonorgestrel-releasing intrauterine system (LNG-IUS) are effective [11, 12].

Drospirenone (DRSP) is a synthetic progestin belonging to the spironolactone group, which has anti-mineralocorticoid, anti-estrogenic, anti-androgenic, and anti-gonadotropic properties [12]. Drospirenone / ethinyl estradiol has been shown to be more effective in treating endometriosis, compared with placebo, in improving dysmenorrhea, pelvic pain, dyspareunia and quality of life [13].

No clinical trials have been published regarding the use of DRSP as an individual treatment in endometriosis; and since symptomatic endometriosis can cause negative long-term effects on personal relationships, quality of life, and labor productivity [11]; it was decided to carry out this research, with the aim of evaluating the efficacy and safety of 4 mg of drospirenone each day in the treatment of endometriosis, in addition to knowing its contraceptive efficacy, adverse effects and influence on sexual function.

Materials and Methods

Design and population: A randomized, controlled, triple-blind, multicenter trial. Women aged 18 to 39 years with diagnosis of endometriosis confirmed by histology and future reproductive interest were included; between July 01, 2020, and June 30, 2025, in the contraception and family planning program of 15 institutions of medium and high complexity. In the Eje Cafetero, Colombia, they serve population belonging to the contributory and subsidized regime of the General Social Security System in Colombia. We excluded women with a diagnosis or history of STIs, a history of pelvic surgery or cancer, with genital malformations or deformities, abortion or childbirth less than one year, contraindications to receiving hormonal contraceptives, and those who did not agree to participate.

Sample size and sampling: A sample size of 152 women was estimated. The sample was calculated based on an expected efficacy for drospirenone of 70%, and 90% for the combination of Dienogest / Estradiol Valerate; a significance level of 0.05 and a power of 80%, an estimate of 76 women per group was established. Randomization was done using a random number chart. The triple blind was guaranteed by masking the intervention both to patients and to researchers and to statisticians and epidemiologists who interpreted the results. The random assignment code generated, using sealed opaque envelopes with a serial number each, was hidden; each envelope contained a card indicating the treatment to which the patient was assigned; those who were opened by a professional nurse, outside the study, once the woman signed informed consent to participate in the research.

Procedure: Women who participated in contraception and family planning program with confirmed diagnosis of endometriosis (in the 15 institutions), were invited to collaborate in the study. Once the selection criteria were verified, and after the signature of the informed consent document, they completed an Excel survey which recorded the sociodemographic and clinical characteristics of the participants, the nurse in charge handed them out an envelope with the medication.

Intervention: Two groups were assigned: drospirenone (DRSP) (experimental group, n=94) and Dienogest / Estradiol Valerate (VE/DNG) (control group, n=91). The women were administered the dosage during the 24 weeks of the study. Those assigned to the experimental group (DRSP) were given a 4 mg oral drospirenone tablet daily for 24 days plus 4 days of placebo to complete the 28-day cycle; while the control group (VE/DNG) received 2 tablets of 3 mg estradiol valerate, 5 tablets of 2 mg estradiol valerate with 2 mg dienogest, 17 tablets of 2 mg estradiol valerate with 3 mg dienogest, 2 tablets of 1 mg estradiol valerate and 2 tablets of placebo to complete the 28-day cycle. The contraceptive pill was taken at bedtime. All women were followed up three times, 8 weeks later, 16 and 24 weeks after the start of the study. Follow-up was performed by a contraceptive specialist that was not part of the study.

Variables measured: Sociodemographic (age, race, marital status, educational level, occupation, place of origin, type of social security (subsidized, contributory, linked); size, weight, Body mass index (BMI); habits (smoking, alcohol use, psychoactive substance use, sedentary lifestyle); gynecologic-obstetric history (age of menarche, number of pregnancies, parity, contraceptive use in the last year); sexual behaviors (sexual orientation, age of onset of sexual life, average monthly frequency of sexual intercourse, number of sexual partners, time of cohabitation); evolution of diagnosis of endometriosis and intake of non-steroidal anti-inflammatory drugs (NSAIDs) to modulate pain. Contraceptive efficacy, safety, tolerability, satisfaction, and adverse effects were assessed. The Visual Analogue Scale (VAS) and the time improvement of symptoms. The domains of the FSFI (Female Sexual Function Index) instrument: Desire, Excitation, Lubrication, Orgasm, Satisfaction and Pain.

Effectiveness evaluation: Each of the women was followed up clinically and evaluated at each control:

a) Pain intensity: by means of the Visual Analogue Scale (VAS).

The Visual Analogue Scale (VAS) of pain (14) allows the intensity of pain described by a person to be measured, with maximum reproducibility among observers. It is represented by a horizontal line of 10 centimeters, at whose ends are the extreme expressions of a symptom. On the left-hand side the absence or lower intensity is located and on the right-hand side the greater intensity. The patient is asked to mark on the line the point that considers intensity and is measured with a millimeter ruler. The intensity is expressed in centimeters or millimeters. The rating is:

1) **Mild pain:** If the patient scores the pain as less than 3.
2) **Moderate pain:** If the score is between 4 and 7.
3) **Severe pain:** Whether the score is equal to or greater than 8.

b) Rescue medication intake: Was evaluated based on the number of patients and number of doses of NSAIDs consumed by self-medication during the follow-up period.

c) Sexual function: with the Female Sexual Function Index (FSFI).

The FSFI is a 19-item questionnaire, which groups six domains (Desire, Excitation, Lubrication, orgasm, Satisfaction and Pain); each question has 5 or 6 answer options, with a variable score of 0 to 5 [15]. The total score is obtained by the arithmetic sum of the products obtained by multiplying the average of each domain

by a factor [16]. The total range of the score ranges from 2 to 36; a score less than or equal to 26.55 points, or when a domain score is less than 3.6 points, it is considered at risk for sexual dysfunction [15, 16].

Safety assessment: This was done by assessing the incidence of adverse effects in each control. The causality categories described by the technical fundamentals of the Uppsala Monitoring Center (UMC), a WHO collaborating center for pharmacovigilance [17], were retained, which classifies the clinical intensity of an adverse reaction as follows:

- **Mild:** Signs and symptoms can be easily tolerated when the patient is distracted, may miss the symptoms and they disappear.
- **Moderate:** Symptoms cause discomfort but are tolerable; they cannot be overlooked and alter the concentration of the subject.
- **Severe:** Symptom's daily activities.

Tolerability assessment: The patient evaluated the treatment, at each control, using a qualitative print scale that included the following options [18]:

- **Very good:** No adverse drug reactions (ADRs).
- **Good:** ADRs do not significantly interfere with patient activity.
- **Regular:** ADRs significantly interfere with normal patient activity.
- **Poor:** ADRs surpass the therapeutic effect.

Satisfaction assessment: It was done through:

a) Overall evaluation of treatment (*efficacy/tolerability*) by a contraceptive specialist (non-study), at each control, using the overall clinical impression scale, which combines therapeutic effect and adverse effects in a double-entry picture.

b) Evaluation of treatment effectiveness by the patient, at each control, using a qualitative print scale that included the options:

- **Very effective:** Significant improvement, complete or almost complete remission of symptoms.
- **Effective:** Marked improvement, partial remission of symptoms.
- **Moderately effective:** Weak improvement that does not alter the patient's condition.
- **Ineffective:** No changes or worsening.

Statistical analysis: It was performed with the SPSS V21.0 program. For categorical variables, frequency tables were developed with percentage analyses, for the continuous, analyzes of central tendency and dispersion (mean and standard deviation (SD) or medium and range) were performed. The two groups were compared using the χ^2 test or Fisher's exact test in categorical variables, and Student's t-test in continuous variables. Statistical significance was defined as $p<0.05$.

Ethical aspects: The study was approved by the Ethics Committee of each participating center. The requirements for medical research in human beings established in the Helsinki Declaration were met. All participants signed the informed consent. Confidentiality of information was guaranteed.

Outcomes

During the study period, 2624 women attended the Contraception and Family Planning programs of the 15 participating institutions, of which 236 (8.99%) had diagnosis of endometriosis confirmed by histology, 14 (5.93%) did not agree to participate. 37 patients were excluded: 12 with a diagnosis or history of STIs, 10 with a history of pelvic surgery, 8 with abortion or childbirth less than one year, and 7 with a history of cancer. The study was conducted with 185 patients (94 were given drospirenone -experimental group-, and 91 Dienogest / Estradiol Valerate -control group-).

The mean age was 32.31±5.06 and 31.84±3.97 years, respectively ($p>0.05$). 80.54% came from the urban area; 86.48% professed the christian faith; 93.51% were straight and 89.72% belonging to the State contributory regime in the General Social Security System in Colombia. There were no differences between the groups in terms of sociodemographic characteristics (Table 1).

Table 1: Sociodemographic characteristics in women with endometriosis, Eje Cafetero, Colombia, 2020 - 2025

Variables	Drospirenone (n=94)	Dienogest / Estradiol Valerate (n=91)	p level
Age: ẍ±SD years	32.31±5.06	31.84±3.97	$p>0.05$
Age of partner: ẍ±SD years	34.49±3.58	33.75±3.14	$p>0.05$
Height: ẍ±DE Cms	158.32 (± 7.54) cm	157.93±7.38	$p>0.05$
ẍ±DE Kg	61.45±4.53	60.73±4.61	$p>0.05$
BMI: ẍ±SD	24.41±3.61	24.15±3.42	$p>0.05$
Race			
White	50 (53.8 9 %)	48 (52.74 %)	$p>0.05$
Afro-Colombians	37 (39.36 %)	39 (42.85 %)	$p>0.05$
Indigenous	7 (7.44 %)	4 (4.39 %)	$p>0.05$
Socioeconomic status			
High	31 (32.97 %)	33 (36.26 %)	$p>0.05$
Middle	54 (57.44 %)	48 (52.74 %)	$p>0.05$
Low	9 (9.57 %)	10 (10.98 %)	$p>0.05$
Civil Status			
Married	34 (36.17 %)	31 (34.06 %)	$p>0.05$
Common law	38 (40.42 %)	35 (38.46 %)	$p>0.05$
Single	15 (15.95 %)	19 (20.87 %)	$p>0.05$
Divorced	7 (7.44 %)	6 (6.59 %)	$p>0.05$
Occupation			
Stay-at-home spouses	41 (43.61 %)	42 (46.15%)	$p>0.05$
Employed	29 (30.85 %)	27 (29.67 %)	$p>0.05$

Unemployed	24 (25.53 %)	22 (24.17 %)	p>0.05
Level of education			
Primary	5 (5.31 %)	7 (7.69 %)	p>0.05
Secondary	44 (46.81 %)	43 (47.25 %)	p>0.05
Technical	17 (18.08 %)	16 (17.58 %)	p>0.05
Professionals	28 (29.78 %)	25 (27.47 %)	p>0.05

Source: authors

The 18.37% of women smoked, with a median consumption of 3 (range between 1 and 12) cigarettes/day; 74.59% consumed alcohol, and 5.94% consumed psychoactive substances; sedentary lifestyle was present in 25.94%, with no differences between groups (p>0.05).

The age of menarche was 12.47±3.58 years (minimum 9 and maximum 19), and the age of onset of sexual life was 16.83±2.94 years (minimum 13 and maximum 23); the number of pregnancies reported a median of 3 (range between 0 and 7), parity returned a median of 2 (range between 0 and 5).

In the use of contraceptive methods, the use of oral hormonal contraceptives (69.72%) prevailed in the last year, followed by the subdermal implantation of LNG (19.45%). The average frequency of monthly sex was 2 (range 0-5); the number of sexual partners was 7 (range 1 - ≥12); the average time of cohabitation was 5.83±2.17 years (minimum 1 and maximum 9). The 58.37% of patients reported predating oral sex to intercourse, and 3.24% reported preferring anal sex, due to less pain.

The average duration of endometriosis was 7.29±4.14 and 8.13±4.37 years in each group. In most (71.35%) of the participants, pain was in the left iliac fossa. In the total population, the median number of pain attacks per year, requiring institutional medical management, was 2 (range 0-4).

In the symptoms of the total participants, dysmenorrhea (85.94%) prevailed, followed by dyspareunia (68.1%) and chronic pelvic pain (60.54%) (Table 2).

Table 2: Symptoms of endometriosis in women, Eje Cafetero, Colombia, 2020 - 2025

Symptoms	Drospirenone (n=94)	Dienogest / Estradiol Valerate (n=91)	p
Menstrual disorders	65 (68.08 %)	60 (65.93 %)	p>0.05
Dysmenorrhea	78 (82.97 %)	81 (89.01 %)	p>0.05
Dyspareunia	66 (70.21 %)	60 (65.93 %)	p>0.05
Disquiecy	4 (4.25 %)	2 (2.19 %)	p>0.05
Cyclical abdominal pain	36 (38.29 %)	33 (36.26 %)	p>0.05
Lower back pain	9 (9.57 %)	7 (7.69 %)	p>0.05
Chronic pelvic pain	59 (62.76 %)	53 (58.24 %)	p>0.05
Constipation	17 (18.08 %)	14 (15.38 %)	p>0.05
Hematoquia	5 (5.31 %)	3 (3.29 %)	p>0.05
Infertility	27 (28.72 %)	24 (26.37 %)	p>0.05
Rectal bleeding	2 (2.12 %)	3 (3.29 %)	p>0.05
Urinary symptoms	24 (25.53 %)	27 (29.67 %)	p>0.05

Source: authors

On admission, according to the Visual Analogue Scale (VAS) of pain, in the drospirenone group (DRSP) 79.78% reported pain as moderate intensity (VAS >4 and ≤7); In 14.89% of women as severe (VAS ≥8), only 5.31% of women described pain as mild (VAS <3). In the VE/DNG group, 84.61% reported pain as moderate intensity; 12.08% as severe; and 3.29% as mild (EVA <3); no statistically significant difference (p>0.05). At the end of the study, an improvement of 75.53% and 71.42% was observed, respectively (p>0.05), where there was a complete absence of pain; only 9 (9.57%) in the DRSP group and 10 (10.98%) in the VE/DNG group rated pain as "moderate"; 14 (14.89%) and 16 (17.58%), respectively, rated it as mild; no patient considered pain to be "severe".

At 24 weeks, the percentage of complete remission of dysmenorrhea was 71.27% for the DRSP group and 70.32% for the VE/DNG group (p>0.05). Dyspareunia improved by 70.21% and 75.82%, respectively (p>0.05).

Women in the DRSP group had a longer average time between administration of the drug and improvement of dysmenorrhea (8.31±2.79 weeks), with no significant difference with the VE/DNG group (8.04±2.58 weeks) (p = 0.123).

In the DRSP group, 10 women (10.63%) warranted the use of NSAIDs to modulate pain (RR: 0.42; CI 95%: 0.18-0.75) and 5 of 91 in VE/DNG group (RR: 0.18; CI95%: 0.12-0.69). The increased risk of needing NSAIDs was further increased in nulligestants (RR: 1.26; CI95%: 1.08-2.07) and married women (RR: 1.11; CI95%: 1.02-20.4); the difference was not statistically significant (p = 0.072).

At the end of the study, in the DRSP group, 65 (69.14%) women showed an increase in the median monthly sexual frequency (4; range between 2 and 6 vs. 3; range 1 to 7 (VE/DNG), with no statistically significant difference (p = 0.93). The IFSF score was 28.14±3.57 (DRSP) and 27.93±4.26 (VE/DNG), (p>0.05).

At baseline, the IFSF score, less than 26.55 points, was observed in 70.81% of the total patients, a percentage that decreased at the end of the study to 36.21%, with no significant differences between groups (38.29% versus 34.06%, p>0.05).

There were no statistically significant differences between groups in the positive influence of contraception on sexual function (79.78% versus 81.31%) (p = 0.18) (Table 3).

Table 3: Female sexual function index, in women with endometriosis, Eje Cafetero, Colombia, 2020 - 2025

Domains	Contraception	Baseline	8 weeks	16 weeks	24 weeks	P baseline vs. end
Desire	Drospirenone	3,04±1,06	3,49±1,08	4,09±1,15	4,17±1,13	*p*<0,05
	Dienogest	3,17±1,05	3,54±1,03	4,02±1,14	4,29±1,14	*p*<0,05
Arousal	Drospirenone	3,62±1,05	3,81±1,01	4,35±1,11	4,68±1,17	*p*<0,05
	Dienogest	3,61±1,02	3,79±1,05	4,39±1,17	4,62±1,15	*p*<0,05
Lubrication	Drospirenone	3,49±1,04	3,65±1,07	4,28±1,13	4,59±1,12	*p*<0,05
	Dienogest	3,57±1,02	3,71±1,08	4,32±1,19	4,56±1,11	*p*<0,05
Orgasm	Drospirenone	3,71±1,04	3,84±1,09	4,59±1,28	4,83±1,14	*p*<0,05
	Dienogest	3,68±1,01	3,87±1,06	4,61±1,23	4,86±1,13	*p*<0,05
Satisfaction	Drospirenone	3,95±1,52	4,19±1,43	4,72±1,39	4,75±1,11	*p*<0,05
	Dienogest	3,97±1,46	4,28±1,52	4,75±1,45	4,81±1,19	*p*<0,05
Pain	Drospirenone	5,32±1,08	5,03±1,29	4,81±1,42	4,17±1,17	*p*<0,05
	Dienogest	5,29±1,53	5,02±1,38	4,73±1,43	4,02±1,16	*p*<0,05
Total	Drospirenone	23,13±6,78	24,01±6,97	26,84±6,48	27,19±6,84	*p*<0,05
	Dienogest	23,29±7,09	24,21±7,12	26,82±7,61	27,16±6,88	*p*<0,05

Source: authors

Depending on the presence or absence of adverse effects, no significant differences were obtained between the groups: 24.46% (DRSP) versus 20.87% (VE/DNG), (p = 0.81), whose intensity was considered by the patients as "mild," in both groups, so no treatment or suspension of contraception was required. The most frequent adverse effect in the DRSP group was amenorrhea, especially after 16 weeks, followed by irregular vaginal bleeding (**Table 4**).

Table 4: Adverse effects of oral contraceptives, in women with endometriosis, Eje Cafetero, Colombia, 2020 - 2025

Adverse effects	Drospirenone (n=94)	Dienogest / Estradiol Valerate (n=91)	p
Acne	10 (10.63 %)	8 (8.79 %)	*p*>0.05
Alopecia	5 (5.31 %)	3 (3.29 %)	*p*>0.05
Amenorrhea	23 (24.46 %)	19 (20.87 %)	*p*>0.05
Weight loss	12 (12.76 %)	10 (10.98 %)	*p*>0.05
Weight gain	4 (4.25 %)	6 (6.59 %)	*p*>0.05
Mood changes	3 (3.19 %)	4 (4.39 %)	*p*>0.05
Headache	7 (7.44 %)	8 (8.79 %)	*p*>0.05
Edema	8 (8.51 %)	7 (7.69 %)	*p*>0.05
Mastalgia	11 (11.7 %)	15 (16.48 %)	*p*>0.05
Irregular vaginal bleeding	14 (14.89 %)	16 (15.28 %)	*p*>0.05

Source: authors

The median adverse effects per woman were 2 (range 0 to 5), which was present in 22.7% (n=42/185) of the total participants; 23.4 % (n=22/94) in the DRSP group, and 21.97% (n=20/91) in the VE/DNG group, with no significant differences between the two (0.672).

In the groups, a decrease was observed over time in the number of women with irregular bleeding or *spotting*, as well as in the number of unscheduled bleedings, especially after 16 weeks (40.42% vs. 43.95%), (*p*>0.05).

Treatment tolerability in the DRSP group ranged from "very good" (70.42%) to "good" (29,.57%), compared with 68.05% and 31.94%, respectively, in the VE/DNG group (*p*>0.05). In any of the patients in both groups, tolerability was considered "regular" or "poor."

At 24 weeks treatment satisfaction was rated as "effective" in 75.53% of the DRSP group and 71.42% of the VE/DNG group (*p*>0.05). Of the 94 women in the DRSP group, in 7 (7.44%) satisfaction was considered "ineffective," while of the 91 participants in the VE/DNG group, "ineffective," satisfaction occurred in 11 (12.08%) of them, with no statistically significant difference (p = 0.27).

During the study, no pregnancy occurred in either group.

Discussion.

Progestins have been used more often for the treatment of endometriosis, and in line with combinations of estrogen/progestin (low doses), they have become a first-line therapy (19.20). Progestins are particularly advantageous in women with dysmenorrhea [21], while combined oral contraceptives are useful in treating pain and other symptoms associated with endometriotic nodules [22]; although the treatment guidelines of the American College of Obstetricians and Gynecologists (ACOG), recommend combined extended-cycle oral contraceptives as initial treatment [23]. Pharmacokinetics, efficacy and tolerability of the combination of ethinyl estradiol/drospirenone for contraception has been confirmed by several authors [24-26]; this has provided a valuable option, by drospirenone, for additional treatment for women with endometriosis.

This research found that, at 24 weeks, chronic pelvic pain showed a significant reduction (75.53 %) with the use of drospirenone, similar to the combination of VE/DNG (71.42 %) (*p*>0.05); results that are similar to those reported by *Vercellini* et al., who, in a two-year prospective, therapeutic, self-controlled clinical trial conducted in Italy, which included 50 women who had undergone endometriosis surgery, and they had experienced recurrent dysmenorrhea despite the use of cyclic oral contraceptives; they reported a significant reduction in dysmenorrhea with the continuous use of combined oral contraceptives (ethinyl estradiol 20 µg and desogestrel 150 µg) [27]. *Muzii* et al., in a meta-analysis that included three randomized trials and a prospective controlled cohort study, for a total of 557 patients with endometriosis, 343 of whom had ovarian endometriomas; they obtained lower recurrence rates for dysmenorrhea with a continuous program of continuous oral contraceptives (RR: 0.24; CI95%: 0.06 - 0.91; p = 0.04) [28].

If the main purpose of medical treatments for endometriosis is to relieve pain, with adequate therapies for long-term use, in addition to being associated with a low incidence of adverse effects [11], in this regard, drospirenone in regimen 24/4, is a viable option, in the light of the results of this study.

Sexual problems are common in women with endometriosis, as they are at increased risk for dyspareunia compared to the normal population; affecting 11.5% (OR: 7.4; CI95%: 6.5-8.5) of women [29]; may affect all domains of sexual function (desire/arousal, orgasm, satisfaction and pain), which led to sexual dysfunction in 70.81% of patients, as described in the total population of this study; percentage that decreased to 36.21% at the end of the investigation, with no significant differences between groups (38.29% versus 34.06%, $p>0.05$).

At the end of the study, drospirenone was associated with an increase in median monthly sexual frequency, with an increase in satisfaction score; no statistically significant difference with the VE/DNG combination (p = 0.93). Regarding these findings, several authors agree that combined oral contraceptives and progestins are effective in relieving pelvic pain and deep dyspareunia in patients with endometriosis [30-32], which may be associated with a positive experience in improving sexual dysfunction.

Once the comprehensive search has been conducted, we note that our study is the first randomized controlled trial, evaluating regimen 24/4 for the control of chronic pelvic pain associated with endometriosis. The results show that, compared with the combination of VE/DNG, pain reduction was associated with improved sexual function, with differences in IFSF scores statistically significant at 24 weeks; there were no statistically significant differences between both groups (p = 0.18).

The adverse effects observed in this study are the same as those already known and published by other researchers [33-35]; therefore, the safety profile is considered similar, with slight percentage differences, lacking statistical significance.

This study indicated that there is no superiority or inferiority of drospirenone in the 24//4 regimen compared with the VE/DNG combination, with very similar satisfaction, safety and contraceptive efficacy; therefore, it becomes an appropriate alternative in pain management in women with endometriosis; results that are consistent with those published by *Archer* et al. [36], regarding clinical contraceptive efficacy similar to that of combined oral estrogen plus progestin contraceptive, with a good safety profile and favorable cycle control.

In his study, *Ludicke* et al., with the combination of 30 µg ethinyl estradiol / 3 mg drospirenone, demonstrated a good suppression of endometrial activity and marked antiproliferative effect, comparable with other combined oral contraceptives [37]; effect we invite to evaluate in future research with the drospirenone regimen 24/4, as it would become the cornerstone in choosing a progestin.

About the patient satisfaction point of view, this study found that there were no dropouts, which is like that published by *Palacios* et al. [38], those who report 3.2% abandonment by women who received 4 mg of drospirenone, compared with 6.6% of those who took 0.075 mg of desogestrel ($p<0.001$).

Comparing oral contraceptives combined with progestins alone, the latter offer multiple advantages because they are associated with a decreased risk of venous thromboembolism [36, 39] and cause fewer metabolic changes [40], this makes them an appropriate choice in women with intolerance or contraindications to estrogens (migraine, cardiovascular risk factors: HTA, hyperlipidemias, obesity, diabetes, smoking, etc.) [41-43]; which puts the drospirenone in a privileged position, since according to *Surrey* et al. [32], progestagens have been used as the first therapy in the management of symptomatic endometriosis, as well as adjuvants to surgical resection. This has been confirmed by both prospective observational studies and randomized clinical trials [30, 32, 44].

Recently, in research (multicenter, open-label trial, phase 3), in Europe and Russia [45], sexually active women (18 to 50 years), with regular menstrual cycles and BMI ≤ 35 kg/m^2; participants were given estetrol (15 mg) / drospirenone (3 mg) in a regimen of 24 assets and 4 placebo for up to 13 cycles, with effective contraception, a predictable bleeding pattern, and a favorable safety profile. With this we can consider, once again, that drospirenone is not only one of the most effective contraceptives, but one of the safest, either alone or combined. More large-scale controlled clinical trials are needed to provide more information on the efficacy and safety profile of drospirenone in the treatment of endometriosis pain, as well as its eventual influence on sexual function.

The main strength of this study is that it covers an unexplored aspect of the use of new progestins in the treatment of endometriosis, being the first to use the drospirenone regimen 24/4; in addition, by performing a simple random sampling, each of the women enjoyed equal opportunities to be selected. Sample size is another important strength, due to the variable prevalence of the disease. Weaknesses include the fact that a placebo-controlled trial is not offered to symptomatic patients, and that there is currently no study where the medical treatment of endometriosis is drospirenone regimen 24/4, which can be used as a comparison; however, it is possible to draw definitive conclusions to generalize the results, although the need for confirmation/validation in larger series of patients is suggested.

Conclusions.

Drospirenone of 4 mg, with the regimen of 24/4, is effective in the treatment of endometriosis, resulting like the combination of Dienogest / Estradiol Valerate, with an incidence of adverse effects without significant differences, which are tolerable, without requiring discontinuation of the drug. Similarly, the positive influence on sexual function is equivalent to the combination of Dienogest / Estradiol Valerate.

It is necessary to individualize each woman, where hormonal treatment for endometriosis should be used. Further studies evaluating the positive influence of drospirenone of 4 mg on the 24/4 regimen in our region are required, as there are often limitations on access to non-invasive laparoscopic procedures. Future randomized clinical trials may confirm the findings of this research.

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