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Efficacy and Safety of Promestriene in the Treatment of Genitourinary Syndrome of Menopause in Women with Breast Cancer

Eficacia y seguridad del promestrieno en el tratamiento del síndrome genitourinario de la menopausia en mujeres con cáncer de mama

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ABSTRACT

Objective: To evaluate the efficacy and safety of vaginal promestriene in women with triple-negative breast cancer who experience vulvovaginal symptoms and signs related to genitourinary syndrome of menopause (GSM). **Materials and methods:** This prospective, multicenter regional, randomized, triple-blind, placebo-controlled study involved women aged 45 years or older who survived breast cancer with triple-negative hormone receptors and were symptomatic of GSM. The participants consulted at three private clinics in the Coffee Region of Colombia between 2019 and 2023. They were randomly assigned to receive either promestriene (n = 77) or a placebo (n = 75), with a 12-month follow-up recording satisfaction with therapy, adverse effects, Vaginal Health Index scores, and Female Sexual Function Index (FSFI) scores. Serum levels of estradiol, androgens, and gonadotropins were analyzed, and descriptive statistics were applied. **Results:** Hormonal concentrations remained within the postmenopausal range, and promestriene treatment significantly improved all variables in the Vaginal Health Index as well as FSFI domains and overall scores (26.92 ± 7.89 vs. 24.38 ± 8.13 in the placebo group; $p<0.015$). Adverse effects were mild and tolerable, including increased vaginal discharge, burning sensation, itching, and vulvovaginal inflammation. Approximately 90% of participants reported satisfaction with the therapy. **Conclusions:** Promestriene was effective and safe for treating GSM symptoms and signs in women with breast cancer, showing no significant changes in serum estradiol levels. Its use is supported as an option for patients experiencing GSM symptoms.

Keywords
efficacy; safety; therapeutics; menopausal hormone therapy; estradiol; menopause.

RESUMEN

Objetivo: Evaluar la eficacia y seguridad del promestrieno vaginal en mujeres con cáncer de mama triple negativo que experimentan síntomas y signos vulvovaginales relacionados con el síndrome genitourinario de la menopausia (SGUM). **Materiales y métodos:** Estudio prospectivo, multicéntrico regional, aleatorizado, triple ciego, controlado con placebo en mujeres ≥45 años sobrevivientes de cáncer de mama con receptores hormonales triple negativo, sintomáticas de SGUM, que consultaron en tres clínicas privadas del Eje Cafetero (Colombia) entre 2019 y 2023. Se aleatorizaron en dos grupos para recibir promestrieno (n = 77) y placebo

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(n = 75). El seguimiento fue de 12 meses, registrando satisfacción con la terapia, efectos adversos, puntuación del Índice de Salud Vaginal e Índice de Función Sexual Femenina (IFSF). Se analizaron las concentraciones de estradiol, andrógenos y gonadotropinas. Se aplicó estadística descriptiva. **Resultados:** Las concentraciones hormonales permanecieron dentro del rango posmenopáusico. El tratamiento con promestrieno mejoró todas las variables del Índice de Salud Vaginal, así como los dominios y la puntuación total del IFSF (26,92 ± 7,89 frente a 24,38 ± 8,13 del grupo placebo; $p<0,015$). Los efectos adversos fueron leves y tolerables (aumento de la secreción vaginal, sensación de quemazón, picor e inflamación vulvovaginal). La satisfacción con la terapia estuvo cerca del 90%. **Conclusiones:** El promestrieno se mostró eficaz y seguro para el tratamiento de los síntomas y signos del SGUM, sin cambios relevantes en el estradiol y se respalda su uso.

Palabras clave
eficacia; seguridad; terapéutica; terapia hormonal de la menopausia; estradiol; menopausia.

Introduction

Breast cancer is a heterogeneous disease influenced by both genetic and environmental factors. Breast cancer stem cells are the primary drivers of tumor aggressiveness and pose a fundamental challenge in treatment. These cells also represent a fundamental challenge in treatment (1).

Among cancers diagnosed in women, breast cancer is the most prevalent (2,3), both in developed (794,000 cases) and less developed countries (883,000 cases) (4). In Colombia, around 7,000 new cases are diagnosed each year, with approximately 2,500 women dying from the disease (5). Fortunately, mortality rates have decreased by 49% since 1986 (6).

About 80% of malignant breast tumors are classified as infiltrative, followed by invasive lobular carcinomas (10%). However, histological classification does not fully capture the pathology's heterogeneity. Immunophenotyping, which categorizes lesions based on mitotic index (Ki67) and HER2/neu overexpression, is necessary (7). HER2/*neu* receptors are expressed in 75% of breast cancers, stimulating normal and neoplastic epithelial growth (8).

Based on gene expression profiles, breast cancer is classified into four subtypes:

1. Luminal A: ER (+), PR ≥ 20%, HER2/*neu* (−), Ki67 ≤ 20%, representing 50% to 60% of luminal tumors."
2. Luminal B: ER (+), PR variable, HER2/*neu* (variable), Ki67 > 20%, representing 10% to 20% of luminal tumors."
3. HER2/*neu* positive: ER (−), PR (−), HER (+).
4. Triple-negative: ER (−), PR (−), HER2/*neu* (−), representing 10% to 15% (9-11).

The diagnosis of breast cancer is made through imaging techniques (ultrasonography and mammography), accompanied by an analysis of the affected tissue (histological and molecular diagnosis) (11,12).

Treatment options include surgery, radiotherapy, chemotherapy, and molecular therapies (13). These treatments often cause persistent menopausal symptoms in breast cancer survivors, as they tend to induce early or premature menopause, which is accompanied by hot flashes, sweating, burning, vaginal itching, dyspareunia, or vaginal dryness (14,15).

The clinical treatment of menopausal symptoms in breast cancer survivors is complicated by the relative contraindication of estrogen hormone therapies (16,17). Promestriene (estradiol 3-propyl ether, 17-β-methyl ether) is an estradiol analogue effective in treating atrophic changes caused by estrogen deficiency, as it acts on the vaginal mucosa without stimulating the endometrium and has insignificant systemic absorption. Even with prolonged treatments, there is minimal risk of harmful estrogenic activity (18-20).

The fact that breast cancer-targeted therapies often lead to primary ovarian insufficiency or early menopause, with resulting vasomotor or urogenital symptoms due to abrupt drops in estrogen levels (21), highlights the need to explore alternative therapeutic options. Therefore, the objective of this study was to evaluate the efficacy and safety of vaginal promestriene in women with triple-negative

breast cancer who experience vulvovaginal symptoms and signs related to genitourinary syndrome of menopause (GSM).

Materials and Methods

Study Design and Population

This was a prospective, multicenter regional, randomized, triple-blind, placebo-controlled study. The participants were women aged 45 or older, survivors of triple-negative breast cancer, who had been in amenorrhea for 12 months or more and were symptomatic for GSM. They were recruited from three private clinics in Colombia's Coffee Region (Caldas, Risaralda, and Quindío) during routine follow-up visits from March 1, 2019, to February 28, 2023.

Triple-negative breast cancer was defined as a distinct subtype of cancer characterized by the absence of estrogen and progesterone hormone receptors and the lack of expression of human epidermal growth factor receptor 2 (HER2/*neu*) (22).

Participants were required to have a Vaginal Health Index score below 15. Women were excluded if they had received any vulvovaginal therapy within the 30 days prior to study initiation; had used hormones, phytoestrogens, or herbal products to treat menopausal symptoms within the previous 3 months; or had vaginal/uterine bleeding and an endometrial thickness of 4 mm or more. Other exclusion criteria included a history of other malignant neoplasms, smoking, thyroid dysfunction, history of hysterectomy or oophorectomy, thromboembolic disease or coagulopathies, cardiovascular disease, inability to follow up, and unwillingness to participate.

Sample Size

To reject the null hypothesis with a statistical power of at least 90%, a significance level of 5%, and a confidence level ($1-\alpha$) of 95%, it was necessary to include 66 patients per group (control and placebo). Accounting for a 10% dropout rate, a total of 73 women were estimated to be needed for each group. Assignment was carried out using a random number table. Triple-blinding of the medication was implemented, facilitated by a pharmacy technician who managed the pharmacy services at each participating clinic. The study drug and placebo were identical in appearance, with similar labeling.

Procedure

Women who met the inclusion criteria were invited to participate. They were interviewed by the principal investigator and the nursing staff, who were part of the research team. The study's objective, confidentiality, participant rights, identified risks, and the option to withdraw freely at any time were explained to them. Written informed consent was obtained from each participant prior to initiating treatment and the study protocol. Once the informed consent was signed, participants were assigned to one of two groups: Group A (promestriene) and Group B (placebo).

The patients were monitored by an obstetrics and gynecology specialist who was not involved in the research and conducted evaluations over the 12-month follow-up period. Data was collected using a specially designed form, completed by a general physician hired for this activity, who accompanied the specialist during each patient's assessment throughout the study. This physician was responsible for recording the variables of interest in a data collection sheet in Excel, specifically designed for this study.

Intervention

Group A was treated with promestriene (10 mg daily for three weeks, then every three days for six months, and finally once a week until completing the 12-month follow-up); meanwhile, Group B received a placebo (water-based intimate lubricant). Both treatments were administered via an intravaginal applicator at a dose of 1 g of cream per application (containing 10 mg of

promestriene), applied at bedtime. During the initial visit, a professional nurse hired for the study provided the products to participants in each group and administered the first dose in the presence of the investigator to explain the procedure and address any questions regarding the intervention.

Treatment adherence was evaluated by counting and recording the number of unused applicators. Follow-up visits were conducted at months 1, 3, 6, 9, and 12, totaling five appointments. At each follow-up, a physical examination including a genital assessment, laboratory tests, transvaginal pelvic ultrasound, Vaginal Health Index evaluation (Table 1), therapy satisfaction, and adverse effects were recorded. Sexual function was assessed, and the domains of the Female Sexual Function Index (FSFI) were evaluated.

Table 1.
Vaginal Health Index

Elasticity	Secretion Flow and Consistency	pH	Epithelial Mucosa	Hydration
1. Absent	Absent	6.1	Petechiae without contact	Absent, inflamed mucosa
2. Poor	Scant, yellow	5.5-6.0	Bleeding with light contact	Absent, non-inflamed mucosa
3. Sufficient	Superficial, thin, white	5.1-5.5	Bleeding with scraping	Minimal
4. Good	Moderate, thin, white	4.7-5.0	Not friable, thin mucosa	Moderate
5. Excellent	Normal	≤4.6	Not friable, normal mucosa	Normal

The Vaginal Health Index was designed to assess the urogenital health of women (it has not yet been validated in the Colombian population). It facilitates a precise and objective clinical evaluation of age-related changes in urogenital tissue (23). The index evaluates each item on a scale from 1 to 5, where a lower score corresponds to greater urogenital atrophy (the score ranges from 5 to 25).

The FSFI is a 19-question questionnaire grouped into 6 domains (desire, arousal, lubrication, orgasm, satisfaction, and pain). Each question has 5 or 6 response options, with scores ranging from 0 to 5. The score for each domain is multiplied by a factor, and the final score is the arithmetic sum of all domains, ranging from 2 to 36. A higher score indicates better sexual function. This questionnaire has been validated in the Colombian population. A score of ≤26.55 is considered at risk for sexual dysfunction (24-26).

At the time of study enrollment, participants underwent the following assessments: transvaginal pelvic ultrasound, cervical cytology (Bethesda), vaginal pH, complete lipid profile, serum concentrations of estradiol, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), dihydrotestosterone (DHT), follicle-stimulating hormone (FSH), luteinizing hormone (LH), fasting blood glucose, thyroid-stimulating hormone (TSH), and total and free testosterone —with concentrations measured using the radioimmunoassay (RIA) method.

Efficacy Evaluation

Efficacy was assessed at months 1, 3, 6, 9, and 12. This included a gynecological exam, the Vaginal Health Index, and the FSFI. Vaginal symptoms (vaginal dryness, dyspareunia, and itching) and signs (thinned mucosa or flattening of folds, mucosal fragility, and dryness) were recorded nominally by the patient (symptoms) and the investigator (signs) on a 4-point scale, where 0 represented absence of the sign/symptom; 1, *mild*; 2, *moderate*; and 3, *severe*. Vaginal pH was measured in vaginal secretions using a test strip.

Safety Evaluation

Safety was evaluated based on the presence of adverse effects, changes in endometrial thickness from baseline to 12 months of follow-up, and changes in serum concentrations of gonadotropins (FSH and LH), estradiol, SHBG, DHEAS, DHT, and total and free testosterone. Other safety evaluations included laboratory parameters (glucose, TSH, and lipid profile), as well as physical and gynecological examinations (breast and pelvic exams).

Clinical Laboratory

Venous blood was drawn after a minimum 12-hour fast, before 10:00 a.m. Serum was separated and frozen for processing within the next 3 hours.

Measured Variables

Sociodemographic variables (age, race, education level, socioeconomic status, marital status, occupation, origin, social security affiliation, and religion), weight, height, body mass index (kg/m^2); habits (alcohol intake, smoking, and physical activity); gynecological and obstetric history (age of menarche, age at first childbirth, pregnancies, parity), and sexual behavior (age at first sexual intercourse, monthly sexual frequency).

Additionally, endometrial thickness, glucose, lipid profile, TSH, and hormone concentrations of estradiol, SHBG, DHEAS, DHT, FSH, LH, and total and free testosterone were recorded. The efficacy in resolving clinical symptoms of GSM and the safety (adverse effects) of the intervention were also evaluated. Finally, the variables of the Vaginal Health Index and the domains of the FSFI were assessed.

Ethical Considerations

This research was conducted following approval from the Ethics Committee (Act 129 of November 21, 2018), adhering to all international recommendations outlined in the Declaration of Helsinki on ethical principles for medical research involving human subjects, and complies with Resolution 8430 of 1993 by the Ministry of Health of the Republic of Colombia, which classifies it as minimal risk. The content of the data collection forms, as well as confidentiality, has been respected and protected at all times. Informed consent was obtained and signed by all participants.

Statistical Analysis

Descriptive statistics were applied. For categorical variables, frequency tables with percentage analysis were prepared, and for continuous variables, central tendency and dispersion analyses (mean or median and standard deviation or range, according to normal data distribution) were conducted. The two groups were compared using the χ^2 test for nominal or qualitative variables, Fisher's exact test, or the Student's t-test for continuous variables. A 5% significance level or the corresponding *p*-value was used for all tests. The software used for this purpose was SPSS 28® (Statistical Package for the Social Sciences).

Results

A total of 197 women were identified, of whom 23 (11.67%) had a history of hysterectomy, 11 (5.58%) were under 45 years of age, 5 (2.53%) had an endometrial thickness >4 mm, 3 (1.52%) were undergoing treatment for thromboembolic disease, and 3 (1.52%) declined to participate, leading to their exclusion. The study was ultimately conducted with 152 participants. There were no losses during follow-up, and all participants completed the study. Thus, 77 women were allocated to the promestriene group and 75 to the placebo group.

Regarding sociodemographic characteristics, most participants identified as Catholic (84.21%), lived in urban areas (71.71%), were enrolled in the contributory health regime (65.78%), were married or in a common-law partnership (57.89%), and were homemakers (48.68%) (Table 2).

Tabla 2.
Sociodemographic Characteristics in Women with Breast Cancer and Genitourinary Syndrome of Menopause

	Group A: Promestriene (n = 77)	Group B: Placebo (n = 75)	*p*-Value
Age (X ± SD [years])	54.86 ± 4.19	55.12 ± 4.27	0.035
Weight (X ± SD [kg])	65.97 ± 4.32	66.13 ± 5.24	0.553
Height (X ± SD [m])	1.59 ± 2.81	1.58 ± 2.47	0.592
BMI (X ± SD [kg/m^2])	25.73 ± 2.16	26.45 ± 3.17	0.587
Race			
Hispanic (n [%])	48 (62.33)	52 (69.33)	0.634
Afro-Colombian (n [%])	21 (27.27)	16 (21.33)	0.853
Indigenous (n [%])	8 (10.38)	7 (9.33)	0.576
Socioeconomic Status			
High (n [%])	28 (36.36)	29 (38.66)	0.712
Middle (n [%])	22 (28.57)	19 (25.33)	0.839
Low (n [%])	27 (35.06)	27 (36.00)	0.851
Education Level			
Primary-Secondary (n [%])	12 (15.58)	11 (14.66)	0.548
Technical (n [%])	61 (79.22)	56 (74.66)	0.172
Professional (n [%])	5 (6.49)	8 (10.66)	0.206

SDstandard deviation; BMI: body mass index.

Overweight/obesity was detected in 67.76% of the participants. Regarding habits, alcohol intake was observed in 57.89%; smoking in 11.84%; and physical activity was practiced by 75.65% of the women.

In gynecological and obstetric history, the average age of menarche was 12.73 ± 1.96 years (range: 11 to 19), and the age of first childbirth was 18.42 ± 2.75 years (range: 15 to 23). The median number of pregnancies was 4 (range: 0 to 11), with a median parity of 3 (range: 0 to 9).

In terms of sexual behavior, the average age at first sexual intercourse was 16.54 ± 2.78 years (range: 13 to 22). The reported median monthly sexual frequency was 2 (range: 0 to 5).

At the time of study enrollment, the mean endometrial thickness in women receiving promestriene was 2.75 mm, and at the end, it was 3.19 mm (95% CI: 2.38; 1.24-3.65; $p > 0.05$), compared to those receiving the placebo (2.81 mm and 2.96 mm, respectively) (95% CI: 2.38; 1.85-3.19; $p > 0.05$).

Compared to baseline values, the lipid profile (total cholesterol: 239.41 ± 45.76 mg/dL; low-density lipoprotein cholesterol [LDL-C]: 125.74 ± 28.63 mg/dL; high-density lipoprotein cholesterol [HDL-C]: 47.95 ± 8.62 mg/dL; and triglycerides: 193.86 ± 52.47 mg/dL) showed no significant difference at 12 months in the promestriene group compared to the placebo group (total cholesterol: 245.37 ± 41.89 mg/dL; LDL-C: 128.62 ± 29.54 mg/dL; HDL-C: 48.23 ± 7.59 mg/dL; and triglycerides: 194.78 ± 53.62 mg/dL). The same was observed with fasting blood glucose: 103.54 ± 26.97 mg/dL versus 107.29 ± 28.43 mg/dL ($p > 0.05$) and TSH: 3.45 ± 1.28 mIU/mL versus 3.61 ± 1.49 mIU/mL ($p > 0.05$).

Serum hormone concentrations did not vary significantly within or between groups over the follow-up period ($p > 0.05$) (Table 3). Women treated with promestriene did not experience significant changes in estradiol levels (the mean difference from study initiation to end was 1.39 ± 1.18; $p > 0.05$).

Table 3.
Serum Hormone Concentrations in Women with Breast Cancer and Genitourinary Syndrome of Menopause Undergoing Promestriene Treatment

	Variable	Baseline	1 Month	3 Months	6 Months	9 Months	12 Months
Promestriene	Estradiol (pg/mL)	23.79 ± 8.16	27.68 ± 5.93	29.14 ± 8.23	28.61 ± 7.94	27.65 ± 5.92	25.18 ± 9.34
Placebo		24.85 ± 7.63	25.73 ± 8.41	26.19 ± 7.34	26.19 ± 8.23	25.69 ± 8.12	24.71 ± 8.96
p-Value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Promestriene	FSH (mUI/mL)	74.29 ± 18.53	67.41 ± 15.23	61.39 ± 17.85	64.93 ± 16.38	67.94 ± 15.38	71.32 ± 14.89
Placebo		76.15 ± 19.42	68.53 ± 17.42	64.18 ± 19.23	68.75 ± 12.94	68.79 ± 13.54	75.91 ± 13.68
p-Value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Promestriene	LH (mUI/mL)	29.51 ± 8.43	25.91 ± 4.67	27.68 ± 9.16	28.61 ± 7.34	29.67 ± 8.35	29.87 ± 5.63
Placebo		28.76 ± 8.35	27.63 ± 5.18	25.94 ± 8.93	27.94 ± 8.31	27.58 ± 9.34	28.93 ± 7.94
Valor de *p*		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Promestriene	SHBG (nmol/L)	52.79 ± 13.48	54.38 ± 12.67	56.19 ± 7.68	53.67 ± 9.18	51.92 ± 10.54	53.69 ± 14.72
Placebo		51.68 ± 14.79	52.19 ± 15.34	54.67 ± 9.31	52.94 ± 8.63	50.87 ± 10.69	52.67 ± 13.98
p-Value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Promestriene	Total Testosterone (ng/dL)	141.36 ± 58.97	147.98 ± 46.31	151.69 ± 37.85	137.45 ± 56.92	134.85 ± 43.69	139.72 ± 46.85
Placebo		138.59 ± 47.61	139.71 ± 54.68	143.67 ± 41.59	135.89 ± 54.72	132.97 ± 46.85	137.65 ± 48.19
p-Value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Promestriene	Free Testosterone (pg/mL)	49.38 ± 15.26	51.67 ± 13.92	49.67 ± 15.38	48.37 ± 16.79	52.67 ± 17.34	57.81 ± 19.26
Placebo		51.67 ± 14.82	50.38 ± 12.69	48.91 ± 13.75	46.97 ± 15.38	56.17 ± 13.89	58.32 ± 12.97
p-Value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Promestriene	DHEAS (µg/dL)	0.71 ± 0.29	0.68 ± 0.32	0.79 ± 0.28	0.65 ± 0.23	0.74 ± 0.28	0.76 ± 0.26
Placebo		0.72 ± 0.37	0.76 ± 0.28	0.73 ± 0.31	0.74 ± 0.25	0.75 ± 0.19	0.71 ± 0.23
p-Value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Promestriene	DHT (pg/mL)	67.18 ± 23.95	65.39 ± 18.72	64.91± 23.57	73.21 ± 40.56	71.68 ± 31.59	63.79 ± 18.52
Placebo		71.54 ± 30.26	69.41 ± 20.28	65.78 ± 21.49	75.12 ± 43.89	70.98 ± 31.64	65.28 ± 21.34
p-Value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

In the promestriene group, 67.53% of women, and in the placebo group, 69.33% of women, reported moderate to severe dryness and dyspareunia, respectively ($p > 0.05$); followed by genital itching (burning sensation) (49.35% and 50.66%, respectively; $p > 0.05$). Treatment with promestriene versus placebo reduced clinical symptoms of GSM (dryness and dyspareunia) from the first month of therapy (total intervention effect −0.58 [95% CI: −0.79 to −0.37] and −0.29 [95% CI: −0.38 to −0.17], respectively; $p < 0.001$) (Table 4).

Table 4.
Analysis of the Intervention Effect (Promestriene versus Placebo)

Sign/Symptom	Coefficient (95% CI)	*p*-Value
Decreased vaginal lubrication	−0.43 (−0.71 a −0.08)	0.02
Dyspareunia	−0.29 (−0.38 a −0.17)	<0.001
Mucosal fragility	1.42 (1.25 a 1.73)	<0.001
Vaginal irritation	−0.32 (−0.56 a −0.07)	0.02
Prominent urethral meatus	−0.25 (−0.52 a −0.07)	0.03
Loss of vaginal folds and rugae	1.64 (1.57 a 1.96)	<0.001
Genital itching (burning sensation)	−0.17 (−0.53 a −0.08)	0.003
Vaginal dryness	−0.58 (−0.79 a −0.37)	<0.001
Urinary symptoms	– 0.28 (– 0.37 a – 0.37)	<0.001
Sinusorrhagia	−0.31 (−0.41 a −0.23)	<0.001

In the Vaginal Health Index, vaginal pH showed a progressive, statistically significant decrease from the first month of treatment in the promestriene group, which was maintained throughout the study (Table 5).

Table 5.
Effect of Treatment (Promestriene versus Placebo) on the Vaginal Health Index

Vaginal Health Index	0	1 Month	3 Months	6 Months	9 Months	12 Months
Average Elasticity						
Promestriene	2.14 ± 0.56	3.19 ± 0.62	4.16 ± 1.27	4.29 ± 1.08	4.36 ± 1.27	4.85 ± 1.36
Placebo	2.17 ± 0.49	2.84 ± 0.51	3.16 ± 1.42	3.08 ± 1.07	3.15 ± 1.42	3.27 ± 1.58
p-Value	>0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Secretion Flow and Consistency						
Promestriene	1.82 ± 0.64	3.12 ± 0.75	4.13 ± 0.92	4.39 ± 0.87	4.53 ± 0.92	4.78 ± 0.91
Placebo	1.85 ± 0.59	2.57 ± 0.79	3.01 ± 0.65	3.07 ± 0.79	3.09 ± 0.74	3.02 ± 0.58
p-Value	>0.05	<0.05	<0.05	<0.05	<0.05	<0.05
pH						
Promestriene	6.39 ± 0.85	4.61 ± 0.92	4.37 ± 0.48	4.21 ± 0.59	4.18 ± 0.74	3.72 ± 0.79
Placebo	6.43 ± 0.91	5.97 ± 0.98	4.98 ± 0.57	4.87 ± 1.34	4.97 ± 0.83	4.63 ± 0.92
p-Value	>0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Epithelial Mucosa						
Promestriene	2.19 ± 0.79	3.47 ± 0.65	4.15 ± 0.82	4.27 ± 0.79	4.35 ± 0.91	4.58 ± 0.83
Placebo	2.34 ± 0.73	2.78 ± 0.91	2.91 ± 0.83	3.05 ± 0.94	3.17 ± 0.68	3.24 ± 0.71
p-Value	>0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Hydration						
Promestriene	2.15 ± 0.83	3.29 ± 0.92	3.85 ± 0.67	4.24 ± 0.83	4.58 ± 0.82	4.79 ± 0.78
Placebo	2.18 ± 0.94	2.37 ± 0.89	2.91 ± 0.83	3.08 ± 0.82	3.41 ± 0.95	3.57 ± 0.91
p-Value	>0.05	<0.05	<0.05	<0.05	<0.05	<0.05

A significant improvement was observed in all six domains of the FSFI after three months of using promestriene compared to the placebo ($p = 0.0018$). The final score in the promestriene group was 26.92 ± 7.89 versus 24.38 ± 8.13 in the placebo group ($p < 0.015$) (Table 6).

Table 6.
Female Sexual Function Index in Women with Breast Cancer and Treatment (Promestriene versus Placebo)

Domain	Promestriene Group		*p*-Value	Placebo Group		*p*-Value
	Baseline	Final		Baseline	Final	
Desire	2.75 ± 1.04	3.81 ± 0.97	0.001	2.69 ± 1.07	3.41 ± 1.52	0.401
Arousal	2.93 ± 1.52	4.38 ± 1.25	0.001	2.94 ± 1.35	4.12 ± 1.09	0.017
Lubrication	2.87 ± 1.36	4.61 ± 1.37	0.001	2.89 ± 1.03	3.89 ± 1.27	0.409
Orgasm	3.24 ± 1.59	4.35 ± 1.09	0.001	3.16 ± 1.25	3.91 ± 1.05	0.403
Satisfacción	3.15 ± 1.82	4.85 ± 1.36	0.001	3.25 ± 1.37	4.16 ± 1.45	0.457
Pain	4.18 ± 2.39	4.92 ± 1.85	0.032	4.31 ± 1.79	4.89 ± 1.75	0.498
Total	19.12 ± 10.26	26.92 ± 7.89	0.001	19.24 ± 7.86	24.38 ± 8.13	0.182

Sexual intercourse increased in the promestriene group starting from the third month of follow-up, with a reported median of 3 (range 1 to 5) times per month. At the end of the study, it was 5 (range 2 to 7) in the promestriene group compared to 3 in the placebo group ($p < 0.05$).

Regarding adverse effects, 4 were detected in the total population (increased vaginal discharge, burning sensation, itching, and vulvovaginal inflammation), all of which were classified as 'non-serious' and did not require discontinuation of the intervention. Most women in the promestriene group experienced an increase in vaginal discharge (92.2%) compared to 17.33% in the placebo group ($p < 0.05$). The rate of burning sensation for the promestriene and placebo groups was 11.68% and 10.66%, respectively ($p > 0.05$) in the first month of treatment; vulvovaginal itching was observed in 7.79% and 6.66%, respectively ($p > 0.05$), and vaginal bleeding was not present in either group.

After three months of follow-up, treatment satisfaction reached 57.14% in the promestriene group compared to 18.66% in the placebo group ($p < 0.001$). At twelve months, satisfaction was 88.31% and 38.66%, respectively ($p < 0.001$).

Discussion

The results of this clinical trial reveal positive scientific evidence on the efficacy and

safety of vaginal promestriene in women with triple-negative breast cancer who experience vulvovaginal symptoms and signs associated with GSM. Treatment with promestriene was found to reduce vaginal dryness and dyspareunia from the first month of therapy, with these effects maintained throughout the follow-up period.

After three months of therapy, vaginal application of promestriene reversed most vulvovaginal symptoms and signs associated with the local hypoestrogenism characteristic of GSM. By improving vaginal dryness and dyspareunia, a positive impact on participants' sexual function was observed. In the Vaginal Health Index variables, a progressive increase in score (statistically significant) was detected from the first month of treatment in the promestriene group, maintained until the end of the study. Four adverse effects were detected in the total population (increased vaginal discharge, burning sensation, itching, and vulvovaginal inflammation), which were well tolerated and did not necessitate discontinuation of therapy.

The findings of this study are consistent with those reported by Espitia de La Hoz (20) in a study of 92 women over the age of 40, treated for HER2/neu-positive breast cancer with GSM symptoms, residing in Armenia (Colombia). At the end of the study, the author found no statistically significant differences in serum estradiol concentrations between the promestriene group (33.16 ± 7.53 pg/mL) and the placebo group (30.75 ± 6.93 pg/mL).

In the Latin American context, a study conducted in São Paulo, Brazil, by Santos et al. (27) on 51 postmenopausal women with GSM symptoms found that the efficacy of promestriene was greater than that of oxytocin ($p < 0.05$). Similarly, these results align with those reported in Oporto, Portugal, by Santos and Clissold (28), who documented that promestriene effectively reverses atrophic changes caused by estrogen deficiency in women with natural or surgical menopause. Due to its lack of systemic activity, promestriene is a good option for women requiring local estrogens, including those who are survivors of or at risk for breast cancer.

In a review by Del Pup et al. (19), the authors highlight nearly 40 years of vaginal use of promestriene across 34 countries and millions of prescriptions. They noted its efficacy in relieving vaginal atrophy and, regarding safety, stated that it is a product without systemic estrogenic effects. Therefore, they consider it a first-line option for cancer patients, due to its negligible or minimal systemic absorption.

In 2023, Fernandes et al. (29) compared the efficacy of carbon dioxide laser, radiofrequency, and promestriene in treating GSM in women receiving adjuvant therapy for breast cancer, analyzing clinical and histological findings of the vulvar vestibule. Seventy women completed the treatment. After the intervention, all histological parameters normalized. Significant symptom improvements were observed, as all three groups showed reductions in visual analog scale scores, with no statistically significant differences between them. High satisfaction levels were reported after treatment across all groups. No damage to the histological structure of the vulvar vestibule or clinically relevant adverse events were identified post-treatment.

The safety of promestriene in treating postmenopausal atrophic vaginitis was evaluated in Beijing, China, by Sun et al. (30) in 53 women (ages 45 to 75). No adverse effects were observed during treatment. Before treatment, the mean FSH level was 71 ± 3 U/L and estradiol was 41 ± 18 pmol/L. The average endometrial thickness was 2.4 ± 0.9 mm. After treatment, the mean FSH level was 67 ± 22 U/L and estradiol was 43 ± 37 pmol/L, while endometrial thickness was 2.5 ± 1.3 mm, with no statistically significant difference ($p > 0.05$). Therapeutic effect was demonstrated with a vaginal maturation index of 42 ± 15 before and 54 ± 8 after treatment. The atrophic vaginitis score was 3.4 ± 1.7 before and 1.5 ± 1.4 after treatment, and the vaginal health score was 7.8 ± 2.4 before and 12.0 ± 2.4 after treatment, all showing statistically significant differences ($p < 0.01$). This supports that promestriene is safe and effective in treating postmenopausal atrophic vaginitis.

Evidence has shown that promestriene does not reach systemic circulation, is not

converted to estradiol, does not alter serum concentrations of gonadotropins or estradiol, and does not stimulate the endometrium, making it an appropriate and beneficial option for treating vaginal atrophy/GSM when active estrogens are contraindicated, as is the case for patients with estrogen-sensitive cancers (31,32). Other authors have also evaluated the efficacy and safety of promestriene in this patient population (20,33) and concluded that vaginal promestriene is promising for treating the clinical manifestations of GSM. Therefore, it can be considered the first alternative for postmenopausal women with contraindications for traditional estrogen therapy.

Although the use of drugs like promestriene has proven not to increase serum estradiol levels (19,30,34,35), caution is warranted in prescribing, especially when higher doses are needed. It is recommended to use it rationally in women with breast cancer. A comparative study of the various available vaginal estrogens at different doses may help establish more specific treatment protocols to address vulvovaginal symptoms and signs associated with GSM in women with breast cancer.

Support provided to women undergoing breast cancer treatment should not only focus on the progression of their clinical condition but should also include a person-centered, holistic approach that considers the adverse effects of oncological therapy to prevent impacts on quality of life and sexual function. GSM, as a chronic and progressive condition affecting women's quality of life (36), warrants both close and preventive monitoring in women undergoing breast cancer treatment.

The main strengths of this study include the follow-up period and the ability to track all participants to the end of the study, as well as the randomized, triple-blind, placebo-controlled design. Additionally, the tools used, such as the Vaginal Health Index and FSFI, have been validated in various studies and countries worldwide. The primary limitations were the sample size—although 77 participants is not insignificant for this study population—and the limited research and published studies on this molecule regarding such a relevant and complex issue.

Conclusions

The use of intravaginal promestriene is safe and effective for treating the symptoms and signs of GSM in women with triple-negative breast cancer, as it results in minimal fluctuations in serum concentrations of estradiol, androgens, and gonadotropins, with no statistical significance. It also demonstrated sustained improvement in pH, vaginal dryness, dyspareunia, and sexual function, with no adverse effects warranting discontinuation of therapy.

Intravaginal promestriene can be used in women with moderate to severe vaginal dryness/dyspareunia or in those unresponsive to non-hormonal therapy, as it is more effective in this population. Restricted use should be considered in women with estrogen-dependent cancer, which should be monitored under close and thorough supervision.

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Conflict of Interest

The author declares no conflict of interest in relation to this study.

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