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Research Article

Effectiveness, Safety and Tolerability of Intravaginal Prasterone for the Treatment of Genitourinary Syndrome in Postmenopausal Women in Spain: The Estip-Es Study

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Abstract

Genitourinary syndrome of menopause has a significant and negative impact on quality of life. The objective of this study was to evaluate the effectiveness, safety, and tolerability of prasterone for the treatment of genitourinary syndrome in clinical practice in Spain. We performed a prospective, observational, and multicenter study in adult postmenopausal women. Female Sexual Function Index (FSFI) questionnaire and Visual Analog Scale (VAS) were administrated and level of satisfaction was analyzed at baseline and after 30±7 days. The study included 184 postmenopausal women with genitourinary syndrome. The FSFI increased from 15.7±6.3 to 19.9±5.38 (P<0.01), with significant improvements in all items. The level of satisfaction with intravaginal prasterone was high (completely/moderately satisfied, 63.5%). Only 6.5% of patients reported side effects. Treatment with intravaginal prasterone in postmenopausal women with genitourinary syndrome, was associated with significant improvements in sexual function and urinary symptoms, and reduction in genital dryness, burning, irritation and pain. The drug was well tolerated, with high satisfaction rates after one month of treatment, suggesting that intravaginal prasterone should be considered a first-line therapy for the management of this population in clinical practice.

Keywords: Dehydroepiandrosterone; Genitourinary Syndrome; Menopause; Prasterone

Abbreviations: VAS: Visual Analog Scale; FSFI: Female Sexual Function Index; DHEA: Dehydroepiandrosterone; n: Absolute Frequency; %: Relative Frequency

Introduction

Menopause is a normal mid-life event associated with a decrease in ovarian synthesis of estrogen, progesterone and dehydroepiandrosterone (DHEA), leading to a group of genital and urinary symptoms known as genitourinary syndrome of menopause, which is usually chronic and progressive without treatment and has a significant and negative impact on quality of life. This syndrome affects up to 50% of menopausal women and is characterized by genital symptoms (dryness, burning, and irritation), sexual symptoms (lack of lubrication, discomfort, pain, and impaired function) and urinary tract involvement (urgent urination, dysuria, and recurrent urinary tract infection). Women may experience some or all of these signs and symptoms [1-5] Despite the high frequency of genitourinary syndrome of menopause, many women do not seek medical advice because of embarrassment, believe that the symptoms are normal with ageing, or think that no effective or safe treatments are available [6].

The first goal in genitourinary syndrome is the improvement in and relief of symptoms. The many currently available options include numerous adjunctive therapies such as moisturizers, lubricants, and laser therapy, as well as systemic hormonal therapies, low-dose vaginal estrogen therapies, and selective estrogen receptor modulators, such as ospemifene [7]. Despite

these treatments, many women remain unsatisfied for a variety of reasons [8-10]. Furthermore, while low-dose vaginal estrogen preparations effectively alleviate the symptoms of genitourinary syndrome, potential systemic absorption of vaginal estrogens may increase systemic exposure to estradiol. Additionally, declining androgen levels cannot be restored by vaginal estrogens [11,12] of note, early discontinuation of these therapies is common [10].

Prasterone (DHEA) is an endogenous precursor steroid hormone that is metabolized into both androgens and estrogens. It has been approved as an intravaginal insert for the treatment of moderate to severe dyspareunia caused by vulvovaginal atrophy secondary to menopause. Additionally, it has proven effective for the treatment of other types of sexual dysfunction that are secondary to menopause [13-15]. As a result, prasterone not only minimizes the potential risks associated with estrogen-based therapy, but also activates the vaginal estrogen and androgen receptors that are necessary for the normal functioning of the vagina (intracrinology), without inducing systemic side effects [15]. However, although data from clinical trials show that prasterone can improve some symptoms of vulvar and vaginal atrophy compared with placebo, data from real-life patients are lacking [16-18]. In addition, given potential cultural differences in the perception of genitourinary symptoms and disparities in treatment options between regions, country-specific approaches may be required [19]. Therefore, data on the role of prasterone in the management of patients with genitourinary syndrome and on the level of satisfaction with treatment and discontinuation rates in clinical practice are warranted. The objective of this study was to evaluate the effectiveness, safety, and tolerability of prasterone for the treatment of genitourinary syndrome in clinical practice in Spain. The clinical profile of women with genitourinary syndrome treated with intravaginal prasterone was also analyzed. Furthermore, the impact of genitourinary syndrome on physical status and sexual functioning was examined.

Methods

The population of this prospective, observational, and multicenter study comprised adult postmenopausal women who were routinely seen in medical centers from throughout Spain for genitourinary syndrome and treated with intravaginal prasterone. Patients had to provide written informed consent before being included in the study. The exclusion criteria were as follows: treatment with intravaginal prasterone and starting other treatments for genitourinary syndrome, such as vulvovaginal laser therapy, vulvovaginal radiofrequency, infiltration of platelet-rich plasma injection, infiltration of autologous fat, systemic or local vaginal estrogen therapy, or ospemifene during the study period; previous treatment with therapies for genitourinary syndrome with an expected residual effect, such as vulvovaginal laser therapy in the previous 12 months, vulvovaginal radiofrequency in the previous 12 months, or infiltrations of hyaluronic acid, platelet-rich plasma, or autologous fat in the previous 6 months; treatment with intravaginal prasterone and starting therapy with options that may worsen genitourinary syndrome, such as radiotherapy and chemotherapy in the previous months; treatment with selective estrogen receptor modulators or aromatase inhibitors, antihistamine drugs, antidepressants, oral retinoids, or oral contraceptives in the previous months; any contraindication for the use of intravaginal prasterone, such as allergy, breastfeeding or pregnancy; any psychological or physical condition that the investigator considered relevant for exclusion. Patients were recruited from August 2019 to December 2019.

The study followed the principles of the Declaration of Helsinki and was approved by the local participating Institutional Review Boards. In order to evaluate the impact of intravaginal prasterone on genitourinary syndrome after 30±7 days of treatment, the short Female Sexual Function Index (FSFI) and the visual analog scale (VAS) were administered, and the level of satisfaction was analyzed. The FSFI is a 19-item multidimensional self-reported instrument developed to assess female sexual function. For this study, a validated short version with 7 items was used. Each item ranged from never (score 0) to always (score 5). Higher scores indicate better sexual function. A score between 0 and 20 suggests that sexual dysfunction may be present. A difference of more than 3 points between the baseline and study end questionnaires was interpreted as considerable clinical improvement, a difference between 2 and 3 points as moderate clinical improvement, and a difference of 1 point as mild clinical improvement [20]. A 19-item VAS was administered to assess the impact of intravaginal prasterone on genitourinary syndrome. Each item ranged from 0 (absence of discomfort) to 10 (extreme discomfort). As a result, there was an inverse relationship between the score and the improvement in symptoms. Thus, higher scores indicate more discomfort. A difference of more than 3 points between the baseline and study end questionnaires was interpreted as considerable clinical improvement, a difference of 2 to 3 points as moderate clinical improvement, a difference of 1 point as mild clinical improvement, and a difference <1 point as absence of clinical improvement. The level of satisfaction with intravaginal prasterone at 30-45 days was determined using a Likert type scale to rate these answers from 1 to 6, where 1 was completely satisfied and 6 completely unsatisfied. In addition, the incidence and severity of side effects during the study period were also assessed. At baseline, biodemographic data (age, weight, height, being in a stable relationship), medical history (smoking, diabetes, thyroid disease), obstetric/gynecologic history (breast cancer, time since menopause, vaginal birth, instrumental birth, cesarean, episiotomy), and baseline treatments (vaginal hormonal therapy, vaginal moisturizer/lubricants, oral contraceptive, antidepressant treatment, antihistamine drugs,

anti-estrogen therapy, hormone replacement therapy, retinoids, chemotherapy, radiotherapy) were recorded. In addition, the FSFI and VAS questionnaires were completed by the patients. A gynecological examination was performed during a routine visit to confirm the presence of genitourinary syndrome, including the determination of vaginal pH and the level of tropism in routine cytology, if necessary. The follow-up visit was at 30±7 days after inclusion. The patient's medical history, obstetric/gynecologic history, and treatments were re-evaluated. The FSFI and the VAS questionnaires were completed by the patients. The presence of side effects and satisfaction with treatment during the study period were also evaluated.

Statistical Analysis

Categorical variables were expressed as absolute frequency (n) and relative frequency (%). Continuous variables were expressed as mean and standard deviation. Categorical variables were compared using the chi-square test or the Fisher exact test when appropriate. When two means were compared, the t test or the Mann-Whitney test was used, as applicable. The changes in the scores of the FSFI and VAS questionnaires during follow-up were evaluated in the overall study population and in the subgroup of patients on vaginal moisturizer/lubricants or on vaginal hormonal therapy. Missing data or lost values were not imputed to avoid information bias. Missing data for important variables were controlled for using filters when collecting data from the case report form. Statistical significance was set at P<0.05. Data were analyzed using the statistical package SPSS (v24.0 or higher).

Results

The study population comprised 184 postmenopausal women with genitourinary syndrome treated with intravaginal prasterone at various centers throughout Spain. Mean age was 57.98±6.06 years, mean time since menopause was 7.56±6.23 years, 6.1% were smokers, and 6.1% had diabetes. In addition, 56.1% had had at least one previous delivery, 65.2% had had an episiotomy, and 21.6% had had a cesarean delivery. With regard to treatment, 42.9% of patients were taking vaginal hormonal therapy and 32.1% vaginal moisturizer/lubricants. Except for less frequent use of vaginal hormonal therapy among patients taking vaginal moisturizer/lubricants (27.1% vs 42.9%; P=0.02), no significant differences were observed in the baseline clinical characteristics of this subgroup of patients compared with the overall study population. The FSFI was lower in the subgroup of patients on vaginal hormonal therapy (13.63±5.77 vs 15.72±6.33; P=0.01), as was the proportion of patients taking oral contraceptives (8.3% vs 24.2%; P=0.02) and antihistamine drugs (8.3% vs 21.2%; P=0.02). In addition, a trend towards reduced use of vaginal moisturizer/lubricants (20.3% vs 32.1%; P=0.05) compared with the overall study population was also observed for this group, with no other significant differences between the groups (Supplementary Table 1). Table 1 shows changes in FSFI during the study period in the overall study population and in patients on vaginal moisturizer/lubricants and vaginal hormonal therapy. In the overall study population, the FSFI increased from 15.7±6.3 to 19.9±5.38 (mean difference, 4.2; P<0.01), leading to a marked improvement, which was observed for all items, albeit with variable intensity. In the subgroup of patients on vaginal moisturizer/lubricants, the FSFI rose from 17.55±6.89 to 21.52±6.09 (mean difference, 3.97; P<0.01), and in the subgroup of patients receiving vaginal hormonal therapy, the FSFI rose from 13.63±5.77 to 19.70±4.40 (mean difference 6.07; P<0.01). Table 2 shows changes in the VAS score during the study period in the overall study population and in patients on vaginal moisturizer/lubricants and vaginal hormonal therapy.

Table 1: Female Sexual Function Index at baseline and after treatment with progesterone in the overall study population and in patients on vaginal moisturizer/lubricants and vaginal hormonal therapy.

	Overall Study Population (n=184)			Patients on Vaginal Moisturizer/ Lubricants (n=59)			Patients on Vaginal Hormonal Therapy (n=79)		
	Baseline	After Treatment with progesterone	P	Baseline	After Treatment with progesterone	P	Baseline	After Treatment with progesterone	P
Desire for or Interest in Sexual Activity	1.78±0.99	2.49±0.92	<0.01	2.06±1.15	2.76±0.97	<0.01	1.73±1.01	2.51±0.83	<0.01
Unhappy with low Interest in Sexual Activity	2.34±1.22	2.70±1.25	<0.01	2.60±1.49	2.91±1.55	<0.01	1.96±1.28	2.96±0.99	<0.01
Take a Long Time to Become Aroused	2.24±1.24	2.98±0.94	<0.01	2.30±1.23	3.30±0.92	<0.01	1.81±1.14	2.63±1.03	<0.01
Feel Indifferent Regarding sex	2.64±1.11	3.20±1.00	<0.01	2.94±1.03	3.48±0.94	<0.01	2.21±0.85	3.04±0.84	<0.01
Low Sexual Desire	2.29±1.15	3.03±1.03	<0.01	2.43±1.17	3.07±1.02	<0.01	1.96±0.82	3.04±0.84	<0.01
Disappointed with My Interest in Sex	2.52±1.49	3.05±1.26	<0.01	2.81±1.57	3.13±1.44	<0.01	2.35±1.47	3.26±1.06	<0.01

Reach Orgasm easily	1.92±1.19	2.42±1.12	<0.01	2.40±1.42	2.87±1.36	<0.01	1.62±0.80	2.26±0.58	<0.01
Female Sexual Function Index	15.7±6.3	19.9±5.38	<0.01	17.55±6.89	21.52±6.09	<0.01	13.63±5.77	19.70±4.40	<0.01

Table 2: Satisfaction, side effects, and adherence during treatment with prasterone in the overall study population.

	Overall Study Population (n=184)			Patients on Vaginal Moisturizer/ Lubricants (n=59)			Patients on Vaginal Hormonal Therapy (n=79)		
	Baseline	After Treatment with progesterone	P	Baseline	After Treatment with progesterone	P	Baseline	After Treatment with progesterone	P
Dryness of the vagina	8.07±1.88	4.73±2.41	<0.01	8.19±2.42	4.83±2.71	<0.01	7.95±1.66	5.11±1.83	<0.01
Dryness of the external genitalia	7.20±2.23	4.16±2.32	<0.01	6.68±2.39	4.17±2.36	<0.01	7.22±2.31	4.29±2.00	<0.01
Dyspareunia of the vagina	8.23±2.32	5.09±2.65	<0.01	7.74±2.64	5.94±2.68	<0.01	8.19±2.43	5.03±2.49	<0.01
Dyspareunia during penetration	7.95±2.14	5.60±2.73	<0.01	8.07±2.29	6.22±2.38	<0.01	7.69±2.12	5.95±2.88	<0.01
Discomfort during exercise	3.80±3.61	1.71±2.21	<0.01	3.24±3.45	1.69±2.27	<0.01	4.46±3.74	2.03±2.22	<0.01
Vaginal bleeding during sexual intercourse	1.43±2.25	0.74±1.56	<0.01	0.53±1.12	0.12±0.44	0.001	2.12±2.79	1.26±2.04	<0.01
Vaginal bleeding during sexual contact	1.17±2.04	0.56±1.30	<0.01	0.51±1.15	0.12±0.44	0.002	1.45±2.61	0.88±1.72	<0.01
Burning or irritation of the vagina	5.41±3.54	2.79±3.00	<0.01	5.04±3.38	2.48±2.97	<0.01	4.72±3.58	2.79±2.97	<0.01
Burning or irritation of the external genitalia	5.02±3.43	2.63±2.79	<0.01	3.97±3.31	1.58±2.09	<0.01	5.59±3.50	3.07±2.98	<0.01
Itching of the vagina	3.40±3.23	1.36±1.90	<0.01	2.64±3.31	1.23±2.03	<0.01	2.97±3.55	1.52±2.05	<0.01
Itching of the external genitalia	3.05±3.47	1.65±2.16	<0.01	2.22±2.94	1.04±1.60	<0.01	3.09±3.75	1.73±2.25	<0.01
Vaginal discharge	2.31±2.73	2.98±2.99	<0.01	1.76±2.35	2.50±2.60	<0.01	2.08±1.99	3.13±3.12	<0.01
Urinary incontinence	2.72±3.11	1.78±2.65	<0.01	2.08±3.00	1.00±1.84	<0.01	3.30±3.40	2.23±3.00	<0.01
Urinary urgency	2.89±2.97	2.09±2.56	<0.01	1.95±2.55	1.62±2.49	<0.01	3.86±3.24	2.42±2.37	<0.01
Urinary frequency	3.73±2.72	2.91±2.70	<0.01	3.41±3.22	2.73±3.30	<0.01	4.59±2.55	3.67±2.43	<0.01
Urinary difficulties	1.56±2.40	1.09±1.91	<0.01	0.85±1.98	1.00±2.08	0.002	2.01±2.75	1.32±1.99	<0.01
Recurrent urinary tract infection	2.29±3.29	1.11±2.32	<0.01	2.20±3.57	1.31±2.58	<0.01	2.80±3.53	1.65±2.82	<0.01
Urinary tract infection associated with sexual intercourse	1.55±2.99	0.76±1.97	<0.01	1.75±2.97	1.28±2.55	<0.01	2.36±3.51	1.33±2.70	<0.01
Abdominal pain	2.42±2.98	1.47±2.21	<0.01	1.63±2.70	1.08±1.90	<0.01	2.47±2.79	1.67±2.38	<0.01

In the overall study population, the only item that worsened was vaginal discharge, in which the score increased slightly but significantly (2.31±2.73 to 2.98±2.99, P<0.01). The score for the remaining 18 items improved significantly, with different levels of intensity, depending on the item. Among patients on vaginal moisturizer/lubricants, a significant decrease (improvement) was observed in 17 items during the study period, with different levels of intensity, depending on the item. The only items in which the score increased (worsened) were vaginal discharge and urinary difficulties (1.76±2.35 to 2.50±2.60 [P<0.01] and 0.85±1.98 to 1.00±2.08 [P=0.002], respectively). Among patients on vaginal hormonal therapy, scores decreased significantly for all items, with different levels of intensity depending on the item, except for vaginal discharge, in which there was a significant increase (worsening), from 2.08±1.99 to 3.13±3.12 (P<0.01). The level of satisfaction with intravaginal prasterone was high in the overall study population (completely/moderately satisfied, 63.5%; completely/moderately/slightly satisfied, 89.5%), as well as in the subgroup of patients on vaginal moisturizer/lubricants (54.5% and 90.9%, respectively) and in the subgroup of patients on vaginal hormonal therapy (62.9% and 87.0%, respectively). Satisfaction was higher in the subgroup of patients on vaginal moisturizer/lubricants than in the overall

study population (P=0.032). In addition, although intravaginal prasterone was safe (only 6.5% of patients reported side effects during follow-up), adverse events were more common in the subgroup of patients on vaginal moisturizer/lubricants (16.9% vs 6.5%; P=0.02). Similarly, adherence to treatment was high during follow-up, as 78.4% of patients remained on prasterone at the end of the study, with no significant differences between the groups. Side effects were the main reason for withdrawal (Supplementary Table 2 & Figure 1).

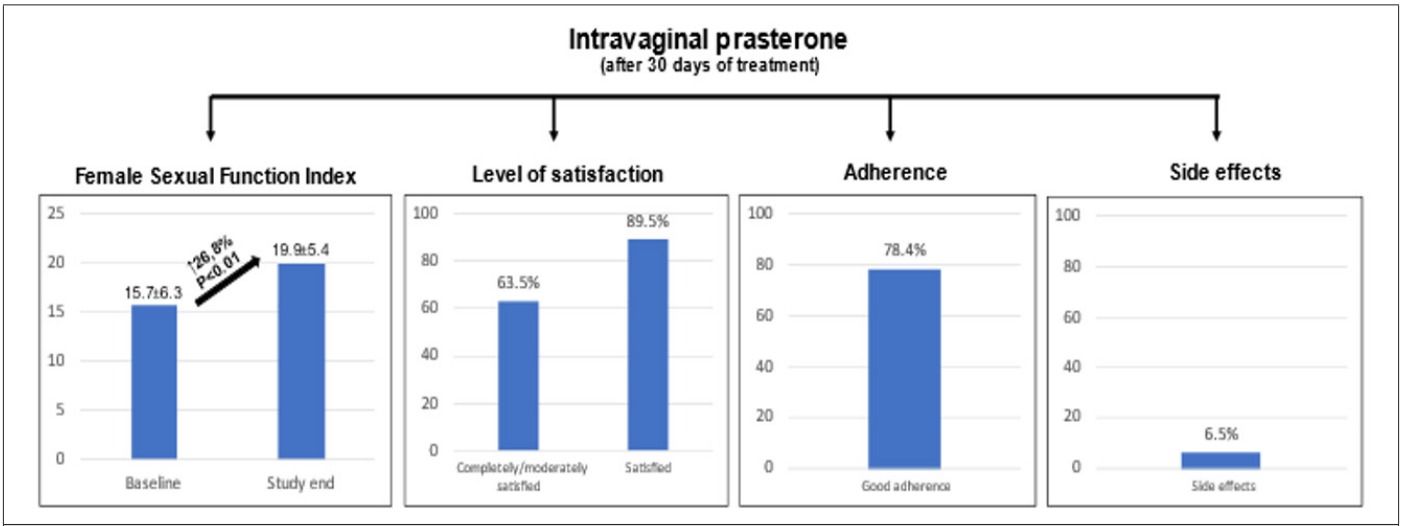

Figure 1: Satisfaction, side effects, and adherence during treatment with prasterone in the overall study population.

Discussion

This study of a wide sample of postmenopausal women with genitourinary syndrome showed that in clinical practice, treatment with intravaginal prasterone was associated with significant improvements in sexual function and in most symptoms of genitourinary syndrome after only one month of treatment. In addition, the tolerability and safety profile was excellent. Our study population comprised almost 200 postmenopausal women with genitourinary syndrome from medical centers throughout Spain. Mean age was 58 years, mean time since menopause was 7.5 years, 43% of patients were taking vaginal hormonal therapy, and 32% vaginal moisturizer/lubricants at baseline. In addition, the clinical profile of patients did not differ greatly according to whether they were using vaginal hormonal therapy or vaginal moisturizer/lubricants. MUMENESP, a cross-sectional study of Spanish postmenopausal women seen in a routine clinical setting, showed that approximately 54% of patients had vaginal dryness, 55% dyspareunia, and one third were taking systemic hormonal therapy or phytotherapy at some time in their lives [21]. As a result, the clinical profile of the patients included in our study may be representative of postmenopausal women seen in clinical practice in Spain.

Genitourinary syndrome of menopause is a progressive condition that has a negative impact on women's quality of life [22]. Of note, despite current treatments, many symptomatic women are disappointed with the available therapeutic options [23]. The management of genitourinary syndrome should be individualized and should consider not only formulation, route of administration, and timing of therapy, but also efficacy and safety [12]. Various clinical trials have shown that, compared with placebo, intravaginal prasterone is effective in the treatment of dyspareunia secondary to vulvovaginal atrophy in women with genitourinary syndrome of menopause and may be also effective among women with other symptoms of genitourinary syndrome, such as decreased lubrication, decreased sexual desire, decreased sexual satisfaction, impaired ability to achieve orgasm and pain [17,22]. Thus, in a 12-week placebo-controlled clinical trial analyzing intravaginal administration of DHEA, pain during sexual activity decreased by 1.42 severity score units from baseline, and moderate to severe vaginal dryness improved by 1.44 severity score units. In addition, gynecological evaluation revealed that vaginal secretions, epithelial integrity, and epithelial surface thickness had also improved, with no increase in serum steroid levels [22].

A systematic review of 14 clinical trials assessing the efficacy of vaginal DHEA in women with vulvovaginal atrophy showed that sexual dysfunction improved with treatment regardless of the level of dyspareunia at baseline [23]. Our data not only confirmed that the results of clinical trials can be translated into clinical practice in Spain, but also provided valuable information about the use of prasterone in real-life conditions after one month of treatment [22]. Overall, there was an increase of 4 points in the FSFI, which represented an intense improvement according to the protocol. This improvement was recorded for all items of the FSFI, indicating that the positive effects of prasterone were consistent in all aspects of sexual function. In addition, the positive impact of prasterone

was observed not only in the overall study population, but also in the subgroup of patients on vaginal moisturizer/lubricants, and, more intensely, in those women on vaginal hormonal therapy at baseline, suggesting that the double effect of prasterone on both androgens and estrogens may be more comprehensive and potent than local estrogen-based therapy. However, this possibility should be analyzed in a specific study. Clinical trials have also shown that treatment with prasterone improves many symptoms of genitourinary syndrome of menopause, such as vaginal dryness and vulvovag¬inal irritation or itching [13,14]. Our study showed that in clinical practice, intravaginal prasterone improved the vast majority of symptoms associated with genitourinary syndrome, such as vaginal dryness or dryness of the external genital, burning, itching, dyspareunia, vaginal bleeding, and urinary symptoms. This also occurred in patients on vaginal moisturizer/lubricants or vaginal hormonal therapy at baseline. With regard to side effects, various clinical trials have shown that the most common adverse event was discharge at the application site, with less than 1% of patients discontinuing treatment owing to this side effect [24-26]. Other adverse events reported in clinical trials with prasterone include urinary tract infections, weight fluctuations, vaginal discharge, and sinusitis [13,14, 21-24]. Our study showed that in clinical practice, treatment with intravaginal prasterone was safe, with only 6.5% of patients exhibiting side effects during follow-up (i.e.blisters on the face, hair loss, constipation, leukorrhea, and dizziness). In addition, no systemic effects are expected with DHEA therapy, as intravaginal prasterone is used locally, and the drug does not pass to the bloodstream [13,14]. In our study, the favorable safety and efficacy profile led to a high adherence rate in clinical practice, thus confirming the results of clinical trials [21].

In contrast to other therapies that are underutilized, mainly owing to concerns about potential side effects or low efficacy [15] our study showed that in real-life patients, the use of intravaginal prasterone was associated with high levels of satisfaction, suggesting that it can be considered a first-line choice for the treatment of genitourinary syndrome of menopause in clinical practice. This study is subject to a series of limitations. First, the lack of control group reduced the possibility of reaching definitive conclusions about the efficacy of intravaginal prasterone in clinical practice. However, the prospective design of the study, as well as the meticulous data collection, may reduce this potential bias. In addition, our data were consistent with those obtained from clinical trials. As our study was performed in Spain and the therapeutic approach of genitourinary syndrome may be country-specific, our results can only be extended to those populations with a similar clinical profile, cultural breakdown, and health care system. In conclusion, in postmenopausal women with genitourinary syndrome treated in Spain, intravaginal prasterone was associated with significant improvements in sexual and urinary symptoms, as well as with reduced genital dryness, burning, irritation, and pain. Furthermore, the drug was well tolerated, with high rates of satisfaction, after only one month of treatment. Therefore, intravaginal prasterone is an effective and safe alternative and should be considered a first-line therapeutic choice for the management of postmenopausal women with genitourinary syndrome in clinical practice.

Contributors

All authors contributed extensively to the work presented in this paper. All authors have contributed significantly to the conception, design, or acquisition of data, or analysis and interpretation of data. All authors have participated in in drafting, reviewing and/or revising the manuscript and have approved its submission.

Competing Interest

Authors declare no conflict of interest.

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