Intravaginal DHEA: A New Alternative for Genitourinary Syndrome of Menopause

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ABSTRACT

Introduction: Menopause, a natural stage in a woman's life, causes hormonal changes that can affect health, particularly the genitourinary tract, leading to the genitourinary syndrome of menopause (GSM). This syndrome usually presents genital and urinary symptoms and sexual dysfunction. Despite its high prevalence, many women do not seek appropriate treatment due to a lack of information or the stigma associated with these symptoms. However, therapeutic options such as intravaginal dehydroepiandrosterone (DHEA) or prasterone (prasterone 6.5 mg) have proven effective in treating GSM symptoms.

State of the Art: DHEA is locally converted into androgens and estrogens in the vaginal mucosa through intracrinology, improving vaginal health and sexual function. In clinical studies, intravaginal DHEA has been shown to reduce dyspareunia, improve vaginal pH, lubrication, and mucosal integrity. The benefits of intravaginal DHEA were comparable to or even greater than those of other treatments, such as vaginal estrogens. The administration of 0.5% DHEA intravaginally in postmenopausal women significantly improved GSM symptoms, reducing dyspareunia and enhancing quality of life. DHEA has also been shown to improve sexual function in women with low levels of dehydroepiandrosterone sulfate (DHEA-S) and testosterone. Regarding safety, it was observed that it does not have significant effects on the endometrium nor does it alter serum steroid levels.

Conclusion: Daily vaginal DHEA is as effective as local estrogens. It has beneficial effects on the anatomy and physiology of vulvovaginal atrophy and all associated symptoms and signs without systemic exposure, according to the intracrinology mechanism. Keywords: menopause, menitourinary syndrome, dehydroepiandrosterone, androgens.

DHEA intravaginal, una nueva alternativa para el síndrome genitourinario de la menopausia

RESUMEN

Introducción: la menopausia, una etapa natural en la vida de las mujeres, provoca cambios hormonales que pueden afectar la salud, especialmente el tracto genitourinario, lo que da lugar al síndrome genitourinario de la menopausia (SGM). Este síndrome se caracteriza por síntomas genitales y urinarios y disfunción sexual. A pesar de su alta prevalencia, muchas mujeres no buscan tratamiento adecuado debido a la falta de información o el estigma asociado a estos síntomas. Sin embargo, opciones terapéuticas como

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Received: 03/1/25 Accepted: 05/28/2025

DOI: http://doi.org/10.51987/rev.hosp.ital.b.aires.v45i3.708

How to cite: Belardo MA, Galarza Taborda ML, Canepa M, Starvaggi AP, Silva Naranjo RF. Intravaginal DHEA: A New Alternative for Genitourinary Syndrome of Menopause. Rev. Hosp. Ital. B.Aires. 2025;45(3):e0000708

ISSN (en línea) 2314-3312

la dehidroepiandrosterona (DHEA) o prasterona intravaginal (prasterona 6,5 mg) han mostrado ser eficaces para tratar los síntomas del SGM.

Estado del arte: la DHEA se convierte localmente en andrógenos y estrógenos en la mucosa vaginal, por intracrinología, lo que mejora la salud vaginal y la función sexual. En estudios clínicos, la DHEA intravaginal ha demostrado reducir la dispareunia, mejorar el pH vaginal, la lubricación y la integridad de la mucosa vaginal. Sus beneficios fueron comparables o incluso superiores a los de otros tratamientos, como los estrógenos vaginales.

La administración de DHEA 0,5% por vía vaginal en mujeres posmenopáusicas mejoró significativamente los síntomas del SGM, con una reducción de la dispareunia y mejoría en la calidad de vida. También se ha demostrado que la DHEA mejora la función sexual en mujeres con bajos niveles de sulfato de deshidroepiandrosterona (DHEA-S) y testosterona. En cuanto a la seguridad, se observó que no tiene efectos significativos en el endometrio ni produce cambios en los niveles séricos de esteroides.

Conclusión: la DHEA vaginal diaria es tan eficaz como los estrógenos locales. Presenta efectos beneficiosos en la anatomía y fisiología de la atrofia vulvovaginal y todos los síntomas y signos asociados, sin exposición sistémica, de acuerdo con el mecanismo de la intracrinología.

Palabras clave: menopausia, síndrome genitourinario, dehidroepiandrosterona, andrógenos.

INTRODUCTION

Menopause is a natural stage in a woman's life that brings about significant hormonal changes, which can affect various aspects of health. One of the most important yet underdiagnosed issues is genitourinary syndrome of menopause (GSM), a set of symptoms resulting from decreased estrogen and androgen levels that primarily affect the female genitourinary tract. This syndrome includes genital symptoms such as vaginal dryness, irritation, vulvar itching, and urinary symptoms such as dysuria, urgency, nocturia, and recurrent urinary tract infections. As a result, sexual function is often impaired, which can significantly reduce the quality of life in postmenopausal women.[1]

It is very common for postmenopausal women not to recognize these vaginal or sexual symptoms or to avoid discussing them with healthcare providers, assuming they are a normal part of aging. This is often due to a lack of information or to stigma associated with menopause. Currently, only about 50% of women with GSM receive treatment, despite the high prevalence of the condition. In recent years, a prevalence of 55.1% has been reported among postmenopausal women.[2] Another study showed a wide range of prevalence, from 13% to 87%, depending on the specific symptom and the population studied.[3] According to the VIVA study, prevalence is 45%, while the VIVA-LATAM study conducted in Latin America reported a prevalence of 57%; the most common symptom was vaginal dryness, and 91% of surveyed women reported that GSM negatively affected their quality of life.

Fortunately, in recent decades, more specific therapeutic options have been developed, such as local hormonal therapies and, more recently, intravaginal dehydroepiandrosterone (DHEA), which has shown benefits in treating symptoms. The United States Food and Drug Administration (FDA) approved the use of prasterone 6.5 mg (DHEA 0.5%) for the treatment of GSM in 2016. Additionally, in 2019, it was also approved by the European Medicines Agency (EMA).[1]

DHEA is a steroid precursor that undergoes conversion into both androgens and estrogens in the vaginal mucosa. That review addresses the use of intravaginal DHEA for GSM, its mechanism of action, efficacy, and safety, highlighting the importance of a comprehensive and personalized approach to managing this condition.[2]

STATE OF THE ART

Mechanism of Action

DHEA is an endogenous prohormone secreted by the adrenal glands (reticular zone). It is a steroid precursor that, in peripheral target tissues, is converted into androgens and estrogens, which are detected by their specific receptors.[4] This conversion is mediated by local enzymatic activity.

The mechanism of action of DHEA is through intracrine conversion, also known as intra-crinology.

In other words, circulating DHEA undergoes conversion to androstenedione, which is subsequently transformed into estradiol or testosterone within peripheral genitourinary tissues, at the intracellular level, where sex hormones bind to estrogen-α/β and androgen-α receptors. The vaginal tissue contains steroidogenic enzymes capable of converting DHEA into estrogens. Estrogen plays a key role in the vaginal wall, influencing the squamous epithelium, lamina propria, and smooth muscle layer. It promotes vasodilation, epithelial maturation, and contributes to tissue elasticity.[5] Complementing the action of estrogen, androgens have been shown to improve vaginal blood flow, muscle contraction, and vulvovaginal lubrication. Furthermore, androgens synthesized from DHEA have been shown

to exert a significant stimulatory effect on collagen production in the vaginal lamina propria.[6]

The main advantage of intravaginal DHEA administration is that the hormone's active metabolites (estrogens and androgens) are generated directly at the site of action, thereby minimizing systemic effects—that is known as intracrine action.

Clinical Efficacy

One of the first studies on intravaginal DHEA evaluated its efficacy at various concentrations –0%, 0.25%, 0.5%, and 1.0%– over 12 weeks. A total of 216 postmenopausal women participated, 114 of whom had dyspareunia as their primary symptom. The study concluded that increasing doses of DHEA reduced the percentage of parabasal cells, increased the percentage of superficial cells, and lowered vaginal pH ($p < 0.0001$ against the placebo). However, the greatest reduction in dyspareunia severity from baseline was observed with the 0.5% DHEA dose ($p < 0.0001$).[7]

In a more recent study, the daily intravaginal administration of 0.5% DHEA was evaluated based on four outcomes: percentage of parabasal cells, percentage of superficial cells, vaginal pH, and moderate to severe pain during sexual activity (dyspareunia).[8] The study included 482 women aged 40 to 80 years, who received either a placebo (157 women) or DHEA (325 women). After daily intravaginal administration of 0.5% DHEA for 12 weeks, compared to baseline, the percentage of parabasal cells decreased by 27.7% relative to placebo ($p < 0.0001$), while the proportion of superficial cells increased by 8.44% compared to placebo ($p < 0.0001$); vaginal pH decreased by 0.6 units ($p < 0.0001$), and pain during sexual activity decreased by 1.42 points in severity from baseline ($p = 0.0002$).

In addition, moderate to severe vaginal dryness, reported by 84% of women at baseline, improved by 1.44 points on the severity scale compared to the baseline, or by 0.27 points relative to placebo ($p = 0.004$). Vaginal secretions, epithelial integrity, thickness, and color also improved by 86% to 121% compared to the placebo effect ($p < 0.0001$). Meanwhile, steroid levels remained within the normal postmenopausal range.

These efficacy data for dyspareunia and vulvovaginal atrophy were confirmed in another study by Labrie et al., an open-label phase III trial lasting 52 weeks, which included 530 postmenopausal women using 0.5% DHEA daily. At the end of the study, a 66.1% reduction in dyspareunia was observed ($p < 0.0001$). In addition, there was a significant improvement in vaginal secretions, vaginal mucosal color, epithelial integrity, and epithelial surface thickness ($p < 0.001$ vs. baseline). The study also assessed whether DHEA could have any effect on the endometrium. Biopsies conducted at screening and week 52 showed that, in all women, the endometrium remained atrophic, confirming the absence of any effect.[9] In 2018, Sauer et al. evaluated the efficacy of vaginal DHEA in women with vulvovaginal atrophy in a review of 14 randomized controlled clinical trials; they concluded that sexual dysfunction improved with treatment regardless of baseline dyspareunia level. They also demonstrated that DHEA outperformed placebo and was at least as effective as vaginal estrogens in relieving symptoms.[10] When comparing the efficacy of intravaginal DHEA, estriol, and promestriene on quality of life, using the simplified 16-item Cervantes Scale (EC 16) before and after treatment, all drugs were shown to increase coital frequency, improve dyspareunia, and reduce the mean EC 16 score, but the decrease in EC 16 score was more significant after DHEA treatment.[11]

Bouchard et al. demonstrated reduced efficacy of intravaginal DHEA when administered twice weekly after 2 weeks of daily treatment. Maximum beneficial changes in vaginal parabasal and superficial cells, and pH were observed during the first 2 weeks of daily treatment, followed by a decline in improvement after switching the dosing frequency to twice weekly. The effect of 0.5% DHEA over placebo was significant at 6 weeks ($p = 0.01$) but lost significance after 4 weeks of reduced dosing frequency.[12]

Safety

Regarding the side effects of vaginal DHEA treatment, vaginal discharge was the most frequently reported in all studies.

In addition, the study by Labrie et al. found abnormal Papanicolaou test results in 11 out of 521 women, with 10 cases of atypical squamous cells of undetermined significance (ASCUS) and one case of low-grade squamous intraepithelial lesions (LSIL)[9].

It should be noted that intravaginal DHEA must be transformed intracellularly into E2 by the enzymes of vaginal tissue. The resulting intracellular estrogens are inactivated by metabolizing enzymes. In fact, they are almost completely inactivated locally into glucuronides and sulfates before being released into the extracellular space and subsequently into the systemic circulation for elimination by the liver and kidneys, which limits the possibility of any E2 reaching the systemic circulation[12]. This was demonstrated in a study where, after 12 weeks of treatment, serum estradiol levels were 19% below normal postmenopausal values, while serum estrone sulfate levels were 5% below normal values. Similarly, serum testosterone levels and their metabolites did not change significantly[10].

In another study, sex steroid levels were evaluated after 12 months of treatment in 435 women[13], concluding that all serum steroids remained within normal ranges without significant differences throughout treatment. Values in the DHEA-treated group were as follows: E1 decreased by 3.4%, E2 decreased by 9.1%, and E1 sulfate increased by 1.8% compared to normal postmenopausal values. Serum DHEA values after treatment remained within the limits for postmenopausal women (approximately 1950 pg/mL). Mean serum testosterone values at 52 weeks were 189 ± 4.79 pg/mL, a 17.4% change from baseline.

Regarding endometrial safety, it was assessed in 722 women using intravaginal DHEA for between 12 and 52

weeks; sufficient material for histological evaluation was obtained from 668 samples. In 668 women, an atrophic or inactive endometrium was observed[14]. The absence of DHEA effects on the endometrium, even in the presence of circulating serum DHEA levels, is explained by the lack of enzymes (especially aromatase) capable of converting DHEA into estrogens in the human endometrium.

Patients with a History of Breast Cancer

One concern when prescribing local hormonal preparations is for patients with a personal history of breast cancer.

Two trials have evaluated DHEA as a treatment for MS in breast cancer patients receiving treatment with aromatase inhibitors (AIs) and tamoxifen. A prospective, open-label pilot study included 10 women with breast cancer treated with AIs, who received DHEA as a vaginal suppository every night for the first month and a suppository every other night for the remaining five months. Mean serum estradiol remained between 3.4 pg/mL and 4.3 pg/mL (p=0.9136) after 6 months of follow-up15.

In a randomized controlled trial, 464 breast and gynecologic cancer survivors with SGM received vaginal DHEA 3.25 mg, 6.5 mg, or vaginal moisturizer for 12 weeks. All three arms showed improvement in vaginal symptoms at 12 weeks. Additionally, women using 6.5 mg of DHEA reported significantly better sexual health. 16 Circulating levels of dehydroepiandrosterone sulfate (DHEA-S) and testosterone increased significantly in women receiving vaginal DHEA in a dose-dependent manner compared with those receiving vaginal moisturizer. Estradiol increased significantly in those using 6.5 mg/day of DHEA but not in those using 3.25 mg/day, and did not increase in patients receiving anastrozole. Estradiol and estrone concentrations were not altered in women taking AI and were not significantly different from concentrations with vaginal moisturizer use[17].

Although the use of vaginal DHEA in women with breast cancer is not contraindicated, caution is advised as DHEA is a metabolite of oestrogen, even though oestradiol and testosterone levels remain within the postmenopausal range.

Other uses of vaginal DHEA

There is evidence supporting that low DHEA-S levels negatively correlate with sexual function in premenopausal and postmenopausal women to a greater extent than testosterone levels. Low serum DHEA-S has also been associated with increased sexual dysfunction during the menopausal transition. A 52-week open-label trial of daily vaginal DHEA use revealed significant improvements in all domains of sexual function studied, including desire, arousal, lubrication, orgasm, pain, and satisfaction ($p < 0.0001$ for all parameters). This could be explained by the fact that studies conducted on rats have shown that DHEA increases the number and surface area of nerve fibres in the vagina through its intravaginal conversion to androgens.[19] It has also been suggested that androgens influence the muscle tone of the erectile tissue of the clitoris, while contributing to genital arousal and vaginal lubrication. Regarding other uses of vaginal DHEA, one study evaluated the impact of vaginal DHEA administration in postmenopausal women with overactive bladder syndrome using incontinence questionnaires (ICQ-OAB/ICQ-IU). Women reported an improvement in daily urinary leakage, but the number of leaks did not improve statistically significantly [28.6% vs. 14.3%, $p < 0.16$].

Another prospective observational study included 34 women with MS and moderate stress urinary incontinence (SUI). Participants received 6.5 mg/day of vaginal DHEA for 12 weeks, and SUI symptoms and pelvic floor function were assessed before and after treatment. After 12 weeks of treatment, a statistically significant reduction in SUI episodes was observed ($p < 0.001$). The median score on the incontinence questionnaire (ICQ-IU) decreased from 12 to 9 ($p < 0.001$), indicating a significant reduction in urinary symptoms. Furthermore, we observed a considerable improvement in pelvic floor muscle tone.

Further studies exploring the potential of androgen therapy in urogynecology are required.

CONCLUSION

A unique advantage of DHEA is that it is an inactive precursor or prodrug, which transforms into active sex hormones (oestrogens and/or androgens) only in specific cells and tissues that possess the necessary enzymes.

Daily prasterone 6.5 mg is as effective as local estrogens. It exhibits beneficial effects on the anatomy and physiology of vulvovaginal atrophy and associated symptoms and signs, without systemic exposure, according to the intracrinological mechanism.

Author contributions: Conceptualization, Writing - original draft, Supervision, Writing - review & editing: MAB. Research, Writing - original draft, Writing - review & editing: MLGT, MC, APS, RFSN.

Conflicts of interest: The authors declare no conflicts of interest related to the content of this work.

Funding: The authors declare that this study received no external funding.

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