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MEDICAL COMORBIDITIES (A GOLDSTEIN, M MINER AND S PARISH, SECTION EDITORS)

Genitourinary Syndrome of Menopause (GSM): the Role of Intravaginal DHEA (Prasterone)

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Abstract

Purpose of Review The purpose of this article is to review of intravaginal DHEA (prasterone), which has been recently FDA approved for the treatment of moderate to severe dyspareunia. The review includes the epidemiology, pathophysiology, and treatment of GSM and summarizes the safety and efficacy of the newest available treatment, intravaginal DHEA.

Recent Findings DHEA is believed to act through an intracrine mechanism, being metabolized and inactivated intracellularly into both androgens and estrogens. When administered intravaginally, DHEA is believed to result in local action, without impact on systemic hormonal levels.

Summary Intravaginal DHEA has been shown to be effective for the treatment of dyspareunia secondary to GSM and has a favorable safety profile.

Keywords Genitourinary syndrome of menopause · Prasterone · Intravaginal DHEA · Vulvovaginal atrophy

Introduction

Genitourinary syndrome of menopause (GSM) is the terminology used to describe a constellation of symptoms that occur from the lack of hormonal influence on the vulva, vagina, and lower urinary tract of postmenopausal women [1]. GSM was adopted by ISSWSH and NAMS in 2014 to replace terms such as vulvovaginal atrophy and atrophic vaginitis and was felt to be more medically accurate and representative of the clinical manifestations encountered from local hormonal deficiency to the genital region. Symptoms of GSM, which is estimated to affect 19 to 50% of peri- and postmenopausal women, can include dryness, irritation, itching, burning, dyspareunia, or pain with vaginal penetration. Urinary frequency, urgency, and dysuria may also occur [2].

Non-hormonal vaginal lubricants, both water and oil based, and moisturizers are recommended as first-line interventions for GSM before other pharmacologic treatments are prescribed. Hormonal treatments currently used for GSM include locally applied vaginal estrogens that can be prescribed in cream, ring, and tablet delivery systems. Local estrogen therapy is an effective treatment for moderate to severe GSM symptoms, and many clinicians often use vulvovaginal estrogen as a primary pharmacologic intervention. For dyspareunia caused by GSM, an oral selective estrogen receptor agonist is also available by prescription [3].

Another pharmacologic treatment recently approved by the US FDA is a DHEA-containing vaginal insert. It is hypothesized that this form of DHEA, when delivered directly into the vagina, acts as a substrate that is converted by vaginal enzymes via intracrinology into androgens. These androgens not only include testosterone but also androstenedione, androstenediole, and dihydrotestosterone (DHT). Aromatase activity will then convert these androgens to estrogens. Intravaginal DHEA is prescribed for women with moderate to severe dyspareunia secondary to menopausal vulvovaginal atrophy. Direct comparisons have shown DHEA vaginal inserts to have similar efficacies to vaginal conjugated equine estrogens (0.3 mg twice a week) and vaginal estradiol tablets (10 micrograms daily for 2 weeks then twice a week) [4]. Additionally, the biology of DHEA suggests local, intracellular metabolism with no biologically significant release of the active sex steroids that would cause levels in the circulation to increase above levels that are expected in the menopausal woman [5••].

This article is part of the Topical Collection on *Medical Comorbidities*

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Epidemiology

In the Women's Health Initiative, 19–27% of 98,705 postmenopausal women self-reported symptoms of vaginal dryness, irritation, or itching [6]. Similarly, the Vaginal Health: Insights, Views and Attitudes (VIVA) Survey, an international online survey of postmenopausal women age 55–65, found 45% of postmenopausal women reported experiencing unpleasant vaginal symptoms. Of the 500 American women in this survey, 80% reported these symptoms negatively affected their lives, 33% their marriage or relationship, and 75% their sexual activity [7]. Comparable data were reported by the 3000 US women with symptomatic vulvovaginal atrophy who participated in the 2013 Real Women's Views of Treatment Options for Menopausal Vaginal Changes (REVIVE) Survey. In this survey, 60–85% experienced negative sexual consequences from vulvovaginal symptoms, 47% felt their relationship suffered, and 27% felt a negative impact on their general enjoyment of life [8].

Negative effects of GSM are not limited only to the woman. The Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) online survey surveyed not only the affected woman (age 55–65) but also her partner. Recognition of the negative effects of the vulvovaginal symptoms on intimacy, libido, and sexual pain were expressed by 58–64% of the women and 52–78% of the men in this survey [9••].

Despite this high incidence of symptoms, women will often not relate these symptoms to menopausal changes, nor will they discuss them with their health care providers [6, 7].

Pathophysiology

Histologically, the vagina consists of a mucosal layer of stratified squamous epithelium, a subepithelial region which is rich in elastic fibers and thin-walled blood vessels, a middle muscular layer (muscularis), and an outer fibrous layer (adventitia). The epithelium of the well-estrogenized vagina contains glycogen, which acts as a substrate for lactobacillus. As a byproduct, organic acids, predominately lactate, are produced, which maintain a vaginal pH (3.2–4.0) which promotes a healthy microbiome. Through a beneficial effect on collagen, acid mucopolysaccharides, hyaluronic acid, and vaginal blood flow, estrogen maintains optimal epithelial thickness and elasticity, moisture, secretions, and lubrication [10].

After menopause, not only do serum estrogen levels drop due to follicular depletion but androgens levels also decline. The loss, primarily of estradiol, results in the loss of glycogen and a shift in the vaginal microbiome, which contributes to a subsequent increase in vaginal pH. Additionally, there is a loss of collagen, decreased elasticity and blood flow, and less vaginal moisture, secretions, and lubrications. Introital narrowing may result with long-term estrogen deficiency, especially noted in the non-sexually active woman.

Endocrinology Versus Intracrinology

In the endocrine system, a hormone is produced and released into circulation where it binds to a specific receptor on a target tissue and exerts an effect. Total circulating, unbound levels exert a feedback mechanism, resulting in up- or downregulation of hormone secretion, receptors, and activation, which occurs throughout any target tissue within the body. Estrogens are an example on hormones which act through an endocrine system.

By contrast, in the intracrine system, an otherwise inactive circulating steroid will be metabolized within the target cells or tissues to the active hormone. The active hormone will be also inactivated intracellularly, without release into the peripheral circulation. Data suggest that DHEA is primarily a prohormone that acts in this manner, converted to androgens and estrogens within target cells which contain the necessary enzymes, including aromatase. These end-products can exert their effect of the target cell or tissue but are then inactivated such that no biologically active sex steroids are released into the circulation. Enzymes, including aromatase, are required for the conversion of DHEA to androgens and estrogens. No feedback mechanism occurs. The metabolism and activity are regulated within the cell [5].

Confirmatory clinical studies have shown that intravaginal application of DHEA 6.5 mg nightly for 12 weeks does not result in a significant increase in serum levels of DHEA or its main metabolites, including estradiol and testosterone, since these levels do not change out of the menopausal range [11].

Clinical Diagnosis of GSM

Presenting symptoms of dryness, irritation, or dyspareunia in a peri- or a menopausal woman should always include GSM within the differential. Physical exam is intended both to look for signs of vulvovaginal atrophy and to exclude other etiologies. No specific tests are necessary for the diagnosis of vulvovaginal atrophy, although a vaginal pH of 5 or more in the absence of blood, semen, or infection will reinforce the diagnosis.

The Maturation Index is a wet preparation microscopic evaluation of a vaginal smear which is evaluated for superficial, intermediate, and parabasal squamous cells. In the premenopausal woman, the glycogen-rich superficial and intermediate cells predominate. A shift to increased parabasal cells (small dark cells with little cytoplasm) and lack of superficial cells (large cells with a small nucleus and abundant cytoplasm) suggests vulvovaginal atrophy. Wright's staining, which stains superficial and intermediate cells, but not

parabasal, can be used in preparing the Maturation Index, but is not necessary for accurate evaluation [12].

Serum estradiol levels less than 50 pg/ml have been suggested to correlate with more severe symptoms; but obtaining a serum estradiol level is not necessary, nor is it recommended, for diagnosis [13].

DHEA and the Treatment of Vulvovaginal Atrophy

Successful treatment of vulvovaginal atrophy may be measured in several parameters: clinically, by symptom relief, physiologically by reversal of atrophic changes, and in terms of safety profiles. Vaginal DHEA has been studied in each of these domains, with results that demonstrate efficacy and safety.

Symptom Relief

Data for intravaginal DHEA in the treatment of GSM has been generated in several ways: (1) by relief of most bothersome symptom as compared to placebo, (2) by open label, and (3) in a literature review which compared DHEA to several local estrogen products.

In a 12-week Phase III trial of vaginal DHEA 6.5 mg (0.50%) nightly, a significant improvement of moderate to severe symptoms of vulvovaginal atrophy including dyspareunia, vaginal dryness, and irritation/itching as the most bothersome symptom was seen compared to placebo, as measured by severity score (DHEA decrease − 1.44, placebo − 1.17; $p = 0.004$) [11].

A 2017 literature review compared independent placebo-controlled Phase III 12-week trials with either 6.5 mg intravaginal DHEA with either daily (21 days on/7 days off) 0.3 mg CEE, twice weekly 0.3 mg CEE, or 10μg E2 daily for 2 weeks followed by twice weekly for 10 weeks. The improvement the most bothersome symptom of VVA (baseline moderate to severe) was determined by participant questionnaires. All treatments were significantly superior to placebo, except for 10 μg estradiol in one of its two reviewed studies. All treatments showed significant improvement in dyspareunia, and all but 0.3 mg CCE dosed twice weekly showed significant improvement in vaginal dryness scores. DHEA, therefore, was at least as effective as the estrogen products for treatment of dyspareunia, and as effective or better for vaginal dryness [4].

Reversal of Atrophic Changes

Intravaginal DHEA has been shown to improve vaginal pH and Maturation Index as compared to placebo.

A prospective, randomized, double-blind, and placebo-controlled phase III clinical trial of 261 postmenopausal women with baseline vaginal pH > 5 and Maturation Index with no greater than 5% superficial cells was undertaken with intravaginal DHEA at concentrations of 0.25, 0.5, and 1.0%. All doses showed significant improvement in both pH values and Maturation Index versus placebo at 12 weeks as compared to the placebo [14].

The 0.5% dose, now FDA approved in the USA for dyspareunia due to GMS, had a 1.3-point decrease in pH from baseline of 6.6 compared to a 0.4% drop from baseline 6.5 in the placebo group. Also at this dose, the Maturation Index achieved significant increase in superficial cells over placebo by 2 weeks and remained significant with a total increase of 6.8% at 12 weeks. Simultaneously, there was a decrease of 45.9% of parabasal cells at 12 weeks, whereas no significant effect was observed in the placebo group.

The gynecologic exam scores for the main signs of vaginal atrophy, namely, vaginal secretions, color, epithelial integrity, and epithelial surface thickness by observation of the investigating gynecologist showed significant improvement over the 12-week period. The improvement observed at exam corresponded both to the patient reported change in symptoms and to the pH and Maturation Index scores.

Similar findings were seen in the Phase III trial of 0.5% (6.5 mg) DHEA with a 5.8-fold greater increase of superficial cells and a 27.7% decrease in parabasal cells over placebo at 12 weeks. Gynecologic evaluation in this trial also reported significant improvement in vaginal secretions, color, epithelial integrity, and epithelial surface thickness over placebo [11].

Vaginal estrogen also shows significant improvement in maturation index, vaginal pH, and gynecologic exam scores, although length of treatment for patient report of symptom relief may be slightly longer for some products (www.accessdata.fda.gov/drugsatfda_docs/label/2016/208470s000lbl). A recent Cochrane review, however, concluded that there is no evidence of a difference in efficacy between the various intravaginal estrogenic preparations when compared with each other. No recommendations or comparisons to DHEA are included in the Cochrane review [15••].

Safety Profile

DHEA has been approved by the US FDA as a steroid treatment, not a hormonal therapy, based on the mechanism of action termed as intracrine. The only absolute contraindication to its intravaginal use is undiagnosed vaginal bleeding. There is no boxed warning stating that intravaginal DHEA is contraindicated in women who have had breast cancer, although it is referenced that DHEA has not been studied in this population [16].

This classification is based on the idea that active hormones, namely, estrogens and androgens, can exert action by binding to a receptor on a target tissue only if they are present into the circulation. DHEA appears to be converted intracellularly to active hormones, which are then inactivated intracellularly. A study by Labrie et al. reported that DHEA, nor any active metabolites of DHEA, including androgens or estrogens, were elevated out of the postmenopausal range after 7 days of intravaginal administration at the 6.5 mg nightly vaginal dosing [17].

Similar results were seen at week 12 in the Phase III trial and week 52 in the open label trial of intravaginal DHEA 6.5 mg nightly [11, 18].

Additionally, in the 7-day pharmacokinetic study, increase in circulating active metabolites of DHEA were not seen in proportion to increased circulating DHEA levels [17].

Any target tissue which contains the necessary enzymes, including aromatase, can utilize circulating DHEA. The endometrium does not appear to be one of those organs, and studies to date have shown no effect of intravaginal DHEA on the endometrium of postmenopausal women after up to 52 weeks of the currently FDA-approved dose [18]. In this study by Portman, et al., all endometrial biopsies obtained after treatment revealed inactive endometrium or endometrial atrophy, similar those in the placebo group.

The adverse events reported in greater than 2% in the 52-week study were vaginal discharge and abnormal Pap smear. Vaginal discharge was reported in about 14% of women, likely the result of the melting of the insert vehicle. Of the 11 abnormal smears in the intervention group, 1 was LGSIL, and 10 were ASCUS (HPV status not reported) (https://www.rxlist.com/intrarosa-side-effects-drug-center.htm#overview).

Male partners of the women in the 52-week trial also participated in a voluntary pre- and posttreatment questionnaire. Of the 66 men who participated, 36% of men whose partners were in the treatment group reported that the sensation of vaginal dryness they had previously experienced during intercourse was improved, compared to 7.8% of the men whose partner was in the non-treatment group. The overall severity score of vaginal dryness, according to the male partner's perception during penetrative sexual activity, showed a statistically significant 81% improvement over placebo. No male partners reported an adverse event [19].

Conclusion

Intravaginal DHEA (prasterone), a new FDA-approved treatment for moderate to severe dyspareunia due to GSM has been shown to be an intervention that provides more significant pain relief during sexual penetrative exchange in women with GSM as compared to placebo. This intervention provides clinicians with another management tool for menopausal women with dyspareunia due to GSM, in addition to vaginal estrogens and an oral selective estrogen receptor agonist. Data also suggest physiologic reversal of atrophic changes. The lack of effect on endometrium in clinical studies conducted to date is reassuring. Studies in breast cancer survivors are needed for further support of safety in this population.

Compliance with Ethical Standards

Conflict of Interest Nancy Phillips and Gloria Bachmann served on an advisory board for AMAG specifically about Intrarosa in Boston, 2017.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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