

## Newer Name, Newer Treatments: The Genitourinary Syndrome of Menopause

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### Case History

**F**IFTY-SEVEN-YEAR-OLD postmenopausal woman presents with complaints of vaginal dryness, burning, and dyspareunia. She had no improvement in her symptoms after regular use of vaginal moisturizers and lubricants with intercourse. She has tried different forms of vaginal estrogen in the past year. She reports that the estrogen cream was “messy” and the estrogen ring caused pain and cramping. She even tried the vaginal estrogen tablets and was not pleased with the results.

Her speculum examination elicited pain and revealed introital narrowing with thinning of the vaginal walls, loss of rugae, and erythema. There is no evidence of infection, or pelvic floor dysfunction. She is otherwise healthy. What treatment options could you offer her?

- A. Change to a different vaginal moisturizer and lubricant.
- B. Review how she was using her vaginal estrogen and discuss all vaginal estrogen therapy options.
- C. Discuss alternative treatment options.
- D. Both B and C.

### Genitourinary Syndrome of Menopause

The genitourinary syndrome of menopause (GSM) refers to a constellation of symptoms and clinical findings involving the genitourinary tract (labia majora, labia minora, vestibule, introitus, clitoris, vagina, urethra, and bladder).<sup>1</sup> Previously referred to as vulvovaginal atrophy or atrophic vaginitis, the newer term is more encompassing and endorsed by a consensus panel of both The International Society for the Study of Women's Sexual Health and the North American Menopause Society.<sup>2,3</sup>

It is estimated that 70% of postmenopausal women experience GSM but only 7% receive treatment,<sup>1</sup> since it is frequently undiagnosed and goes untreated in a majority of women. The urogenital tissues have an abundance of both estrogen and androgen receptors with both androgens and estrogen exerting independent effects on vaginal health. Therefore, the changes of GSM are due to both low estrogen and testosterone levels.<sup>4</sup> The loss of estrogen leads to a decrease in vaginal collagen, elastin, and hyaluronic acid content with impaired smooth muscle proliferation, denser

connective tissue arrangement, and reduced vascularity leading to shortening and narrowing of vagina, which can cause dyspareunia.<sup>5-7</sup> Vaginal and cervical secretions are reduced leading to dryness, itching, burning, and lack of lubrication, which can also lead to dyspareunia, bleeding, or spotting during intercourse. Urinary symptoms include frequency, urgency, dysuria, and frequent urinary tract infections.<sup>3</sup>

GSM is diagnosed clinically by symptomatology and physical examination findings, and requires no confirmatory testing. Women with mild to moderate GSM are usually asymptomatic with minimal correlation between symptom severity and physical examination findings. Physical examination can show introital narrowing, reduced vaginal depth and stenosis, dry thin pale vaginal epithelium with loss of rugae, and sometimes ulcers and fissures. Symptoms usually become bothersome 4–5 years after menopause.<sup>8</sup> Unlike the vasomotor symptoms of menopause, symptoms of GSM do not improve with time from menopause and may even get worse.

### Treatment Options for GSM

It is important to always ask women about bothersome genitourinary symptoms as they for many reasons may be reluctant to discuss their symptoms. Treatment of GSM is indicated if symptoms are bothersome and the therapeutic goal is to achieve adequate symptom relief. There are several treatment options for GSM starting initially with the regular use of over-the-counter vaginal moisturizers (two to three times a week) and supplemental use of lubricants during intercourse.<sup>9</sup> Even though these measures provide improvement for women with mild symptoms, they do not improve the vaginal epithelial changes caused by the hypoestrogenic state of menopause.<sup>10</sup> In a study of 300 women with symptoms suggestive of GSM their most bothersome symptom was pain with penetrations followed by vaginal dryness.

Low-dose vaginal estrogen has been the gold standard for treating symptoms of GSM and is effective in relieving symptoms of dryness and dyspareunia. Estrogen therapy restores the thickness of the vaginal epithelium, the acidic milieu of vagina, and increases bacterial numbers most notably species of *Lactobacillus* in comparison with postmenopausal women not receiving treatment. It also helps to prevent urinary tract infections.<sup>11</sup> There are many different preparations of vaginal estrogens, including estradiol tablets

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(Vagifem<sup>®</sup> or Yuvaferm<sup>®</sup>), cream (Estrace<sup>®</sup>; Premarin<sup>®</sup>), or ring (Estring<sup>®</sup>), and most recently an estradiol gel capsule (Imvexxy<sup>®</sup>) in 4 and 10 mcg dosages. The frequency and delivery methods differ for these various estrogen preparations allowing providers to tailor to individual patient needs. Asking about your patient's satisfaction with the product and their understanding about how to reliably use it is a necessary first step to evaluate treatment efficacy. Oftentimes women express dissatisfaction with their prescribed therapy, for a variety of reasons, including not being shown how to use it.

### Role of Dehydroepiandrosterone in Treating GSM

Better understanding of genitourinary physiology and the role of androgens has led to the use of vaginal androgens such as dehydroepiandrosterone (DHEA) for the treatment of GSM. DHEA, the most abundant of all the androgens, is an inactive prohormone in the biosynthetic pathway of sex steroids. Similar to other androgens, its production declines with aging, with levels after menopause falling by 60% compared with those in premenopausal women in their third decade of life.<sup>12</sup> The United States Food and Drug Administration (FDA) has approved the use of vaginal DHEA, prasterone (Intrarosa<sup>®</sup>), a synthetic steroid, for the treatment of postmenopausal women with moderate to severe dyspareunia due to GSM. The exact mechanism by which it improves dyspareunia is not clearly known, but it may be explained by the process of intracrinology, whereby vaginally administered DHEA is converted locally to androgens such as androstenedione, testosterone, and 5-dihydrotestosterone, and estrogens through enzymatic activity of 5- $\alpha$  reductase and aromatase in the tissue.<sup>13</sup> Both estrogens and androgens are then locally activated in the vaginal cells, presumably without causing any systemic side effects.<sup>14,15</sup> Intravaginal DHEA improves symptoms of GSM by both estrogenic and androgenic actions.<sup>16</sup> It is effective on all three layers of the vagina (epithelium, lamina propria, and muscularis) by improving epithelial integrity and maturation index<sup>12,17,18</sup> stimulation of collagen production, and increasing the density of collagen fibers in the lamina propria.<sup>12,19,20</sup> These effects due to DHEA are not sustained if the dose is reduced to twice a week, so it must be used daily.<sup>21</sup>

The serum levels of sex steroids, including estradiol, DHEA, DHEA-S, androstenedione, and testosterone, after the administration of vaginal DHEA are likely dose dependent, but have not been found to increase in current studies, including in women on aromatase inhibitors.<sup>22</sup> Vaginal DHEA has not yet been well studied in women with breast cancer so its safety in this population has not been established. It is not recommended for women with abnormal vaginal bleeding, which must be evaluated. Daily vaginal DHEA inserts are usually well tolerated with the most common side effect being increased vaginal discharge.<sup>22</sup> Vaginal DHEA administration does not require a progestogen for endometrial protection. Penetrative sexual activity is not precluded while using intravaginal DHEA. There are currently no FDA-approved vaginal testosterone products in the United States.

### Other Treatments

For women who prefer oral therapy over vaginal treatments, Ospemifene<sup>®</sup>, a selective estrogen receptor blocking agent, improves vaginal dryness and dyspareunia, by re-

generating vaginal cells and improving lubrication. In addition, it demonstrated endometrial, cardiovascular, and breast safety.<sup>23</sup> Even though there are studies of efficacy with vaginal laser treatments, there are limited random control studies and no long-term safety data, so the FDA has recently issued a warning that "the safety and effectiveness of energy-based devices for treatment of these conditions has not been established" and the North American Menopause Society has concurred with this mandate citing lack of long-term safety data.<sup>24</sup>

### Answer: D

Answer A is incorrect as the patient is already using moisturizers and lubricants on a consistent basis, and changing to a different type or brand will not lead to improved symptoms. Answer B or C would be a reasonable choice to see if a different formulation or route of vaginal estrogen or mechanism (DHEA) will help alleviate her symptoms making answer D the correct answer.

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