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Genitourinary syndrome of menopause:

A new name for an old condition

Abstract: Genitourinary syndrome of menopause (GSM) is the new name for the conditions that formerly included vulvovaginal atrophy and atrophic vaginitis. GSM better describes the range of conditions associated with low estrogen levels in menopause and invites patient discussion without the use of words that might be uncomfortable to say. This article discusses the physiology of GSM and reviews both hormonal and nonhormonal treatment options.

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Ovarian production of estrogen diminishes during the menopause transition. Although cessation of menstrual bleeding and the temporary characteristic vasomotor changes are most often identified with menopause, the vulva, vagina, and lower urinary tract are made of epithelial tissue that is highly sensitive to hormonal changes. As estrogen declines, these areas undergo significant and progressive changes, including shrinking of the labia minora and a narrowing of the introitus aperture. There is a loss of collagen leading to decreased elasticity.

The vagina itself becomes shorter as the vaginal mucosa thins while the vaginal pH increases; there are subtle changes in the vaginal microbiome. There is less blood flow, and therefore, diminished lubrication.[1] These changes are inevitable and progressive post menopause. Atrophic changes can also occur due to cancer treatment, surgical oophorectomy, and in the postpartum period—especially during lactation.

The net effect of the physiologic changes of genitourinary syndrome of menopause (GSM) is that women may experience vaginal dryness, pain with intercourse, and possibly injury or trauma to the tissue. In addition to pain during sexual activity, the loss of collagen and elasticity in the urethra and bladder neck can lead to urinary problems, including nocturia, dysuria, and incontinence. There is an increase in susceptibility to infection and to irritation from chemicals in lubricants, soaps, and hygiene products.[1]

Women may refer to these symptoms collectively as "vaginal dryness," but that does not adequately define the extent of the problem. GSM is a term that begins to describe the constellation of tissue changes while providing patients with a more socially acceptable vocabulary for their complaints.

GSM symptoms are estimated to occur in more than 40% of women at midlife and beyond.[1] Although GSM affects

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women whether or not they are sexually active, dyspareunia is often noted as the most bothersome symptom and may be the presenting complaint.[2] Since studies show that 52% of women ages 50 to 79 have been sexually active in the past year, a complaint of dyspareunia in a postmenopausal woman should prompt a thorough evaluation for GSM and a discussion of treatment options.[3] The North American Menopause Society (NAMS) has endorsed a new terminology for what was formerly known as vulvovaginal atrophy (VVA) or atrophic vaginitis (AV).[4] The new suggested term is GSM (see *New terminology*).

Diagnosis of GSM can be made on the basis of symptoms and physical findings once other conditions have been ruled out.

Diagnosis

Diagnosis of GSM can be made on the basis of symptoms and physical findings once other conditions, such as infection, dermatitis (contact or allergic), dermatoses, and neuropathic conditions, have been ruled out. There currently is no consensus on objective findings.[4,5] Evaluating a vaginal maturation index (VMI) is a simple and inexpensive tool used for diagnosis and to monitor response to therapy. A VMI can be prepared by collecting epithelial cells from the upper third of the vaginal wall with a spatula and fixing this on a slide with spray fixative. These cells can be examined under the microscope by comparing the number of parabasal, intermediate, and superficial cells to each other.

In any clinic that performs wet mounts, a crude VMI can be calculated by preparing a saline-based slide and calculating the percentage of parabasal cells to mature epithelial cells per high-power field. This percentage can be monitored to evaluate a treatment's effectiveness. For research purposes, consensus is lacking on a specific formula to be used to calculate a VMI with high interrater reliability; however, in the clinical setting, a large number of parabasal cells (smaller epithelial cells with a large nucleus) relative to mature epithelial cells per high-powered field indicate atrophy. This can be expressed as percentage per high-power field or as a shift to the right.[6] A vaginal pH can be used in conjunction with the VMI for greater sensitivity. As GSM improves, the vaginal pH should become more acidic.

Use of the Most Bothersome Symptom (MBS) approach is also helpful for diagnosis and to evaluate response to treatment.[2] Itching, irritation, and dyspareunia are likely to be indicative of GSM. If any of these symptoms are identified as the MBS at the time of diagnosis, it is retained to measure response to therapy. Combining the MBS with the physical exam is the most valid approach to diagnosis. Physical exam findings indicating GSM include friability or petechiae on the vaginal wall, an absence of rugae or decreased elasticity of the vaginal wall, and a loss of normal labial architecture.

The skin is frequently pale pink, and the vaginal introitus may be constricted (see *Findings and features of GSM*). There is no consensus as to the minimum number of findings that need to be present to make the diagnosis. Variation in provider perception of subjective ratings (such as tone or elasticity) is a persistent problem in research studies; however, documenting and comparing initial findings to subsequent findings following treatment can help guide topical therapy.

Ideally, anticipatory guidance regarding GSM would be provided to women approaching menopause, and asking postmenopausal women about GSM should be a part of every visit; however, following the Women's Health Initiative (WHI) results in 2002, both patients and providers became reluctant to use hormonal treatments in menopause.[7] The WHI pointed to a slight increased risk for venous thromboembolism, coronary heart disease, breast cancer, and stroke seen with oral administration of conjugated equine estrogens at a dose much higher than is obtained with local treatments.[7]

New terminology[4]

In 2014, the NAMS introduced a new terminology for what was formerly known as VVA or AV. The new suggested term is GSM, which more accurately describes the range of expression of changes that occur throughout the vulva, vagina, urethra, bladder neck, and lower bladder in the low estrogen state of menopause. This particular name was chosen by a panel of experts as descriptive, comprehensible, and acceptable to researchers, clinicians, and the public at large. The former terms were considered inadequate because they described the appearance of the tissue but not the extent of the condition. In addition, the old terms required the use of words (vulva and vagina) that both patients and the media might be uncomfortable saying. This was modeled on the successful rebranding of impotence to erectile dysfunction, a change that made discussion of the condition more socially acceptable and prompting patient-provider conversations. This transition in terminology is likely to be adopted slowly, and for purposes of many articles, GSM maybe used interchangeably with the former terms VVA and AV.

However, there are limitations to the generalizability of the WHI to all populations of menopausal women due to the single oral preparation used, the advanced age of the participants, and the fact that the WHI did not evaluate for quality-of-life issues.[7] In the wake of the WHI, providers stopped routinely offering hormonal therapies, and patients were either unaware or afraid to ask for treatment. The NAMS position statement, along with recommendations from the American College of Obstetricians and Gynecologists (ACOG), lists locally absorbed estrogen therapies as a first-line treatment for moderate-to-severe GSM symptoms (see *NAMS 2013 position statement*).[8,9]

Findings and features of GSM[5]

Finding	Normal	Features suggestive of GSM
pH	3.5–4.5	Higher pH associated with GSM
VMI 0.2 ×% parabasal cells + 0.6 ×% intermediate cells + 1.0 ×% superficial cells	>52	<52
Physical exam	Normal color, rugae present in vagina Prominent labia minora Urethra is not prominent	Pallor Petechiae Friability, ulcers, or fissures Loss of architecture Constricted introitus Urethra appears prominent Loss of elasticity Absent vaginal moisture

NAMS 2013 position statement[9]

Symptoms of GSM tend to be progressive and are unlikely to resolve without intervention. Because these symptoms have a significant impact on the quality of women's lives, both physically and sexually, NAMS supports treatment based on severity of symptoms. Recommendations include utilizing nonhormonal lubricants and moisturizers with intercourse for mild symptoms and low-dose estrogen or ospemifene in women with moderate-to-severe symptoms. In women with an intact uterus, progesterone is generally not indicated for women taking low-dose estrogen. NAMS notes that long-term studies, beyond a year, of local low-dose estrogen and ospemifene on the endometrium are lacking. If a woman has a history of either breast or endometrial cancer, management of symptoms would depend on the woman and her oncologist preferences to use either estrogen or ospemifene for treatment. NAMS did not review DHEA in their position statement.

Using petroleum jelly increases the risk of bacterial vaginosis by 2.2-fold, and using oils increases *Candida* species by 44.4% compared with 5% of nonusers (*P* less than 0.01).[10] Additionally, women may benefit from either gentle stretching of the vagina with graduated dilators or a referral for pelvic floor physical therapy.

A Cochrane Review of local low-dose estrogen treatment for what was then VVA/AV found no significant differences in hyperplasia (endometrium greater than 5 mm) or increased incidence of adverse reactions with any of the three types of local estrogen delivery methods (tablets, cream, or ring). However, it should be noted that the safety of these products has not been studied beyond 1 year.[8,11]

Advise patients to report any vaginal bleeding, which should be thoroughly investigated with ultrasound and endometrial biopsy. In a recent committee opinion, ACOG states that "data do not support an increased risk of cancer recurrence among women undergoing cancer treatment or those with a personal history of breast cancer who use vaginal estrogen to relieve urogenital symptoms." However, they do recommend nonhormonal treatments as first-line therapy.[12]

Nonhormonal and over-the-counter options

Nonhormonal options for vaginal dryness and pain with intercourse can be used as a first-line therapy—especially if the woman is opposed to hormonal options. Long-acting vaginal moisturizers, lubricants, and regular sexual activity may be all that is needed to treat women who have mild symptoms. In one study, 49% of all women reported using an intravaginal product within 1 month.[10] Women should be cautioned that lubricants containing flavors or warming properties (as well as propylene glycol and parabens) can be irritating to the vaginal epithelial tissue.

Pharmaceutical treatment options

If a patient has only genitourinary symptoms, systemic hormone therapy is not recommended, and localized vaginal therapy will suffice in most cases. Intravaginal low-dose estrogenic preparations have been widely researched and documented for effectiveness; however, additional therapies will be reviewed. There are no known drug interactions with these preparations.

A Cochrane review of 16 studies indicated that all methods of low-dose estrogenic preparations of cream, vaginal tablet, and ring were equally and highly effective in relieving genitourinary syndrome symptoms, maturing

vaginal mucosa, and decreasing dyspareunia.[11] Additionally, low-dose vaginal estrogen products have a higher safety profile than systemic estrogens because of the very low (if any) systemic elevation in estradiol serum levels.[12]

Ospemifene was approved by the FDA in 2013 for moderate-to-severe dyspareunia, a symptom of GSM.

However, there may be concern among women and providers about a small theoretical increased risk of breast cancer, stroke, and deep vein thrombosis (DVT) due to product safety profiles.

A woman with a history of breast cancer taking an aromatase inhibitor has an increased rate of vaginal dryness and dyspareunia compared with the general population.[13] Breast cancer can have detrimental consequences in sexual relationships of women; GSM compounds both the physical and psychosocial burden of this disease. Women and providers concerned about using an estrogen preparation in this population have the following two options available.

Ospemifene, a selective estrogen agonist and antagonist receptor modulator, was approved by the FDA in 2013 for moderate-to-severe dyspareunia, a symptom of GSM, and has been shown to be effective in relief of long-term symptoms, improving VMI, decreasing vaginal pH, and relieving dyspareunia and vaginal dryness. Ospemifene carries a Black Box Warning noting an increased risk for endometrial cancer, stroke, and DVT.[14] A meta-analysis conducted by Cui and colleagues and a study by Bachmann and Komi of ospemifene compared to placebo found that it was a generally safe and effective treatment for GSM.[15,16] It was reported that women experienced an increase in hot flashes with ospemifene, but they were not significant enough to drop out of the study.[15] Due to the antiestrogenic effect, ospemifene may be as beneficial as tamoxifen and raloxifene in preventing breast cancer recurrence; however, further studies are needed to determine the chemopreventive effects of ospemifene.[17] No studies have been conducted comparing the effectiveness and satisfaction of ospemifene to estrogen preparations.

The second option, which can be used in patients with a history of breast cancer, is dehydroepiandrosterone (DHEA), a hormone produced in the adrenal gland that is converted to estradiol and/or testosterone in peripheral target cells. A commercial DHEA product is not FDA approved and is not currently available in the United States and would need to be compounded.

Daily vaginal application of DHEA rapidly and effectively reversed symptoms of GSM.[18] The effectiveness in sexual functioning was lost if dosing was reduced to twice a week.[19]

Compounded estradiol in cream or ovules for GSM can be prescribed in various doses. The safety, efficacy, and reliability of these compound medications have been controversial. However, the advantage of compounded preparations is that other hormones (such as DHEA or testosterone) can be added. Additionally, if women have been diagnosed with lichens sclerosis, 1% hydrocortisone can be added after initial treatment with a stronger corticosteroid to control symptoms. For women with vulvodynia, off-label use of 4% topical aqueous lidocaine has been shown to be effective in controlling symptoms of dyspareunia.[20] All of these prescriptions can be prepared in a variety of hypoallergenic bases.

Moving forward

GSM is chronic and progressive condition affecting over 50% of postmenopausal women. Women may not connect their genitourinary symptoms to menopause and may not seek effective treatments due to embarrassment, discomfort with the vocabulary required to discuss their symptoms, or fear about hormonal therapies. Anticipatory guidance about GSM is an important component of primary care. NPs in family health, women's health, and midwifery are likely to see women in peri- and postmenopause who would benefit from treatment.

Locally applied estrogen therapy is safe and effective for moderate-to-severe symptoms and does not carry the same risk as systemic hormone replacement therapies. Alternatives to estrogens are available to treat patients with a history of breast cancer, DVT, or stroke if they are concerned about using low-dose estrogen preparations.[17-20] The use of the term GSM opens doors for discussion of this condition that has profound effects on women's sexual self-esteem, sexual functioning, and quality of life. NP

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