Female Sexual Dysfunction: Genitourinary Syndrome of Menopause (GSM)

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Last Updated:

Friday, March 3, 2023

1. Epidemiology

With menopause, loss of estrogens and androgens leads in most cases to vaginal and vulvar tissue atrophy. This causes **genital symptoms** (e.g. dryness, burning, and irritation) and **sexual symptoms (**e.g. lack of lubrication, discomfort or pain, and decreased libido and difficulty with arousal and orgasm). As the lower urinary tract, vagina and vestibule have a shared embryologic origin, lack of these hormones can also result in **urinary symptoms** (e.g. urgency, dysuria, and recurrent urinary tract infections). The decline in estrogen also disrupts the vaginal microbiome leading to a decrease of glycogen, lactobacilli and an elevated pH resulting in a decreased defense against Enterobacteriaceae colonization leading to recurrent urinary tract infections.[1] These symptoms are known as the Genitourinary Syndrome of Menopause (GSM), a term which has replaced the earlier used vulvovaginal atrophy and atrophic vaginitis. Symptoms increase in severity over time, and do not improve without treatment.[2,3,4,5] While GSM is associated with the changes that occur during menopause, it can also occur with other hormonally depleted states including premature ovarian failure, surgical-induced menopause (bilateral oophorectomy), patients who are breast feeding, taking oral contraceptives, receiving adjuvant hormonal deprivation therapy for breast cancer or gender-confirming treatment, and women with thyroid disorders or pituitary tumors.

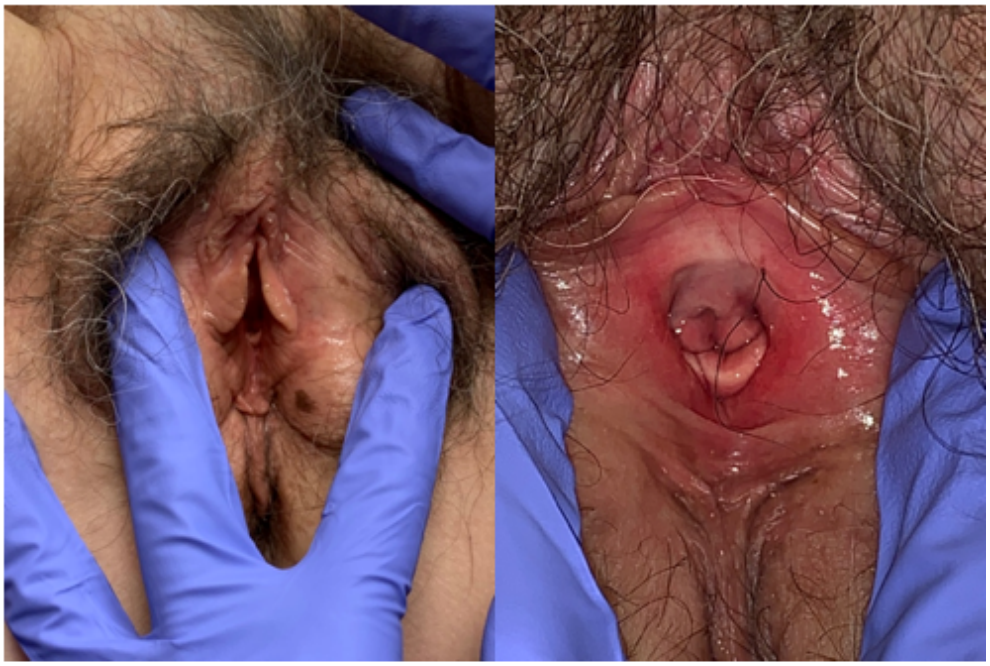
2. Diagnosis

2.1 History

Given the sensitive nature of symptoms associated with GSM, it's imperative to gather a patient history while they are fully dressed and comfortable. A detailed history should include inquiry about the patient's urinary, genital and sexual symptoms (**Table 1**). One should identify the frequency of and bother associated with the presence of these symptoms and any exacerbating or alleviating behaviors particularly sexual activity or prior attempted treatments with over the counter options. If a patient suggests they are not sexually active it's imperative to ascertain if this is secondary to symptoms of GSM or personal choice and if they would prefer to become sexually active in the future.

Table 1

Urinary	Genital	Sexual
• Frequency • Urgency • Dysuria • Pain after urination • Nocturia • Hematuria • Recurrent urinary tract infections and associated symptoms	• Dryness • Irritation/burning/itchining of vagina or vulva • Erythema • Tissue fragility/fissures/petechiae • Changes in appearance of anatomy including labial shrinkage or fusion, clitoral hood retraction or vaginal stenosis	• Decreased lubrication • Dyspareunia • Post-coital bleeding • Decreased arousal, orgasm or desire



A B

Figure 1A: The 50% resorbed and thin labia minora. Figure 1B. Note the protruding urethra, pallor and erythema of the vestibule. Patient's vaginal pH was 7.5 while the goal should be 4.5. Photos courtesy of Rachel S. Rubin MD.

2.2 Examination

All patients with GSM should undergo a genital examination. Visual examination may reveal thinning of the pubic hair, the labia majora can appear flattened and the labia minora may be resorbed or fused. Vaginal epithelium can become pale and friable with loss of normal rugae.[6] In addition, one should assess the vestibule for hyperemia or erythema and the entire vulva and vagina for signs of trauma, **dermatologic changes** consistent with lichen sclerosis or other dermatologic conditions and infection. The vaginal introitus may be narrowed limiting speculum exam. In this case, a digital exam to assess for concomitant pelvic floor disorders (vestibulodynia, pelvic organ prolapse, high tone pelvic floor dysfunction) is sufficient. When possible the smallest available vaginal speculum should be used as to minimize discomfort and trauma to the thinned vaginal epithelium (see **Figure 1**).

As the surrounding tissue atrophies, the urethra often protrudes. The urethra may develop a caruncle which is a portion of the urethral tissue extending beyond the meatal opening, a polyp or a full prolapse. Friction against the urethral tissue may cause pain with penetration. This can be managed conservatively with vaginal estrogen and if not resolved the prolapsed portion of urethra may be excised (see **Figure 1**).

Vaginal pH testing with narrow-banded pH paper may be used to confirm the diagnosis and follow treatment. Normal vaginal pH ranges from pH 3.5-5.0. Vaginal pH levels often reach 5.5 or higher in

women with GSM.[6] GSM is diagnosed primarily from history and physical examination. Serum hormone levels do not offer any additional value in confirming or ruling out the presence of GSM.

3. Treatment

Also see **AUA Update Series 2019 Lesson 22 Hormonal Treatment in Women: What a Urologist Should Know**

When treating GSM, the primary goals are to relieve the patient's symptoms, restore vaginal pH, and prevent recurrent urinary tract infections. The benefits also include improving vulvovaginal discomfort particularly when exacerbated by intercourse. There are a range of treatment options but the cornerstone of treatment is low-dose vaginal hormone therapy. This treatment will improve the integrity, microbiome, elasticity and flexibility of the tissue. In addition to vaginal estrogen, topical treatments, lubricants, moisturizers, laser therapy and pelvic floor physical therapy can all be acceptable treatment adjuncts, but the gold standard remains low-dose vaginal estrogen or DHEA supplementation. **Table 2 outlines the benefits of different non-hormonal treatment options.**

Table 2

Treatment	Use	Symptomatic Relief	Considerations
Vaginal Moisturizer (Replens, Vagisil, Feminease, Moist Again, K-Y Liquibeads, Hyalo GYN)	routinely, typically two or three days per week, not just during sexual activity	mild-moderate symptoms; improve coital comfort and increase vaginal moisture, but they do not reverse most atrophic vaginal changes	Some have bacteriocidal properties that disrupt the vaginal microbiome
Lubricant silicone-based (Pjur, ID Millennium) water-based (Astroglide, Slippery Stuff, K-Y Jelly) oil-based (Pjur, ID Millennium)	used as needed, prior to intercourse	relieve discomfort during intercourse, reduce friction and trauma to the tissues	silicone- main ingredient glycol and its metabolite glycerine, degraded into sugar can predispose to candidal growth water- evaporate quickly, require reapplication and may exacerbate symptoms oil- latex breakdown

Pelvic Floor Muscle Training (PMFT)	as needed, for patients with contraindication to hormone therapy and women with high-tone pelvic floor dysfunction	improved vaginal blood flow parameters, increased pelvic floor muscle strength, and improved vaginal atrophy index	
Vaginal Dilators and Vibrators	consistent use	increase vaginal elasticity, decrease dyspareunia with deep penetration, stimulate blood flow and preserve vaginal function in women with or without sexual partner	

3.1 Topical

There are a range of treatment options for GSM. Vaginal moisturizers can be purchased over the counter and have been shown to maintain tissue integrity, elasticity, and pliability with regular use. While vaginal moisturizers do offer some improvement in vaginal symptoms associated with GSM, they often have bactericidal properties that can disrupt the vaginal microbiome and they do not reverse most of the tissue changes associated with atrophy, such as vaginal innervation density and vaginal pH. Vaginal innervation density specifically is strongly associated with dysesthesia, and only hormonal treatments have been shown to reverse this atrophy-related change. [7]

Vaginal lubricants are used “as needed”, typically for sexual activity, to temporarily alleviate vaginal dryness and prevent dyspareunia. Lubricants may have a water, silicone, or oil base. Water-based lubricants are effective but may require repeat applications as they may evaporate/absorb. Silicone-based lubricants are less prone to drying out but may be harder to clean and may have an unpleasant taste/odor. Oil-based lubricants may be effective but should not be used with latex condoms as the oil content will tend to lead to condom breakage. Ultimately the choice of lubricants should be based on patient and partner preference and may require experimentation. Similarly to vaginal moisturizers, they are effective for acute symptom relief but do not reverse the vaginal changes associated with GSM.

Table 3 shows all the FDA approved options for treating GSM. Topical low-dose vaginal estrogen works locally to restore hormone levels within the tissue without significant systemic absorption. This typically results in rapid improvement of vaginal symptoms (vaginal dryness and/or dyspareunia) within 2 to 3 weeks. [8,9] Local vaginal estrogen is also recommended in the **AUA guidelines for recurrent UTI** in peri- and post-menopausal women who do not have a contraindication to estrogen therapy. Patients with active breast or endometrial cancer and those with a history of those cancers who are still on endocrine therapy should be discussed with the treating oncologist. The Women’s Health Initiative study showed the risk of cardiovascular complications and breast cancer increased in older women with combined systemic hormonal therapy but decreased in younger women who were close with menopause with systemic estrogen therapy alone. [10] Vaginal estrogen use was not associated with any increased risks of cancer or cardiovascular outcomes over an 18-year follow-up period.[11]

Vaginal DHEA suppositories are converted by enzymes in the vulva, vestibule and vagina to become estrogens and androgens while not affecting the endometrial tissue in the uterus. Vaginal DHEA suppositories are specifically approved for treatment of dyspareunia due to GSM and result in improvement in all domains of sexual function.[12]

Some small studies, which have included breast cancer patients not eligible for vaginal estrogen therapy, have shown topical vaginal testosterone may reduce dyspareunia and improve sexual function. [13,14]

Vaginal testosterone may be an option in select cases. The discovery of the androgen receptor and

of the essential enzymes involved in androgen synthesis suggests that androgens play a crucial role in the differentiation of the vagina. Testosterone is necessary for the complex neurovascular processes that control arousal and lubrication (vascular smooth muscle relaxation via the NO/cGMP/PDE5 pathway, nerve fiber density, and neurotransmission), the integrity of vaginal tissue structure (including non-vascular smooth muscle thickness and contractility, and collagen fiber compactness). In the vagina, nociception, inflammation, and mucus secretion have all been reported to be modulated by testosterone. Despite numerous physiologic pathways involving testosterone, there have only been smaller-scale studies showing potential benefits with vaginal testosterone use, and to date intravaginal testosterone has not been approved by the FDA. In postmenopausal women with breast cancer on aromatase inhibitors, vaginal testosterone has been shown to improve vaginal maturation index (VMI), dyspareunia, and dryness symptoms without affecting serum estradiol levels. [13,14] Further high-quality studies are needed to evaluate the safety and efficacy of testosterone on GSM symptoms.

3.2 Oral

Ospemifene is a selective estrogen receptor modulator (SERM), a systemic non-hormonal therapy approved for the treatment of dyspareunia due to vulvovaginal atrophy. This is particularly helpful for patients who prefer an oral versus vaginal treatment. In clinical trials, ospemifene reduced pain with sexual intercourse and increased vaginal mucosal maturation as well as vaginal pH. Contraindications include estrogen-dependent neoplasia, active or prior venous thromboembolism, previous stroke, and active heart disease or prior myocardial infarction. The most commonly reported adverse reactions from ospemifene were hot flushes, vaginal discharge, and muscle spasms. This medication has not been adequately studied in women with breast cancer. [15]

Systemic estrogen therapy may also be used in the treatment of GSM when a patient has concomitant vasomotor symptoms, although patients may also need local estrogen replacement. [16]

3.3 Non-medication treatments

Once a patient begins treatment for GSM she may benefit from regular use of vaginal dilators. Proper dilator use has been found to reduce pain with vaginal penetration by improving vaginal elasticity [17] and decreasing pain. Dilators are used in a sequential fashion and can most effectively be learned with the help of a subspecialized pelvic floor physical therapist. If specialized training is not possible, there are several internet guides available to help patients trying to learn dilator therapy.**https://www.mskcc.org/cancer-care/patient-education/how-use-vaginal-dilator**.

Pelvic Floor Physical Therapy PFPT improves vulvovaginal tissue elasticity, pelvic floor muscle relaxation capacity, and vaginal introitus width in women with GSM. As such, it can be a useful adjunct for women who experience urinary incontinence and increased discomfort with vaginal friction. However, postmenopausal women with GSM can have variable lower urinary tract and pelvic floor symptoms. For example, women with urinary incontinence often have decreased pelvic floor muscle (PFM) tone, whereas women with heightened vulvovaginal pain or dysesthesia (such as

vestibulodynia) may have heightened PFM tone. Effective treatment of the underlying pelvic floor dynamic problem requires an experienced pelvic floor physical therapist who can avoid exacerbating underlying pelvic floor dysfunction through the implementation of a discordant PFM treatment program. The preponderance of evidence in support of PFPT in women with GSM points towards an improvement in symptoms for women who experience concomitant GSM and urinary incontinence,[18,19] with smaller studies also supporting the role of PFPT in women with dyspareunia.[20]

Vaginal laser therapy utilizing CO2, Erbium laser and radiofrequency (RF) devices are thought to improve vascularization and connective tissue within the vaginal canal. They have been used to treat vaginal atrophy, dyspareunia, and vaginal laxity, however the FDA issued a recent notification urging caution in marketing these devices ahead of the scientific evidence. [21,22,23] A recent study looked at 6 month follow up after CO2 laser compared to use of conjugated vaginal estrogen cream. Results showed 85.8% of laser participants rated their improvement as “better or much better” and 78.5% reported being either “satisfied or very satisfied” compared to 70% and 73.3% in the estrogen group, respectively. The difference was not statistically different. [24]

Table 3: Pharmacologic treatments for genitourinary syndrome of menopause (GSM)

Treatment	Product Name	Dose
Vaginal Cream		
17-beta- estradiol cream	Estrace, generic	0.5-1 gm daily for 2 weeks then 0.5-1gm 1-3x per week
Conjugated equine estrogens cream	Premarin	0.5-1 gm daily for 2 weeks then 0.5-1gm 1-3x per week
Vaginal Inserts		
Estradiol vaginal tablets	Vagifem®, Yuvafem®	10 mcg inserts daily for 2 weeks and then 2x per week
Estradiol soft gel capsules	ImVexxy®	4, 10 mcg inserts daily for 2 weeks and then 2x per week
DHEA (prasterone) inserts	Intrarosa®	6.5 mg capsules daily
Vaginal Ring		
17-beta-estradiol ring	Estring®	1 ring inserted every 3 months
SERM		
Ospemifene oral tablets	Osphena®	60 mg tablet daily

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