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Practical CE Newsletter for Clinicians

Genitourinary Syndrome of Menopause: Updated Terminology, Diagnosis, and Treatment

Dana R. Siegel, MD,* Megan Masten, MD,* and Nanette F. Santoro, MD

Learning Objectives: *After participating in this continuing professional development activity, the provider should be better able to:*

1. Explain genitourinary syndrome of menopause, including its typical presenting clinical signs and symptoms.
2. Identify predisposing factors for genitourinary syndrome of menopause and outline an appropriate patient assessment.
3. Summarize recommendations for patients regarding pharmacologic and nonpharmacologic treatment options.

Key Words: Genitourinary syndrome of menopause, Menopause

Menopause is defined by the American College of Obstetricians and Gynecologists (ACOG) as the period in a woman's life after the complete cessation of menses for at least 12 months.[1] This time in a woman's life is marked by fluctuations in several hormones as the ovaries cease to produce estradiol and progesterone, and is commonly associated with a variety of bothersome symptoms as a result of the eventually permanent hypoestrogenic state. The minimal amount of circulating estradiol present in the postmenopausal period is associated with a significantly decreased quality of life (QOL) in many women, including adverse effects on sexual health.[2,3]

One particularly bothersome and pervasive constellation of symptoms is genitourinary syndrome of menopause (GSM), a term coined in 2014 by the International Society for the Study of Women's Sexual Health and the North American Menopause Society. GSM encompasses the signs and symptoms related to changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and/or bladder that occur in menopausal women.[4] The symptoms of GSM are highly prevalent, with estimates ranging from 27% to 85% of postmenopausal women.[5-7] Despite the widespread nature of this condition, the majority of women do not discuss their symptoms with their health care provider.[7] It is important for providers to identify this condition and perform a comprehensive evaluation to provide patients with appropriate recommendations for treatment options and lifestyle modifications.

Definition, Prevalence, and Pathogenesis of Genitourinary Syndrome of Menopause

GSM describes the signs and symptoms related to bothersome changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and/or bladder that occur in menopausal women as a result of menopause. Symptoms can include vaginal dryness, burning or irritation, sexual discomfort or pain as a result of a lack of lubrication, and/or urinary symptoms. The diagnosis of GSM is made based on

Dr. Siegel and Dr. Masten are Residents, and Dr. Santoro is Professor and Chair, Department of Obstetrics and Gynecology, University of Colorado–Anschutz School of Medicine, 12631 East 17th Ave, Room 4007, B198-6, Aurora, CO 80045; Email: dana.siegel@cuanschutz.edu. *Both authors contributed equally to this work.

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symptoms and not physical findings, all of which may vary in affected women. Although the terms "vulvovaginal atrophy" and "atrophic vaginitis" have previously been used to describe these symptoms, neither term encompasses lower urinary tract symptoms and therefore the term "GSM" is preferred.

There have been many studies conducted to establish the prevalence of this condition. Although often limited by subjective reporting of symptoms and variations in defining bothersome symptoms, cross-sectional internet surveys suggest that vaginal symptoms may occur in up to 85% of postmenopausal women, with the most prevalent symptom being vaginal dryness.[6-8] Additionally, vaginal itching affects 26% to 77% of women, with an additional 29% to 59% reporting dyspareunia. In the REVIVE-US and Women's EMPOWER surveys, vaginal itching or irritation was the first symptom to occur and vaginal dryness was the last vaginal symptom to occur. Over half of these women reported that their vaginal symptoms impacted their QOL on a daily basis.[8] Despite the widespread nature of this condition, similar surveys suggest that less than half the women had discussed their vaginal symptoms with their health care provider.[7]

GSM is caused in part by decreasing levels of estrogen. Estrogen stimulation is responsible for maintaining a well-epithelialized vaginal vault during the reproductive years. Estrogen acts on its receptors in the vagina, vulva, urethra, and trigone of the bladder to maintain the collagen content of epithelium, which affects its thickness and elasticity, maintains acid mucopolysaccharides and hyaluronic acid, keeps epithelial surfaces moist, and maintains optimal genital blood flow.[1,4] Decreased vaginal blood flow is believed to lead to a decrease in vaginal secretions. This decrease in secretions, in turn, may lead to increased tissue fragility and susceptibility to bleeding and fissures and decreased flexibility and elasticity.[9] Additionally, with age there is a loss of superficial epithelial cells in the genitourinary tract and decreased levels of subcutaneous fat in the labia majora, which together with decreased collagen content can contribute to a loss of vaginal rugation.[4]

Symptoms related to the urogenital tract including recurrent or persistent urinary tract infections (UTIs) may also be a result of changes to the vaginal flora and microbiome in postmenopausal women. For example, after menopause the vaginal pH becomes more alkaline, predominantly as a result of a decreased proportion of vaginal *Lactobacillus* species. This increase in pH may lead to an increased risk of infection and often improves with hormonal therapy.[10]

Risk Factors for GSM

By definition, GSM affects peri- and postmenopausal women. Although GSM most often develops as a result of natural menopause, these bothersome symptoms can also occur in other hypoestrogenic states such as surgical menopause and hypothalamic amenorrhea. Additionally, women who are postpartum and breastfeeding, are being treated with gonadotropin-releasing hormone analogs or aromatase inhibitors, or have undergone gonadotoxic cancer treatments may experience GSM. Women with surgical menopause, premature ovarian insufficiency, or medication-related side effects may present with more severe GSM symptoms—particularly

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related to sexual dysfunction—compared with women who undergo natural menopause.[11] This article focuses on GSM related to natural menopause as opposed to these other hypoestrogenic states. Providers caring for patients with other causes of bothersome genitourinary symptoms should initiate evaluation and treatment according to the primary diagnosis in such cases. Nonetheless, when surgical or medically induced menopause is the likely cause of GSM in younger women, treatment options will be similar.

Diagnosis and Evaluation

The diagnosis of GSM can generally be made by history and physical examination alone. By definition, women with GSM must be symptomatic. It is important to be aware of other diseases that can cause similar symptoms when evaluating patients for this condition.

History

The most common presenting bothersome symptoms related to GSM reported in clinical trials and drafted by the FDA are vaginal dryness, vaginal (or vulvar) irritation/itching, and dyspareunia.[12] Typical presenting symptoms are shown in Table 1. It is important to keep in mind that symptoms may be present in women who are not sexually active, and women may not always spontaneously report GSM symptoms without specific inquiry. Many practitioners who care for menopausal patients will include specific questions about GSM symptoms in their intake history forms, and this documentation can form the basis for further discussion. Providers should include a history and review of GSM symptoms as part of their routine assessment of all perimenopausal and postmenopausal patients. Inquiry should include timing, onset, and duration of symptoms, provoking and alleviating factors, level of associated distress and effect on QOL, and response to previous treatment(s), if applicable. Additionally, a sexual history including the effect of GSM symptoms on sexual satisfaction and partner relationship(s) is important.

Some women may present with vaginal bleeding as the chief symptom related to their GSM. This is a particularly important symptom to be aware of, as other conditions, such as endometrial malignancies, can also present with vaginal bleeding and must be ruled out.

Table 1. Common Symptoms of Genitourinary Syndrome of Menopause[4,13]

Vulvovaginal dryness
Decreased vaginal lubrication during sexual activity
Dyspareunia (vulvar or vaginal pain)
Vulvar or vaginal bleeding (postcoital, fissures, and excoriations)
Decreased arousal, orgasm, or sexual desire
Vulvovaginal burning, irritation, or itching
Vaginal discharge (leukorrhea or yellow and malodorous)
Urinary tract symptoms (urinary frequency, dysuria, urethral discomfort, hematuria, and recurrent urinary tract infections)

Physical Examination

A pelvic examination is necessary in the diagnosis of GSM predominantly to rule out other pathologic conditions that may cause similar symptoms. The pelvic examination should first start with inspection of the external genitalia, paying close attention to the appearance of the labia majora, labia minora, mons pubis, urethral meatus, and clitoris. Practitioners should note whether excoriations or lesions are present. Although visual inspection of the vaginal vault and the cervix may be helpful in the diagnosis of GSM, sometimes this may not be possible due to severe narrowing of the introitus and subsequent intolerable discomfort. Practitioners may want to first assess for vaginal stenosis with a lubricated finger before examining with a speculum. When a speculum can be tolerated, using smaller specula (Pederson or pediatric) and lubrication can improve patient comfort. Regardless, physical examination findings that are consistent with GSM include but are not limited to reduced bulk of external genitalia, hypopigmentation, loss of rugation of vaginal mucosa, vaginal friability, labial fusion, fissures, urethral prolapse, inability to see the cervical os, attenuation of the vaginal fornices, and in some cases, malodorous brown or yellow discharge.

Physical examination findings that may be suspicious for an alternative diagnosis include erythematous, white or lichenified plaques, atypical appearing hyperpigmentation, changing vascular patterns, lesions that are raised with an irregular surface, or lesions that do not resolve with standard therapy.[14] Vulvar dysplasia, cancer, and all of the vulvar dystrophies including lichen sclerosus et atrophicus can cause symptoms consistent with GSM, and must be ruled out before appropriate therapy can be provided.

Additional Testing

It is currently not recommended to obtain routine laboratory evaluations in women presenting with typical signs and symptoms consistent with GSM. In some cases, however, it may be appropriate. A urinalysis with reflex to urine culture should be obtained for women with urinary symptoms. Women with vaginal bleeding always need a comprehensive workup for endometrial hyperplasia or malignancy with a transvaginal ultrasound and/or an endometrial biopsy, if applicable. Additionally, a vulvar biopsy, wet-mount microscopy, vaginal pH, amine (whiff) test, and/or vaginal fungal culture may be warranted if there is a suspicion for an alternative and/or confounding diagnosis such as infection, lichen planus, lichen sclerosis, contact dermatitis, desquamative inflammatory vaginitis, vulvar intraepithelial neoplasia, or other pathologies.

Treatment

Nonhormonal Options

Treatment depends on the predominant presenting or elicited symptom(s) of the patient. Regardless, first-line treatments for GSM are typically nonhormonal and include

Table 2. Topical Hormonal Treatment Options for Genitourinary Syndrome of Menopause[1,15,16]

Predominant Symptom	Recommended Treatment	Formulation	Regimen
Recurrent cystitis	17β-estradiol 0.01%	Vaginal cream	0.5–1 g/d × 2 wk → 1 g 1–3 times/wk
	17β-estradiol	Vaginal ring	2-mg ring into upper one-third of vagina × 90 d
	17β-estradiol	Vaginal insert	4-μg tablet/d × 2 wk → 1 insert twice/wk → 1 insert every 3–4 d
Vulvar/vaginal atrophy (mild)	17β-estradiol 0.01%	Vaginal cream	2–4 g/d × 1–2 wk → ½ the initial dose × 1–2 wk → 1 g 1–3 times/wk
	17β-estradiol	Vaginal insert	4- to10-μg tablet/d × 2 wk → 1 insert twice/wk → 1 insert every 3–4 d
	17β-estradiol	Vaginal ring	2-mg ring into upper one-third of vagina × 90 d
	Estradiol hemihydrate	Vaginal insert	10- to 25-μg tablet/d × 2 wk → 1 insert twice/wk
Vulvar/vaginal atrophy (moderate to severe)	Conjugated equine estrogen	Vaginal cream	0.5 g/d × 21 d on, 7 d off → 0.5–2 g twice/wk
	Dehydroepiandrosterone (prasterone)	Vaginal insert	6.5-mg insert once daily at bedtime

vaginal moisturizers and lubricants. Options for lubricants can include water, silicone, or oil-based lubricants such as coconut oil. Lubricants can be used as needed typically before and during sexual activity. Vaginal moisturizers are bioadhesives that are recommended to be used routinely, 2 or 3 days a week, and not just with sexual activity. Other nonhormonal options include referral to a pelvic floor physical therapist (PFPT) and/or use of lubricated vaginal dilators.[15] There are several additional treatment methods that require more research, such as laser or radiofrequency devices, oral vitamin D and E, and vaginal probiotics.

Hormonal Treatment

Hormonal therapy, typically in the form of topical estrogen, may be prescribed for patients with persistent symptoms if there are no contraindications. In general, there are two main forms of local estrogen therapy (ET): estradiol and conjugated estrogens. Estriol is another formulation but is not available in the United States. Formulations are available in various different dosages and forms depending on the predominant symptom and patient preference as described in Tables 2 and 3. Low-dose systemic estrogen (±progesterone) may also be used for persistent vaginal symptoms; however, this is not routine for women with solely vulvovaginal symptoms and thus is not the focus of this article.

Other hormonal options can be offered, such as vaginal dehydroepiandrosterone (DHEA), testosterone, or oral ospemifene. DHEA is a corticosteroid hormone precursor that is metabolized to estradiol and testosterone by vaginal mucosal cells. It is FDA-approved for treatment of dyspareunia in women with GSM. Some clinicians prescribe vaginal testosterone off-label for GSM; this is usually with the concurrent goal of treating low libido. Oral ospemifene, a selective estrogen receptor modulator (SERM), is another FDA-approved option for patients who prefer oral medications or for those who are not able to insert a vaginal medication.

Efficacy

A randomized clinical trial of 302 postmenopausal women with GSM demonstrated that women treated with topical ET, over-the-counter vaginal moisturizer, or placebo gel all had similar reductions in their most bothersome vaginal symptoms.[17] These findings imply that many women can be effectively treated with nonhormonal options, and reinforce the importance of this first line of therapy. However, many women who have persistent symptoms despite the use of vaginal lubricants or moisturizers wish to proceed with ET. A systematic review of 19 randomized trials including over 4000 patients showed that local estrogen creams, inserts, and rings were all similarly effective in relieving symptoms of vaginal atrophy.[18] For patients with symptoms such as fissures, vaginal creams may be applied directly to the area and may improve symptoms more quickly. Topical ET has also been shown to help ameliorate some urinary symptoms of GSM including recurrent UTIs or urethral prolapse, and is also recommended for women who use a pessary for pelvic organ prolapse.[16]

Table 3. Systemic Hormonal Treatment Options for Genitourinary Syndrome of Menopause[1,15,16]

Predominant Symptom	Recommended Treatment	Formulation	Regimen
Vulvar/vaginal atrophy (moderate to severe)	Conjugated equine estrogen	Oral	0.3–0.45 mg/d
	Micronized 17β-estradiol	Oral	0.5 mg/d
	17β-estradiol	Transdermal	0.025 mg/d applied once/wk
	Ospemifene	Oral	60 mg/d

Safety

It is important to caution patients about the content of the vaginal lubricants and moisturizers available on the market. These products are not FDA-approved, and a recent analysis of their content revealed a wide variation in pH and osmolality, with a number of products falling well outside of the physiologic range.[19] This supraphysiologic osmolality of certain lubricants has the potential to cause vulvar irritation and tissue damage. Additionally, certain additives and preservatives in lubricants may cause alterations in the vaginal microbiome leading to an increased susceptibility to bacterial and other sexually transmitted infections.

In terms of hormonal therapy, studies have shown that women who use the recommended dose of vaginal ET have similar serum estrogen levels to untreated postmenopausal women. However, estradiol levels in women using vaginal ET seem to be related to the specific preparation and the duration of use. A recent systematic review of all clinical trials involving FDA-approved vaginal estrogen preparations showed that the average baseline level of serum estradiol in untreated postmenopausal women is 11.2 pg/mL whereas the average serum estradiol level among all treated postmenopausal women is 30.0 pg/mL.[20] Higher estradiol levels seem to be associated with initial phases of use (first 12 weeks), when the vaginal epithelium poses less of a barrier to systemic absorption. The use of vaginal creams also seems to produce higher serum estradiol levels as compared with tablets, rings, or inserts.

The clinical significance of a small, sustained increase in circulating estradiol is not known. Although current data lack sufficient statistical power to definitively rule out an association between local ET and endometrial hyperplasia or endometrial cancer, all studies to date have been reassuring.[20] In light of the reassuring clinical data, progestin therapy is generally not believed to be necessary with the currently available low-dose estrogen preparations. Additionally, several prospective cohort studies have shown that vaginal ET is not associated with an increased risk of invasive breast cancer, coronary heart disease, venous thromboembolism (VTE), or colorectal cancer.

The most common reported side effects of vaginal ET include vaginal discharge, "messiness" of vaginal creams, vulvovaginal candidiasis, vaginal bleeding, and breast pain.[21] Women who use ospemifene should be apprised of similar side effects experienced by those using other SERMs including hot flushes, vaginal discharge, and muscle spasms. Data are lacking regarding long-term safety of DHEA or topical testosterone.

Treatment Considerations (Hormone-Related Malignancies)

For patients with estrogen-dependent breast, ovarian, or uterine cancers, nonhormonal options (eg, lubricants, moisturizers, and PFPT) are first-line therapy.[22-24] However, low-dose vaginal ET or vaginal DHEA may be reasonable subsequent-line choices if symptoms do not improve with nonhormonal treatments for patients with breast cancer treated with SERMs or aromatase inhibitors, patients who have completed a full course of adjuvant endocrine therapy, or for those with hormone receptor-negative disease. However, these should be initiated only after consultation with the patient's oncologist and after comprehensive counseling about potential risks. Vaginal DHEA, ospemifene, and testosterone are not recommended at this time for patients with breast cancer treated with aromatase inhibitors due to lack of long-term safety data.

Follow-up and Outcomes

Although many women will experience an improvement in subjective GSM symptoms within a few weeks of starting treatment, some women may require several months of treatment before noticing an improvement.[15] Although clinical trial safety data are limited to 1 year of follow-up, observational studies have shown promising long-term safety data and therefore the current recommendation is to continue treatment for as long as needed in the absence of contraindications. In terms of follow-up, there is currently no consensus or recommendations for routine surveillance. In the absence of personal or familial risk factors for endometrial hyperplasia, routine evaluation of the endometrial lining is not recommended unless there is a concern for endometrial cancer.

Barriers

Although almost half of women worldwide experience vaginal symptoms related to GSM with over two-thirds of these women stating that their symptoms negatively impact their QOL, only a small percentage of affected women obtain care or seek treatment for their condition.[13] Results from the EMPOWER study conducted by Kingsberg et al[7] highlighted the top 3 reasons women do not discuss these symptoms with a health care provider, which were (1) they believe that it is just a natural part of aging (42%), (2) they are uncomfortable discussing their symptoms with their health care provider (18%), and (3) they are unaware of potential treatment options that exist (13%). Due to the significant morbidity and impact on QOL that this condition can cause, it is imperative that both women and health care providers feel comfortable initiating a discussion surrounding the topic of GSM so that treatment can be initiated effectively and efficiently.

An additional barrier to effective treatment may be a woman's understandable hesitation to initiate ET due to the black box warning present on low-dose vaginal estrogen preparations despite the reassuring safety data. Currently, vaginal ET and systemic ET contain the same aggressive warning labels that may cause treatment reluctance in many women. Health care providers must be prepared to discuss these uncertainties and provide an evidence-based and individualized treatment plan for their patients.

Conclusion

GSM is a condition that providers caring for women will encounter frequently in their practice. Providers should

consider a diagnosis of GSM if a patient presents with bothersome genitourinary symptoms not explained by another cause. The diagnosis of GSM is typically made clinically. A pelvic examination is warranted in cases of GSM-related symptoms to rule out other possible causes of the presenting symptoms. Women with additional symptoms or concerning features should undergo further testing as indicated. Treatment options for most women with GSM include lubricants, vaginal moisturizers, and local ET. Some women with associated comorbidities, such as a history of endometrial and/or breast cancer, will require additional counseling and considerations for treatment. In most cases, a suitable treatment approach for women with GSM can be identified that will be effective and well-tolerated.

Practice Pearls

- GSM is defined as bothersome symptoms related to the genitourinary tract in menopausal women that are not explained by a secondary diagnosis.
- Common symptoms include vaginal dryness, vaginal (or vulvar) irritation, and/or dyspareunia. Other symptoms may include urinary urgency, dysuria, recurrent UTIs, vaginal discharge, decreased sexual desire, vulvar, or vaginal bleeding.
- Diagnosis is made on the basis of history and physical examination. Some physical examination findings may warrant an additional workup, such as biopsy, if abnormal-appearing vulvar plaques or lesions, hyperpigmentation, or abnormal vascularity is/are present. Exclude endometrial hyperplasia and/or infection, if applicable.
- First-line treatment is vaginal moisturizers, lubricants, and/or PFPT. Second-line options include vaginal ET, vaginal DHEA, or oral ospemifene. Local estrogen preparations are available in creams, inserts, or rings. Testosterone may be used off-label but is not FDA-approved.
- All estrogen preparations are similarly effective, and it may take several months to see the fullest effects. There is no increased risk of endometrial hyperplasia, breast cancer, VTE, or cardiovascular disease with ET. In some patients with breast cancer, ET may be safe to use; however, the oncologist should be consulted before prescribing.
- Although GSM affects more than half of all menopausal women, only a small percentage obtain care or treatment. Reviewing symptoms related to GSM should become a routine part of providers' visits with menopausal women.

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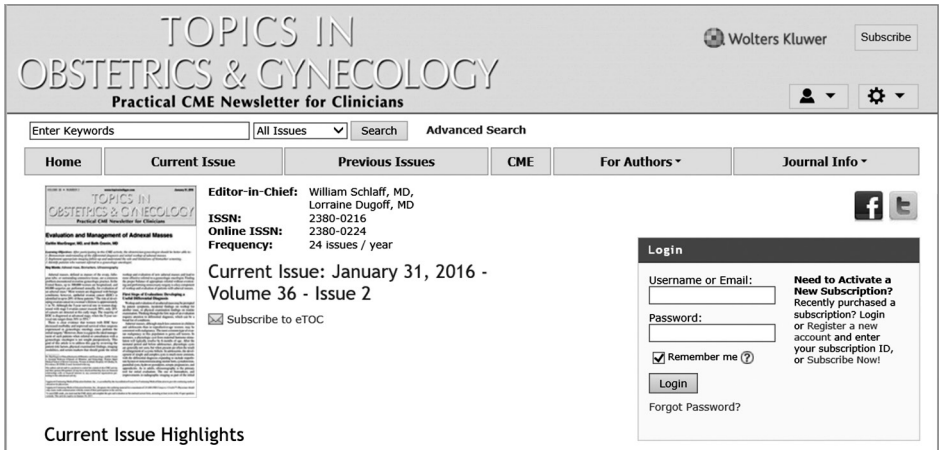

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1. A 56-year-old G1P1 woman who has been postmenopausal for 5 years presents with decreased libido, decreased vaginal lubrication with intercourse, and intermittent bleeding. Physical examination reveals a normal-appearing cervix. Bimanual examination is normal, but vaginal atrophy is noted. Which one of the following is the appropriate next step?
- **A.** Vaginal estrogen cream
- **B.** Vaginal estrogen ring
- **C.** Transvaginal ultrasound or endometrial biopsy
- **D.** Order follicle-stimulating hormone and luteinizing hormone levels

2. All of the following can be signs or symptoms of GSM *except*
- **A.** vulvovaginal dryness
- **B.** dyspareunia
- **C.** vaginal fissure
- **D.** urinary frequency
- **E.** white vulvar plaques

3. A 59-year-old, postmenopausal, G4P4 woman presents for annual examination. She describes vaginal dryness and painful intercourse for the past year. Which one of the following is the *best* advice for this patient?
- **A.** Let her know that, unfortunately, this is a normal part of aging.
- **B.** Express dismay but advise that there are no treatments available.
- **C.** Counsel her regarding conservative nonhormonal options to try first, such as moisturizers and lubricants.
- **D.** Recommend systemic hormone replacement therapy.

4. All of the following are FDA-approved formulations for the treatment of GSM, *except*
- **A.** testosterone
- **B.** 17β-estradiol vaginal cream
- **C.** estradiol hemihydrate tablets
- **D.** DHEA (prasterone)
- **E.** ospemifene

5. Commonly reported side effects of vaginal ET include
- **A.** vaginal discharge
- **B.** vulvovaginal candidiasis
- **C.** vaginal bleeding
- **D.** breast pain
- **E.** all of the above

6. Diagnosis of GSM requires which one of the following?
- **A.** Bothersome genitourinary symptoms not explained by another cause
- **B.** Fusion of the labia minora
- **C.** Attenuation of the vaginal fornixes
- **D.** Wet-mount microscopy showing a pH more than 5

7. A 60-year-old, postmenopausal patient reports persistent vaginal dryness 1 week after starting 17β-estradiol 0.01% 1-g/d vaginal cream. Which one of the following is the *best* advice to this patient?
- **A.** Come into the office immediately to be seen.
- **B.** Increase the dose to 2 g/d.
- **C.** Continue using the current dose; a change may be appropriate if symptoms have not improved at 4-week follow-up.
- **D.** Stop using the cream as it is clearly not working.

8. A 54-year-old patient presents with vaginal dryness. She has a history of estrogen receptor, progesterone receptor-positive breast cancer, and is in remission. She has never sought treatment for her symptoms. Which one of the following is an appropriate first-line recommendation?
- **A.** Vaginal lubricant or moisturizer
- **B.** Vaginal estrogen cream
- **C.** DHEA (prasterone)
- **D.** Testosterone
- **E.** Pelvic floor physical therapy

9. Vaginal ET is *not* recommended in a patient
- **A.** using an aromatase inhibitor
- **B.** with estrogen receptor-positive breast cancer
- **C.** with human epidermal growth factor receptor 2/neu-positive breast cancer
- **D.** using a SERM

10. All of the following contribute to GSM pathogenesis *except*
- **A.** decreased collagen in epithelium of genital tissues
- **B.** decreased genital blood flow
- **C.** increase in *Lactobacillus* species
- **D.** increased tissue fragility