

## CONSENSUS RECOMMENDATIONS

# Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health

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### Abstract

The objective of The North American Menopause Society (NAMS) and The International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel was to create a point of care algorithm for treating genitourinary syndrome of menopause (GSM) in women with or at high risk for breast cancer. The consensus recommendations will assist healthcare providers in managing GSM with a goal of improving the care and quality of life for these women. The Expert Consensus Panel is comprised of a diverse group of 16 multidisciplinary experts well respected in their fields. The panelists individually conducted an evidence-based review of the literature in their respective areas of expertise. They then met to discuss the latest treatment options for genitourinary syndrome of menopause (GSM) in survivors of breast cancer and review management strategies for GSM in women with or at high risk for breast cancer, using a modified Delphi method. This iterative process involved presentations summarizing the current literature, debate, and discussion of divergent opinions concerning GSM assessment and management, leading to the development of consensus recommendations for the clinician.

Genitourinary syndrome of menopause is more prevalent in survivors of breast cancer, is commonly undiagnosed and untreated, and may have early onset because of cancer treatments or risk-reducing strategies. The paucity of evidence regarding the safety of vaginal hormone therapies in women with or at high risk for breast cancer has resulted in avoidance of treatment, potentially adversely affecting quality of life and intimate relationships. Factors influencing decision-making regarding treatment for GSM include breast cancer recurrence risk, severity of symptoms, response to prior therapies, and personal preference.

We review current evidence for various pharmacologic and nonpharmacologic therapeutic modalities in women with a history of or at high risk for breast cancer and highlight the substantial gaps in the evidence for safe and effective therapies and the need for future research. Treatment of GSM is individualized, with nonhormone treatments generally being first line in this population. The use of local hormone therapies may be an option for some women who fail nonpharmacologic and nonhormone treatments after a discussion of risks and benefits and review with a woman's oncologist. We provide consensus recommendations for an approach to the management of GSM in specific patient populations, including women at high risk for breast cancer, women with estrogen-receptor positive breast cancers, women with triple-negative breast cancers, and women with metastatic disease.

**Key Words:** Atrophic vaginitis – Breast cancer – Breast cancer risk – Breast cancer survivors – Genitourinary syndrome of menopause – Vulvovaginal atrophy.

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## INTRODUCTION

There are currently 3.1 million US survivors of breast cancer;<sup>1</sup> however, despite advances in screening and treatment resulting in increased survivorship, breast cancer continues to be a major health concern in terms of both mortality and quality of life (QOL) for women living with breast cancer or with a history of breast cancer.

Genitourinary syndrome of menopause (GSM) is a constellation of physical changes and symptoms including vulvovaginal dryness, burning, or irritation; dyspareunia; and urinary symptoms of urgency, dysuria, or recurrent urinary tract infection (UTI) associated with estrogen deficiency.<sup>2</sup> Although GSM affects more than 50% of the general population of postmenopausal women, it is even more pervasive in survivors of breast cancer,<sup>3-7</sup> most of whom are undiagnosed and untreated.<sup>8,9</sup>

Many survivors of breast cancer experience earlier onset of GSM symptoms because of chemotherapy-induced ovarian insufficiency, surgical removal of the ovaries, or radiation therapy.<sup>10,11</sup> Compounding the situation, the use of adjuvant endocrine therapy with gonadotropin-releasing hormone (GnRh) agonists, aromatase inhibitors (AIs), or selective estrogen-receptor modulators (SERMs; eg, tamoxifen, raloxifene) has increased from 69.8% in 2004 to 82.4% in 2013 in women with hormone-receptor positive cancers.<sup>12</sup> Additionally, the recommended duration of these therapies has extended from 5 to 10 years.<sup>13</sup> For the menopausal population who have been diagnosed with or are at high risk for breast cancer, many have the added burden of not being a candidate for or being reluctant to use hormone therapies to manage symptoms.

Given that GSM is highly prevalent in women with breast cancer, it is important for clinicians to query women about symptoms.<sup>14</sup> Data suggest that long-term survivors of breast cancer often report normalization of physical and emotional functioning but experience continued difficulty with sexual functioning and satisfaction for 5 or more years after treatment.<sup>15</sup> Women may be reluctant to bring up the topic of vaginal and sexual health and are often relieved when their clinicians begin a conversation. Even women who are not comfortable discussing sexual health at the first encounter may be willing to do so in subsequent visits. A retrospective

chart review of 800 women from a breast cancer survivorship clinic at a major national cancer center found that only 39.8% of the 279 women with documented GSM symptoms received any form of treatment or referral for treatment.<sup>8</sup>

Clinician reluctance to treat may reflect the paucity of evidence regarding safety of currently available therapies for GSM in women with or at high risk for breast cancer.<sup>16</sup> The unintended consequence is that women are driven to untested and non-FDA-approved therapies. In women with a history of breast cancer, the decision of how to treat GSM depends on many factors, including receptor status, genetic characteristics, extent of disease, time interval since diagnosis, and response to prior therapies. Care for women with or at high risk for breast cancer would be enhanced by an evidence-based compilation of available GSM treatment options, along with a discussion of limitations in the science concerning risks specific to this population.

In these consensus recommendations, prepared by a multidisciplinary group of experts, we review current evidence and provide recommendations for assessment and treatment of GSM in women with or at high risk for breast cancer and highlight the substantial research gaps in clinical evidence for safe and effective treatment strategies.<sup>16-22</sup>

## IDENTIFICATION AND ASSESSMENT

## Screening

The simplest approach for clinicians to detect sexual problems related to GSM is to start a conversation with the woman when it feels relevant during the encounter. Clinicians can begin with a ubiquity statement such as, “Many women after menopause . . . undergoing breast cancer treatment . . . have concerns about sexual functioning,” followed by a close-ended question: “What about you?” and an open-ended inquiry to patient responses: “Tell me about it.”<sup>23</sup> This demonstrates that the clinician thinks discussing sexual health is important and normalizes and universalizes sexual concerns for women.<sup>24</sup> Clinicians can also ask a direct screening question such as, “Do you have any problems or concerns related to sex or pain with sexual activity?”

Structured approaches to incorporating sexuality into clinical practice provide strategies for identification, assessment, management, and/or referral for sexual health concerns. The

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PLISSIT model (P - permission, LI - limited information, SS - specific suggestions, IT - intensive therapy) has been widely used.<sup>25</sup> The BETTER model (B - bringing up the topic, E - explaining the importance of sexuality, T - telling the patient about resources, T - addressing timing, E - educating about sexual side effects of treatment, and R - recording the discussion) was devised specifically for patients with cancer.<sup>26</sup>

**Assessment**

**Assessment of GSM**

It is important to gain a clear understanding of a woman’s genitourinary symptoms and how they affect her QOL and intimate relationship (s). In history taking, validate her concerns and elicit her priorities. There are readily available, simple, and effective tools for identification of symptoms and assessment of effect on QOL, including the Day-to-Day Impact of Vaginal Aging questionnaire<sup>27</sup> and the Sexual Symptom Checklist for Women After Cancer.<sup>28</sup>

In addition to a complete history, which includes review of potential medications that might cause vaginal dryness, women with genitourinary complaints should undergo a physical examination before starting treatment. The examination should include visual external inspection, speculum, and bimanual pelvic examination as clinically relevant and to exclude other conditions that might mimic GSM, such as vaginitis, lichen sclerosus, or other dermatopathology. During an examination, the woman and clinician can review areas of concern, and women can be educated regarding anatomy and instructed in the application of local therapies, using a hand mirror as needed.

**Assessment of breast cancer risk**

Identification of women at high risk for breast cancer may factor into shared decision-making regarding the use of local hormone therapies for GSM. Breast cancer risk is increased in women with a family history of breast cancer or a personal history of breast biopsy and in women with a history of Hodgkin lymphoma treated with mantle radiation. Breast cancer risk assessment tools including the Breast Cancer Risk Assessment Tool,<sup>29</sup> Claus,<sup>30</sup> Breast Cancer Surveillance Consortium,<sup>31</sup> Tyrer-Cuzick (International Breast Cancer Intervention Study),<sup>32</sup> and others are useful to more accurately

define risk.<sup>33-35</sup> There is no single cut-off for defining high risk for breast cancer; however, the American Society of Clinical Oncology concludes that women with an estimated 5-year risk of 1.67% or greater are candidates for chemoprevention,<sup>36</sup> and high-risk women, defined by a lifetime risk of more than 20%, are candidates for enhanced surveillance with breast magnetic resonance imaging.<sup>37</sup>

When assessing women with GSM with a history of breast cancer, it is important for the clinician to identify factors that may affect decision-making. These factors include balancing the risk of recurrence, which is influenced by the stage and grade of the cancer; presence of lymphovascular invasion; hormone-receptor status; use of endocrine therapy; and the time since diagnosis, with the severity of genitourinary symptoms, QOL, and efficacy of conservative therapies (Table 1). Although data are lacking, based on our consensus opinion, women with an overall lower risk of recurrence versus higher risk; with receptor-negative versus receptor-positive disease; using tamoxifen versus AIs; and with severe symptoms and greater concerns about quality of life versus fewer symptoms and concerns may be better candidates for local hormone therapy.

**TREATMENT**

Validating the effect of GSM on survivors of breast cancer and the importance of seeking treatment for relieving symptoms and improving QOL is critical. The clinician should explain the pathophysiology of GSM and review potential genitourinary effects of breast cancer treatment.

Counseling patients with or at high risk for breast cancer about treatment options for GSM should include a shared decision-making approach employing principles of informed consent.<sup>38</sup> The discussion about treatment options should include the mechanism of action, if known; potential adverse effects; current data regarding efficacy and safety; and the benefits and risks of each treatment option.<sup>39</sup> Clinicians should evaluate the woman’s perceived need for treatment versus fears regarding breast cancer risk or recurrence risk. Additionally, consultation with a woman’s oncology team is suggested.<sup>18,40,41</sup> Finally, when therapy is initiated, follow-up care should be arranged to ensure improvement in or resolution of symptoms and to assess compliance and barriers to treatment.

**TABLE 1.** Factors affecting decision-making regarding local hormone therapy

	More desirable candidates	Less desirable candidates
Stage of disease	Stage 0, 1, and 2 or metastatic with limited life expectancy	Stage 3 or metastatic disease with extended life expectancy
Grade of disease	Low or intermediate grade	High grade
Lymph node involvement	No	Yes
Hormone-receptor status	Negative	Positive
Endocrine therapy	Tamoxifen	AIs
Risk of recurrence	Low	High
Time since diagnosis	Remote	Recent
Symptom severity	Severe	Mild
Nonhormone therapies	Failed	Effective
Effect on QOL	Severe	Mild

AIs, aromatase inhibitor; QOL, quality of life.

### Nonpharmacologic treatment

Although there are limited data to support the efficacy of over-the-counter products,<sup>42,43</sup> vaginal moisturizers and lubricants are considered the initial and mainstay treatment options for GSM for women with breast cancer.<sup>3</sup> However, these products are poorly differentiated and characterized.<sup>44</sup> Vaginal moisturizers maintain tissue integrity, elasticity, and pliability and should be used on a regular basis independent of sexual activity.<sup>45,47</sup> Expert opinion, perhaps more than labeling instructions, advocates frequent use. A 12-week multicenter, randomized clinical trial compared a 10- $\mu$ cg vaginal estradiol tablet plus placebo gel versus placebo tablet plus vaginal moisturizer versus dual placebo. All three groups demonstrated similar reductions in the most bothersome symptom, with no evidence for superiority of vaginal moisturizer or 10- $\mu$ cg vaginal estradiol tablet over placebo gel. Limitations of this study include its short duration and use of a placebo gel that could have augmented the placebo response.<sup>46</sup>

Lubricants reduce friction and discomfort during penetrative sexual activity. The World Health Organization suggests the use of lubricants with an osmolality of < 380 mOsm/kg. However, most clinically available lubricants do not list osmolality on the product label and have an osmolality that exceeds this. An osmolality of < 1,200 mOsm/kg is generally considered acceptable, with higher osmolality associated with mucosal irritation.<sup>47</sup> Although lubricants with pH levels in the normal range for healthy adult women (3.8-4.5) are acceptable, those with pH levels  $\leq$  3.0 are considered unacceptable

for human use, given the association with vaginal irritation in animal models.<sup>47,48</sup> Additives such as parabens, glycerin, warming properties, flavors, and spermicides should be avoided because they may irritate vaginal and vulvar tissues.

Lubricants may be water-, silicone-, or oil-based, and patient selection depends on individual preferences and sexual activity. Hybrid products may have characteristics of both lubricants and moisturizers. Hyaluronic acid gel has been associated with reduced clinical symptoms of vaginal dryness in women without breast cancer.<sup>49</sup> There is concern regarding the use of natural oils (eg, olive, coconut) for lubrication because these products are associated with vaginal infections.<sup>50</sup>

In addition to the use of vaginal moisturizers and lubricants, regular use of vaginal dilators has been recommended for symptomatic vaginal atrophy<sup>3</sup> and has been found to reduce pain with vaginal penetration by improving vaginal elasticity.<sup>51</sup> Patients should be counseled regarding the use of vaginal dilators in graduated sizes (either by themselves or with their partners) to promote stretching of vaginal tissues. Vibratory stimulation, applied either to the vagina or directly to the clitoris, has also been studied as a modality to reduce pain with vaginal penetration.<sup>52</sup> Finally, pelvic floor therapy under the care of a physical therapist trained in the management of pelvic floor disorders is recommended to reduce pain with vaginal penetration; physical therapists may also be helpful in the direction of vaginal dilator therapy.<sup>53,54</sup>

See Table 2 for a summary of nonpharmacologic treatment strategies.<sup>55</sup>

**TABLE 2.** Nonpharmacologic treatment strategies for the management of GSM

Treatment type	Specific therapy	Typical use	Notes
Education	Educate regarding potential vulvar and vaginal changes associated with menopause or other low estrogen state; offer therapy as indicated		Education should be offered to women regardless of partner status; regular painless sexual activity or vaginal stimulation can help maintain sexual function
Counseling and sex therapy	Cognitive behavioral therapy; mindfulness exercises		Counseling or sex therapy with a qualified counselor/therapist may be useful for women with dyspareunia or relationship discord. AASECT.org
Lubricants	Water-based Silicone-based Oil-based	Used as needed for sexual activity	Used to increase comfort and pleasure; avoid potential irritants (eg, glycerin, parabens, propylene glycol); can be used with other therapies (hormone and nonhormone)
Moisturizers		Used daily or every few days on a regular basis independent of sexual play to maintain vulvar and vaginal moisture	Mimics normal vaginal secretions; does not restore or reverse cellular/pH changes of GSM; can be used with other therapies (hormone and nonhormone)
Self-stimulators/ Vibrators	May be a variety of materials (eg, latex, nonlatex, silicone, hard plastic)	Can be used as needed during sexual play, alone, or with partner	Gently stimulates vulvar and vaginal tissues; may facilitate natural lubrication; may help maintain function
Dilators	May be a variety of materials (eg, plastic, silicone, glass)	Ideal duration or frequency of use is unknown	Stretches vaginal tissues
Pelvic floor physical therapy	Examples: education on kinesthetic awareness; pelvic floor muscle relaxation; manual therapies; biofeedback	Used as needed for nonrelaxing pelvic floor muscle dysfunction	Identify a physical therapist who specializes in pelvic floor disorders <a href="http://www.womenshealthpta.org/">www.womenshealthpta.org/</a>

AASECT, American Association of Sexuality Educators, Counselors, and Therapists; GSM, genitourinary syndrome of menopause. Adapted from Faubion S, et al.<sup>55</sup>

## Pharmacologic treatment

### Vaginal estrogen

Most breast cancer prevention and treatment strategies have focused on lowering or antagonizing ambient estrogen concentrations because estrogen has been demonstrated to increase breast epithelial cell and breast cancer cell proliferation under a variety of *in vitro* and *in vivo* conditions, and lowering estradiol levels or tissue responsiveness has proven to reduce development of breast cancer or cancer recurrence.<sup>1,56,57</sup> Whether the antiestrogen effect is induced by SERMs (eg, tamoxifen or raloxifene) or by lowering endogenous estrogen production (eg, bilateral oophorectomy, ovarian suppression with GnRH agonists, use of AIs), the goal of reducing the estrogen environment to lower breast cancer risk has remained the same. Therefore, both systemic and local estrogen-based treatments are controversial or discouraged for women with a history of or at high risk for breast cancer.<sup>20</sup>

Consensus to date has been to avoid systemic estrogens in women with a history of breast cancer or at a high risk thereof.<sup>58-61</sup> Two Swedish randomized clinical trials (RCTs) of systemic hormone therapy (HT) in survivors of early breast cancer have been reported, with conflicting results.<sup>62,63</sup> The HABITS trial was prematurely stopped after a median follow-up of 2.1 years because of a statistically significant increased breast cancer recurrence in the HT group.<sup>62</sup> In the Stockholm trial, at a median follow-up of 4.1 years, the risk of breast cancer recurrence was not associated with systemic HT.<sup>63</sup>

However, clinical trials of local estrogen therapies (ET) in survivors of breast cancer all suffer design or sample-size flaws. As a result, the applied dose or the amount of active ingredient absorbed into the systemic circulation have become surrogates for breast cancer risk.<sup>64</sup> The assumption that less estrogen absorption would be less likely to stimulate the breast or foster growth of recurrent breast disease has not been fully established because several lines of evidence suggest that some estrogenic treatments may act more like SERMs *in vivo*, and estrogens may cause breast cell apoptosis after a period of estrogen deprivation.<sup>65</sup> The FDA-approved prescribing information cites a prior history of breast cancer as a contraindication to estrogen, with rare exception.<sup>66</sup> For this discussion, and based on our consensus opinion, we will assume that less systemic absorption confers lower risk.

Absorption of local ET varies by the active ingredient (potency: conjugated equine estrogens (CEE) > estradiol > estrone > estriol).<sup>67</sup> It also varies according to the amount of active ingredient applied (eg, creams applied to a greater surface area in the vagina are more readily absorbed than vaginal tablets or rings); a product's formulation (bioadhesives are less absorbed than those with penetration enhancers); where in the vagina the treatment is actually applied (lower one-third of the vagina preferred over upper two-thirds due to the vascular connection with the uterus in the upper vagina and potential for greater systemic absorption);<sup>68</sup> and whether the estrogen is applied topically to the vulvar skin and/or vestibule versus the highly absorptive vaginal epithelium. Absorption also varies greatly by the

condition of the vagina (atrophic vs estrogenized) and how long after application the assessment of absorption is determined. The thin, atrophic vagina is highly absorptive, and this diminishes when the epithelium thickens in response to estrogenization.<sup>69</sup>

Without evidence to support value in clinical decision-making, clinicians should be discouraged from measuring serum estrogen levels to assess systemic absorption of local estrogens as an indirect measure of risk for breast cancer recurrence. Although the use of local vaginal estrogens has inconsistently increased serum estradiol levels,<sup>70-72</sup> there is a lack of clarity regarding whether higher levels within a narrow postmenopause range associate with increased risk for breast cancer recurrence, and similarly, whether lower levels are reassuring.<sup>71</sup> Even unmeasurable levels by commercially available estrogen assays can effect changes in distant tissues (ie, bone,<sup>73</sup> liver<sup>74</sup>).

Observational studies have suggested the relative safety of local ET, although definitive placebo-controlled, RCT data are lacking. A large Finnish observational study identified no elevated risk of *de novo* breast cancer associated with the use of vaginal ET.<sup>75</sup> Crandall and colleagues reported no increased breast cancer risk in healthy participants in the Women's Health Initiative (WHI) observational study despite a very large sample size and duration of follow-up.<sup>76</sup> In one nested case-control study, local ET was not associated with an increased risk of recurrence in women with a history of breast cancer.<sup>77</sup>

### Vaginal DHEA

Intravaginal 0.5% (6.5 mg) dehydroepiandrosterone (DHEA) ovules, also known as prasterone, are FDA-approved for postmenopausal women with moderate to severe dyspareunia caused by vulvovaginal atrophy. Two 12-week, randomized, double-blind, placebo-controlled efficacy trials in women using 6.5 mg DHEA nightly showed significant improvement versus placebo in vaginal cell maturation, pH, and dyspareunia because of GSM.<sup>78,79</sup> The most common adverse effects are vaginal discharge (5.71%) and abnormal pap tests (2.1%). Intravaginal DHEA tested for 52 weeks showed improvement in all domains of sexual function on the Female Sexual Function Index (FSFI).<sup>80</sup> One RCT of survivors of cancer (most with breast cancer) with moderate vaginal dryness or dyspareunia compared 3.25 mg versus 6.5 mg compounded vaginal DHEA versus placebo over 12 weeks, and although neither dose of DHEA showed improvement in either dryness or dyspareunia, the cohort using the 6.5 mg DHEA showed significant improvement in sexual health on the FSFI.<sup>81</sup>

Clinical studies with highly sensitive assays show a slight but statistically significant increase in plasma estradiol and testosterone to the lower half of postmenopause values after prasterone administration.<sup>82</sup> FDA-approved vaginal DHEA has not been studied in survivors of breast cancer, and its label includes a warning against this use. There are no studies directly comparing vaginal DHEA to vaginal estrogen in

**TABLE 3.** Pharmacologic treatments for management of GSM

Treatment	Product name	Initial dose	Maintenance dose	Notes
<i>Vaginal cream</i>				
17 $\beta$ -estradiol	Estrace, generic	0.5-1 gm/d x 2 wk	0.5-1 gm 1-3 x wk	FDA-approved dose is higher (2-4 g/d loading dose; 1 g 1-3 x wk maintenance)
Conjugated estrogens	Premarin	0.5-1 gm/d x 2 wk	0.5-1 gm 1-3 x wk	FDA-approved dose is higher; administration cyclical: 0.5-2 gm/d for 21 d, off 7 d for GSM; 0.5 gm/d for 21 d, off 7 d for dyspareunia or 0.5 g twice wk for dyspareunia
<i>Vaginal inserts</i>				
Estradiol hemihydrate	Vagifem, Yuvaferm	10 $\mu$ g insert 1/d x 2 wk	1 twice wk	
17 $\beta$ -estradiol soft gel caps	TX-004HR	4, 10, or 25 $\mu$ g/d x 2 wk	1 twice wk	Not yet approved by FDA
DHEA (prasterone)	Intrrosa	6.5 mg 1/d	1/d	
<i>Vaginal ring</i>				
17 $\beta$ -estradiol	Estring	2 mg releases approximately 7.5 $\mu$ g/d x 90 d	Changed q 90 d	
<i>SERM</i>				
Ospemifene	Osphena	60 mg/d	60 mg/d	FDA approved for dyspareunia
<i>Other</i>				
Topical lidocaine		4% aqueous lidocaine	Applied to the vestibule a few minutes before sexual activity	Can be used as an adjunct to other therapies including lubricants, moisturizers, physical therapy

DHEA, dehydroepiandrosterone; GSM, genitourinary syndrome of menopause; SERM, selective estrogen-receptor modulator. From The North American Menopause Society<sup>3</sup> and Faubion S, et al.<sup>55</sup>

efficacy or hormone levels, and for this reason, there can be no recommendation of one over the other in survivors of breast cancer.

### SERMs

Ospemifene is a systemically administered SERM approved for the treatment of moderate to severe dyspareunia associated with postmenopausal vulvovaginal atrophy, with favorable effects on bone density and negligible endometrial safety concerns. Despite antiestrogenic effects on the breast in preclinical trials, the effects of ospemifene on breast density or breast cancer risk have not been systematically established in healthy women nor has ospemifene been studied in women with breast cancer. Although it is not contraindicated for women in Europe with a history of breast cancer who have completed treatment,<sup>83</sup> it is not approved by FDA for use in US women with breast cancer.<sup>21</sup>

### Lidocaine

Topical lidocaine for insertional dyspareunia was studied in 46 postmenopausal survivors of breast cancer with severe GSM, dyspareunia, increased sexual distress scores, or abnormal sexual function.<sup>84</sup> A double-blind RCT evaluating 4% aqueous lidocaine versus saline applied with a cotton ball to the vestibule for 3 minutes before vaginal penetration showed a reduction in dyspareunia of 88% versus 33% with saline.

See Table 3<sup>3,55</sup> for a summary of pharmacologic treatment options.

### Off-label hormone options

#### Vaginal testosterone

The off-label use of vaginal testosterone therapy for treatment of GSM is controversial. Advocates cite evidence that

genitourinary tissues derived from the embryonic urogenital sinus are rich in testosterone as well as estrogen receptors (ERs).<sup>85,86</sup>

Clinical use of vaginal testosterone therapies is limited because no currently available local (or systemic) testosterone formulations are FDA-approved for administration to women. In one trial, treatment of 80 healthy postmenopausal women for 12 weeks with a compounded vaginal cream containing 300  $\mu$ g of testosterone propionate improved vaginal signs and symptoms.<sup>87</sup>

Because testosterone is converted by the aromatase enzyme to estradiol, concerns with increasing serum estradiol levels in response to testosterone therapy have confined participants in the few trials of vaginally administered testosterone in women with a history of breast cancer to those also taking AIs, which block this conversion.<sup>88-90</sup> In two of these trials, serum testosterone levels were not fully characterized,<sup>88,90</sup> whereas in the third, serum testosterone reached the supraphysiologic range (200 ng/dL) after 4 weeks of treatment. Despite the fact that women in the third trial were taking AIs, 12% had persistently elevated estradiol levels as well.<sup>91</sup>

#### Vaginal estriol

Estriol vaginal preparations (gels, creams, and suppositories) are manufactured and government regulated in a number of countries outside the United States where placebo-controlled trials have found benefit for vaginal symptoms in healthy postmenopausal women.<sup>92,93</sup> Limited evidence reported in a small RCT suggests that 0.5 mg vaginal estriol cream may also prevent recurrent UTIs.<sup>94</sup> In one 12-week, open-label pilot study of 16 women with a history of breast cancer taking an AI, 0.03 mg estriol tablet in combination with lactobacilli improved vaginal symptoms.<sup>95</sup>

Claims for breast safety of estriol administration have not been substantiated in RCTs in either healthy women or those with a history of breast cancer. In vitro studies demonstrate stimulation of breast cancer cells by estriol.<sup>96</sup> Estriol is not FDA approved for any indication.

### Vaginal laser

The FDA has approved laser therapy for several medical indications (eg, refractive eye surgery, dental procedures, tumor and cataract removal, cosmetic surgery). Available data suggest that inducing morphologic changes in vaginal tissue with laser intervention can alleviate the symptoms of vaginal dryness and dyspareunia accompanying GSM.<sup>97-103</sup>

When treating GSM in women with or at high risk for breast cancer, the microablative fractional CO<sub>2</sub> laser or the non-ablative vaginal Erbium YAG laser (VEL) are options that avoid hormone interventions, a potential advantage over pharmacologic therapies. Although the CO<sub>2</sub> laser appears to target more superficial tissue, the VEL appears to remodel deep collagen and promote collagen synthesis. This effect may promote production of new collagen that ultimately could result in improved tissue integrity and elasticity.

A recent parallel-group, short-term Brazilian clinical trial of the CO<sub>2</sub> laser compared with 1 mg estriol cream in a cohort of 45 women suggests efficacy of laser alone or in combination with estriol after 20 weeks.<sup>104</sup> Recently, Pagano and associates published a retrospective case series of 82 survivors of breast cancer who failed to have adequate relief of their GSM symptoms with nonestrogenic local treatments.<sup>105</sup> These women were treated with three cycles of CO<sub>2</sub> laser at 30- to 40-day intervals and demonstrated significant improvements in genital sensitivity during intercourse, vaginal dryness, decreased itching/stinging, dyspareunia, dysuria, bleeding, and movement-related pain when assessed after the three treatments. These benefits were significant regardless of the woman's age or type of adjuvant breast cancer therapy. The authors noted that the optimal number of treatment cycles and the need for and number of retreatments remained to be defined and called for randomized, prospective comparative trials.<sup>106</sup> A prospective study of CO<sub>2</sub> laser in 20 survivors of breast cancer demonstrated reduction in clinical symptoms of GSM in addition to significant changes in inflammatory and modulatory cytokines, but no change in the vaginal microbiome 30 days after the second laser treatment.<sup>107</sup>

A small Argentinian trial compared the Erbium laser (three treatments over 8 weeks; pretreatment with estriol 0.5 mg ovules for 2 weeks) with 0.5 mg estriol ovules administered for 8 weeks and noted significant and long-lasting improvement in symptoms in the laser-treated group after up to 18 months of follow-up.<sup>108</sup>

Although large, sham-controlled, RCTs have not been completed to date in women with or without breast cancer, one is planned (IBC Alliance trial). Available data suggest the VEL or CO<sub>2</sub> lasers have the potential to ameliorate distressing GSM for survivors of breast cancer without the need for local

hormone intervention. Placebo or active-controlled trials, long-term safety follow-up, and additional economic analyses are needed.

### SPECIFIC PATIENT POPULATIONS

In this section, we review the data regarding management of GSM in specific patient populations. Treatment should be individualized, taking into account recurrence risk, the severity of symptoms, effect on QOL, and personal preferences. In general, women with or at high risk for breast cancer should be offered nonhormone therapies as first-line treatments for management of symptoms (Table 2).<sup>55</sup>

Consideration of the use of local hormone therapies should include a woman's oncologist. Local hormone therapies, including intravaginal estrogens and DHEA, lack data in breast cancer populations but can be considered for use in some women, using a shared decision-making approach. Ospemifene is not FDA approved for use in women with breast cancer, but as with DHEA and vaginal ET, can be considered for use in high-risk women who are not concurrently taking another SERM for breast cancer risk reduction. The use of compounded local hormone therapies is not recommended because of concerns about the lack of FDA regulation and monitoring and the possibility of overdosing or underdosing. Laser therapies lack adequate RCTs and long-term safety and efficacy data but may be considered in women who prefer nonhormone treatments after a discussion of potential risks, benefits, potential need for ongoing treatments, and cost (Table 4).

#### Women at high risk for breast cancer

Because approximately 75% of breast cancers are hormone-receptor positive, it is understandable that some women at high risk for this disease or with a biopsy that confirms high-risk lesions, as well as the clinicians caring for them, may be apprehensive about the use of local hormone therapies.

In women with a higher risk of breast cancer because of family history, data suggest that the use of systemic ET does not increase the risk of invasive breast cancer. In the WHI, use of CEE in women with an affected first-degree relative was not found to significantly increase risk of breast cancer compared with those receiving placebo.<sup>109</sup> In the observational Two Sister study, neither systemic ET nor estrogen plus progesterone therapy (EPT) was found to elevate the rate of breast cancer diagnosed before age 50 in sisters of women with invasive or in situ breast cancer.<sup>110</sup>

Three observational studies suggest that use of systemic HT does not further increase the risk of breast cancer in carriers of the *BRCA*-mutation over baseline risk after oophorectomy.<sup>111-113</sup> Although these studies are limited because of observational design, limited size, and short duration of follow-up, they provide some reassurance that systemic HT does not increase breast cancer risk in carriers of the *BRCA1* or *BRCA2* mutation with intact breasts, a finding concordant with a systematic review.<sup>114</sup> However, risk-reducing

**TABLE 4.** Treatment options for management of GSM in specific patient populations

General guidelines
<ul style="list-style-type: none"> <li>• Individualize treatment, taking into account risk of recurrence, severity of symptoms, effect on QOL, and personal preferences</li> <li>• Moisturizers and lubricants, pelvic floor physical therapy, and dilator therapy are first-line treatments</li> <li>• Involve treating oncologist in decision making when considering the use of local hormone therapies<sup>a</sup></li> <li>• Ospemifene, an oral SERM, has not been studied in women at risk for breast cancer and is not FDA-approved for use in women with or at high risk for breast cancer</li> <li>• Off-label use of compounded vaginal testosterone or estriol is not recommended</li> <li>• Laser therapy may be considered in women who prefer a nonhormone approach; women must be counseled regarding lack of long-term safety and efficacy data</li> </ul>
Women at high risk for breast cancer <sup>b</sup>
<ul style="list-style-type: none"> <li>• Local hormone therapies are a reasonable option for women who have failed nonhormone treatment</li> <li>• Observational data do not suggest increased risk of breast cancer with systemic or local estrogen therapies beyond baseline risk</li> </ul>
Women with ER-positive breast cancers on tamoxifen
<ul style="list-style-type: none"> <li>• Tamoxifen is a SERM that acts as an ER antagonist in breast tissue; small transient elevations in serum hormone levels noted with local hormone therapies in women on tamoxifen are less concerning than in women on AIs</li> <li>• Women with persistent, severe symptoms who have failed nonhormone treatments and who have factors suggesting a low risk of recurrence may be candidates for local hormone therapy</li> </ul>
Women with ER-positive breast cancers on AIs
<ul style="list-style-type: none"> <li>• AIs block conversion of androgen to estrogen, resulting in undetectable serum estradiol levels; transient elevations in estradiol levels may be of concern</li> <li>• GSM symptoms are often more severe</li> <li>• Women with severe symptoms who have failed nonhormone treatments may still be candidates for local hormone therapies after review with the woman's oncologist vs consider switching to tamoxifen</li> </ul>
Women with triple-negative breast cancers
<ul style="list-style-type: none"> <li>• Theoretically, the use of local hormone therapy in women with a history of triple-negative disease is reasonable, but data are lacking</li> </ul>
Women with metastatic disease
<ul style="list-style-type: none"> <li>• QOL, comfort, and intimacy may be a priority for many women with metastatic disease</li> <li>• Use of local hormone therapy in women with metastatic disease and probable extended survival may be viewed differently than in women with limited survival when QOL may be a priority</li> </ul>

AI, aromatase inhibitor; ER, estrogen receptor; GSM, genitourinary syndrome of menopause; QOL, quality of life; SERM, selective estrogen-receptor modulator.

<sup>a</sup>Local hormone therapies are vaginal estrogen and intravaginal DHEA (prasterone).

<sup>b</sup>Lifetime risk > 20%, carriers of the *BRCA* mutation, atypical ductal hyperplasia, lobular carcinoma in situ, or ductal carcinoma in situ.

salpingo-oophorectomy in patients with *BRCA1* and *BRCA2* mutations was associated with a lower risk of both developing a first diagnosis of breast cancer and breast cancer-specific mortality, suggesting that reduction of estrogen is beneficial in this population.<sup>115</sup>

Given the reassuring findings in studies assessing the safety of systemic ET in high-risk women, it is plausible that local, low-dose vaginal ET, which results in substantially less systemic absorption than systemic ET, should not elevate risk of breast cancer in women at elevated baseline risk and thus can be discussed as part of shared decision-making. Oral ospemifene and vaginal DHEA have not been studied in high-risk women and lack a specific indication for use in this population.

### Women with ER-positive breast cancers

Estrogen deprivation is a key therapeutic approach for the treatment of both early stage and metastatic ER-positive breast cancers and prevention of new primary breast cancers.<sup>116</sup> The principal strategies employed are to block estrogen at the level of the receptor with tamoxifen or to reduce estrogen production with AIs. Tamoxifen is a SERM, which has both partial estrogen agonist and antagonist effects.<sup>117</sup> Vaginal effects of tamoxifen vary, and some women note vaginal dryness with or without an increase in vaginal discharge.<sup>118</sup> Aromatase inhibitors inactivate or block the peripheral conversion of androgens to estrogen by inhibiting aromatase, potentially resulting in worsening or development of vaginal dryness and dyspareunia, decreased libido, and changes in sexual response.

The two estrogen preparations with the lowest systemic absorption are 10 µg estradiol tablets, which result in a typical serum level of 4.6 pg/mL and a maximum annual delivered systemic dose of 1.14 mg, and the estradiol vaginal ring, which has a typical serum level of 8.0 pg/mL and a maximum annual delivered systemic dose of 2.74 mg.<sup>64</sup> As vaginal tissue is progressively estrogenized and restored to health, estrogen absorption declines, and serum concentration stabilizes.<sup>67</sup> The initial increase in serum estradiol is usually transient and with the estrogen ring and 10 µg estradiol tablets usually remains within the postmenopause range (< 20 pg/mL).

First-line therapy for the treatment of GSM in women with ER-positive breast cancer, as with all women with a history of breast cancer, should start with nonhormone options (Table 2).<sup>55</sup> Local hormone treatment of women on either tamoxifen or AIs should be individualized, taking into account the uncertainties of risks along with the risks of disease recurrence and severity of vaginal symptoms.<sup>16</sup> The use of intravaginal estrogens in women on tamoxifen whose ERs are blocked is less worrisome to most oncologists than the use of intravaginal estrogens in women on AIs in which estrogen levels are significantly lowered and any systemic absorption may negate the efficacy of treatment. Women on tamoxifen with persistent, severe symptoms who have failed nonhormone therapy and who have a low risk of recurrence may be candidates for local estrogen or intravaginal DHEA. However, use of intravaginal DHEA should be used with caution in women who have androgen-receptor positive tumors and are using either an AI or tamoxifen. There are



no data on safety or efficacy of DHEA in women on AIs. In women with more remote cancers, local hormone therapies may be considered in those at lower risk for recurrence, those with more severe genitourinary symptoms affecting QOL, and those who have failed nonhormone, conservative treatments. Recommendations issued from The American College of Obstetricians and Gynecologists (ACOG), the Endocrine Society, and The North American Menopause Society (NAMS) cautiously support the use of local HT in consultation with the woman's oncologist.<sup>18,40,41</sup>

### Women with triple-negative breast cancers

No data address the safety or efficacy of local HT in survivors of triple-negative breast cancer. Given that hormone manipulation and lowering of estrogen levels is not a mainstay of adjuvant treatment in this patient population, it is reasonable to consider use of local HT for vaginal symptoms. However, it must be noted that tumors can be heterogeneous, and some ostensibly ER-negative disease may have some ER-positive components.<sup>119-123</sup> Further, in women with remaining breast tissue and especially those who are at high risk of new primary disease (eg, carriers of *BRCA1* or *BRCA2* mutation), theoretical elevation of systemic estradiol levels may increase the risk of new primary disease, given that prophylactic oophorectomy decreases the risk of the development of new breast cancer in women at risk but without cancer and in survivors with mutations.<sup>115</sup> Nevertheless, despite a lack of data, in women who are long-term survivors of ER-negative disease for which risk of recurrence is low and symptomatology is troubling, consideration of local HT is reasonable.

### Women with metastatic disease

Women with metastatic breast cancer are a diverse group with significant heterogeneity in prognosis, and there are no data to inform decisions regarding the treatment of GSM. Despite the lack of data in this population of women, if symptoms are severe enough and QOL is a priority, the decision to use local HT in women with receptor-positive metastatic disease may be reasonable after a discussion of risks and benefits, particularly for those not using AIs. In women with ER-negative disease or disease that no longer appears to be responsive to endocrine therapy, any of the available treatment options can be discussed as part of shared decision-making that takes into account the importance of QOL, comfort, and improved sexual function.

### CONCLUSION

It is estimated that more than 2 million US survivors of breast cancer are affected by GSM, with most receiving no treatment.<sup>8</sup> There are numerous, well-documented barriers to the treatment of GSM in postmenopausal women, and the paucity of data in women with breast cancer is an additional barrier for this population.

Despite current evidence and the cautious support of multiple medical societies, including ACOG and NAMS, for the

use of local ET for management of GSM when other non-pharmacologic and nonhormone therapies have failed,<sup>18,40,41</sup> the safety of these therapies in women with or at high risk for breast cancer has not been definitively established, and recommendations for use remain controversial. Adding to the confusion is the FDA-required class labeling of all products containing estrogen, including local ET, to warn of risk for multiple diseases, including breast cancer, despite the lack of data for low-dose local therapies with systemic absorption within normal postmenopause levels.<sup>124,125</sup> As a result, clinicians often take the path of nonmaleficence or *primum non nocere*, and women are left without treatment.

Engaging clinicians caring for this population to ask about and treat GSM is important for QOL and requires consensus about treatment because clinical data are lacking. Additional research to further define safety and efficacy of available therapies, including vaginal estrogens, intravaginal DHEA, and different types of lasers, and to develop new therapies is critical. Modifying the product labeling of low dose vaginal estrogen products to appropriately reflect the safety profile will help inform both women and their providers. Women with or at high risk for breast cancer deserve high quality, comprehensive care, including evidence-based management of GSM. Consensus from this multidisciplinary group, while awaiting more data, provides a framework for therapy.

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