Management of Genitourinary Syndrome of Menopause in Female Cancer Patients: A Focus on Vaginal Hormonal Therapy

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Disclosure Statement:
KKCT has no disclosures
SSF consults for Mithra Pharmaceuticals, AMAG, and Procter & Gamble
HJP consults for Myriad Genetics
JAV has no disclosures
PB has no disclosures

Financial Support:
There was no financial support for this article.

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Condensation: Discussion of national guideline-based management options for female cancer patients with genitourinary syndrome of menopause, with emphasis on safety and efficacy of vaginal hormonal therapy.

Short Title: GSM in Female Cancer Patients: Focus on Vaginal Hormonal Therapy
Abstract:

Genitourinary syndrome of menopause is a condition describing the hypoestrogenic effects on the female genitals and lower urinary tract leading to symptoms such as vaginal dryness, vulvar and vaginal burning, dyspareunia and dysuria. Genitourinary syndrome of menopause is experienced by over half of postmenopausal women, and is even more pervasive in women with cancer. Due to treatments such as surgery, chemotherapy, radiation, and hormonal therapy, women may experience early menopause resulting in earlier and more severe symptoms. Understanding the scope of this issue in female breast and gynecologic cancer survivors and identifying treatment options for this complex patient population are paramount. Tailored patient treatments include nonhormonal therapies (vaginal moisturizers, lubricants, pelvic floor physical therapy, dilator therapy, counseling), systemic and local hormonal therapies. Consensus recommendations by medical societies and associated evidence are reviewed, with emphasis on safety and efficacy of local vaginal hormonal therapies, and management variations noted depending on cancer type and characteristics.

With knowledge and understanding of the unmet need associated with under-recognition and under-treatment of genitourinary syndrome of menopause, providers caring for women with cancer are in a position to improve the quality of life of their patients by providing safe and effective treatments.

Key Words: atrophic vaginitis, breast cancer, cancer survivorship, dehydroepiandrosterone, dyspareunia, endometrial cancer, estrogen-progestin therapy, genitourinary syndrome of menopause, gynecologic cancer, nonhormonal vaginal therapy, quality of life, sexual health, sexual dysfunction, vaginal hormonal therapy.
**Introduction**

With over 1 million U.S. women living with gynecologic cancer and over 3 million living with breast cancer, quality of life in female cancer survivors is an essential aspect of patient care. Among the multiple quality of life issues experienced after cancer, nearly 90% of survivors note sexual health as a major concern. This is seen in gynecologic and breast cancer survivors, as well as other types of cancer (e.g., those involving the pelvis or lower abdomen, including anal or colorectal malignancies). Many of the treatments provided for female cancers affect the hormonal milieu, sometimes leading to early menopause. Hormonal therapy to treat breast cancer also affects sexuality. Challenges with sexual health are multifactorial in cancer survivors.

Genitourinary syndrome of menopause (GSM) is a condition resulting from menopause-related hypoestrogenic effects on the female genitals and lower urinary tract, including the labia minora, clitoris, vestibule/introitus, vagina, urethra, and bladder. Symptoms can include vaginal dryness, vulvar and vaginal burning and irritation, lack of lubrication, dyspareunia, urinary urgency, frequency, and dysuria, and recurrent urinary tract infections. In 2014, the International Society for the Study of Women’s Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) adopted the term GSM to better encompass the array of genitourinary symptoms attributed to the loss of estrogen associated with menopause. GSM affects over 50% of postmenopausal women, and is even more pervasive in the female cancer population. As breast cancer is often diagnosed after menopause, women with breast cancer may experience GSM prior to diagnosis, and breast cancer treatments may intensify symptoms. Broeckel et al compared women with breast cancer treated with chemotherapy to age-matched controls without cancer and found that breast cancer patients experienced worse sexual function, with vaginal dryness as one of the most significant predictors of poorer sexual function. Similarly, endocrine therapies such as tamoxifen and aromatase inhibitors (AI) may worsen symptoms of GSM; AIs in particular are associated with difficulty with lubrication, dyspareunia, and global dissatisfaction with one’s sex life. Surgical treatment of breast or gynecologic cancers that involve oophorectomy in premenopausal women leads to early menopause which is associated with sexual dysfunction and GSM. Chemotherapy and radiation therapy can result in ovarian insufficiency, similarly leading to GSM symptoms in premenopausal patients or intensified symptoms in postmenopausal patients.

Cancer survivors endure a multitude of insults on their reproductive system throughout their course of disease, and sexual health generally and GSM specifically are often overlooked. We will discuss management options for GSM in women with cancer, focusing here on women with breast and gynecologic cancer, including nonhormonal and hormonal options (systemic and local vaginal). We will also review clinical guidelines on this topic and discuss other considerations for sexual health in female cancer survivors.

**Nonhormonal treatments for GSM**

Nonhormonal regimens are an important first line therapy for symptoms of vulvar and vaginal dryness and related dyspareunia in all women, and particularly in those with hormone-dependent cancers. These include vaginal moisturizers and lubricants, topical anesthetics, pelvic floor...
physical therapy, and counseling. A study of 175 women with gynecologic cancers who received focused education on vaginal moisturizers, lubricants, pelvic floor exercises, vaginal dilator therapy, and psychosexual education after cancer care demonstrated significant improvements in sexual function, sexual activity, vaginal and vulvar assessment scores and vaginal pH compared to baseline.\textsuperscript{2}

Lubricants work to relieve discomfort and pain by reducing friction against thinned, atrophic genital tissue. These are available as water-, silicone-, mineral oil- or plant oil-based products. The World Health Organization recommends lubricant use with condoms for postmenopausal women.\textsuperscript{13} In contrast, vaginal moisturizers are applied regularly, providing pain relief from vaginal penetration as well as general atrophy. Moisturizers work by hydrating the vaginal mucosa and lowering the vaginal pH,\textsuperscript{14} and are available as plant-based or synthetic polymers. Two studies found that Replens, an FDA approved vaginal moisturizer, caused equivalent subjective improvement of vaginal dryness when compared with vaginal estrogen therapy.\textsuperscript{15,16}

Another nonhormonal treatment option for GSM is topical lidocaine. In a randomized study of survivors of breast cancer with severe GSM and dyspareunia, 4% aqueous lidocaine applied three minutes prior to penetration was associated with an 88% reduction in dyspareunia versus 33% with placebo.\textsuperscript{17}

Micro-ablative fractional CO\textsubscript{2} laser and non-ablative vaginal Erbium YAG laser have been explored in women with and without a cancer history who have GSM. The mechanism of action of laser therapy is thought to be through the remodeling and synthesis of collagen.\textsuperscript{18} In an observational study of women with GSM who underwent fractional CO\textsubscript{2} laser treatment, significant symptomatic improvements in pain, dryness, dyspareunia, and sexual function were found at 3 months and 1 year.\textsuperscript{18} Limited data also suggest that laser treatments are effective in breast cancer survivors.\textsuperscript{19–21} Case reports of pain, scarring, and sexual dysfunction after laser treatment have been reported.\textsuperscript{22} Further studies are needed to assess the long term risk versus benefits of vaginal laser and thermal treatments.

Treatment of GSM in cancer survivors is often complex, and a multidisciplinary approach is often needed.\textsuperscript{23} Pelvic floor physical therapy and counseling address other associated sexual health issues such as pelvic floor myalgia and underlying mood disorders or relationship issues. Please see “Special Considerations” below for further discussion of these topics.

**Vaginal hormonal therapies**

Although systemic hormone therapy (HT) is typically avoided in women with estrogen sensitive cancers (i.e., breast, endometrial), discussion regarding safety and efficacy of vaginal hormonal therapy is important when nonhormonal treatments fail to provide sufficient relief. Systemic HT may not adequately control GSM symptoms in up to 45% of patients, whereas low dose vaginal hormonal therapy is highly effective in providing symptomatic relief of sexual dysfunction, lower urinary tract infections, and other genitourinary symptoms and is associated with minimal systemic absorption. Several factors may play a role in the decision to use vaginal hormone therapy after breast cancer (Table 1).\textsuperscript{24} These factors are used to assess overall lower vs higher risk of recurrence, with a focus on factors such as hormone receptor status, anti-estrogen therapy
use, and severity of symptoms. These factors should be considered together, as, for example, a
patient with advanced or metastatic cancer with extended life expectancy but with severe
symptoms and negative hormone status should be considered for hormone therapy given the
impact on quality of life and less likely recurrence due to hormone activity.

**Vaginal estrogens**

Vaginal estrogen therapy is administered locally to the vulvar and vaginal tissues via cream, ring,
insert or tablet. Most preparations are delivered locally in a low dose, with minimal systemic
absorption. FDA-approved dosing regimens are often higher and/or more frequent than those
used in clinical practice. Examples of different vaginal estrogen therapies and their variable rates
of systemic absorption are summarized in Table 2.

Many studies have shown the overall safety and efficacy of vaginal estrogen in treating GSM. In
a Cochrane review including 30 randomized control trials and over 6000 patients, different
vaginal estrogen preparations were compared to each other and to placebo and were found to be
similarly efficacious in GSM treatment with no differences in adverse events. Older studies using
the 25 mcg vaginal estrogen tablet (no longer available) reported a slight increase in serum
estradiol levels, although data are difficult to interpret as several studies utilized older assays that
may have shown falsely elevated levels. The 10 mcg estradiol tablet is associated with serum
estradiol concentrations that remain within the postmenopausal range when measured by gas
chromatography and mass spectrometry, and has good evidence for clinical benefit.

Santen et al assessed symptomatic improvement in genitourinary symptoms with a questionnaire as well as
vaginal cytology, pH, endometrial biopsy and serum LH, FSH, estradiol and estrone levels
throughout treatment with different doses of vaginal estrogen; they found that 10 mcg provided
improvement in both symptoms and objective endpoints, while maintaining an atrophic
endometrium and estrogen levels within the postmenopausal range (3-10 pg/mL). An analysis
assessing endometrial biopsies in women after 52 weeks of treatment with 10 mcg vaginal
estradiol tablets showed an atrophic endometrium in 86% of women with less than 1%
demonstrating endometrial hyperplasia or carcinoma, similar to the background incidence of
endometrial hyperplasia and carcinoma in postmenopausal women. While most regimens of
vaginal estrogen result in estradiol levels within the normal postmenopausal range (<20 pg/mL),
the exact safety threshold of serum estradiol in those with a history of breast cancer is unknown.
Vaginal estrogen products associated with lower serum estradiol levels may be preferable for
hormone receptor-positive breast cancer survivors, including the 4 mcg vaginal inserts, 10 mcg
inserts and tablets, and the vaginal ring providing 7.5 mcg estradiol daily.

Vaginal estrogen therapy has not been found to increase primary breast cancer risk or breast
cancer recurrence in survivors. In a review of over 18,000 women from a Finnish registry,
vaginal estrogen was not associated with an increased risk of breast cancer. This finding was
supported by both the Women’s Health Initiative Observational Study and the Nurse’s Health
Study where vaginal estrogen use was not associated with increased breast cancer risk. In
breast cancer survivors, vaginal estrogen therapy has not been associated with an increased risk
in breast cancer recurrence or mortality. In a nested case-control study of women with breast
cancer receiving tamoxifen or AI treatment, no increased recurrence risk was found in vaginal
estrogen users versus non-users.
Data regarding vaginal estrogen therapy and risk of recurrence of endometrial and ovarian cancers is limited. Extrapolating from studies on systemic HT in these populations, most endometrial and ovarian cancer survivors would benefit from vaginal hormonal therapy if indicated (see Table 3). Vaginal estrogen therapy in the setting of cervical, vaginal, and vulvar cancers is considered safe as these gynecologic cancers are not considered hormonally-sensitive.\textsuperscript{41,42}

\textbf{Vaginal DHEA}

Dehydroepiandrosterone (DHEA) is an inactive precursor from the adrenal gland that is transformed to active androgen in the peripheral tissues, exerting action locally in the same cells where synthesis takes place. Androgens are then aromatized to form estrogens. This mechanism, known as intracrinology, leads to local cellular effects with subsequent intracellular inactivation of the hormones, leading to minimal active hormone release into the systemic circulation.\textsuperscript{43}

Treatment with vaginal DHEA (prasterone) has shown improvement in vaginal health and sexual function. In vivo studies of vaginal effects after oophorectomy found that DHEA increased mucification of epithelium, muscularis thickness, and collagen fiber compactness in the lamina propria, thus affecting three layers of the vaginal wall for a robust, physiologic local response.\textsuperscript{43} In a prospective, double-blind randomized control trial, daily vaginal DHEA 0.5\% 6.5 mg was administered for 12 weeks and compared with placebo. DHEA was associated with significant improvement in vaginal secretions, epithelial thickness, color, vaginal pH, and vaginal cytology with increased vaginal parabasal and superficial cells.\textsuperscript{44} In another open label study, 52 weeks of daily vaginal DHEA use revealed significant improvements in all domains of sexual function studied, including desire, arousal, lubrication, orgasm, pain and satisfaction.\textsuperscript{45}

Head to head studies of the safety and efficacy of vaginal estrogens versus DHEA are not available. Studies assessing the safety of FDA-approved DHEA in cancer survivors are limited. In one randomized, controlled trial, 464 breast and gynecologic cancer survivors who experienced GSM were given either compounded vaginal DHEA 3.25 mg, 6.5mg DHEA, or plain moisturizer over 12 weeks. While all three arms showed improvement in vaginal symptoms at 12 weeks, women who used 6.5mg DHEA reported significantly improved sexual health. There was no increase in provider-graded toxicity or self-reported side effects, and similar results were appreciated if the patient was on concurrent AI therapy.\textsuperscript{46} The authors reported that serum DHEA-S and testosterone levels were significantly increased in women on 6.5 mg DHEA compared to those using plain moisturizers. Estradiol levels significantly increased in those on 6.5 mg/day DHEA, though levels remained in the lower half of the postmenopausal range. No elevations in serum estradiol levels were seen in women on AIs.\textsuperscript{47}

In contrast, other studies (not done in cancer survivors) indicate there is no significant change in serum steroid levels, including estradiol, estrone, DHEA, and testosterone.\textsuperscript{48} DHEA 6.5 mg (0.5\%) use for up to 52 weeks in 422 women was associated with endometrial atrophy or inactive endometrium on endometrial biopsies.\textsuperscript{49}
Taken together, the studies to date on vaginal DHEA indicate significant improvements in objective determinants of vaginal health as well as subjective symptomatic improvement in GSM, with minimal change in serum estrogen or androgen levels. Additional studies of DHEA use in cancer survivors are needed, as well as studies directly comparing vaginal DHEA and estrogen.

**Vaginal testosterone**

Vaginal testosterone is an off-label therapy sometimes used for GSM given that female genitourinary tissues are known to be rich in testosterone receptors. Clinical data on local testosterone use is limited. Given the aromatization of testosterone to estradiol, there is concern about safety when used after a diagnosis of hormone dependent cancer. In a randomized trial of 80 postmenopausal women who received 12 weeks of compounded vaginal testosterone versus placebo lubricant, those receiving compounded testosterone had improved vaginal assessment scores, improved vaginal pH and vaginal flora. A few studies assessed local testosterone use in breast cancer patients with vaginal atrophy on AIs and indicated improved symptoms including dyspareunia, dryness, vaginal pH, and sexual function scores. However, these studies either failed to fully describe the serum testosterone levels or found levels to be elevated well above physiologic range, with one study indicating 12% of patients also had persistently elevated estradiol levels after testosterone therapy. Given these findings, the administration of vaginal testosterone is not routinely recommended after breast cancer.

**Systemic hormone therapy**

Systemic hormone therapy (HT) is often considered for women with menopausal symptoms or for women experiencing early (< age 45 years) or premature (< age 40) menopause to protect against the potential adverse health consequences of early estrogen deprivation. Although vaginal hormonal therapies are more effective at treating GSM, systemic HT is available when patients have vasomotor symptoms impacting quality of life, or in women with early or premature menopause. Many guidelines recommend avoiding systemic HT in women with hormone responsive cancers. The evidence for these recommendations is conflicting, and depends on cancer type.

The safety of systemic HT in breast cancer survivors is still debated, and use is generally discouraged in these women. The primary subtypes of breast cancer include luminal (luminal A and luminal B), human epidermal growth factor 2 (HER2) over-expressing, and triple negative (ER, progesterone receptor (PR), and HER2 negative). These subtypes are clinically important in determining management at diagnosis, with targeted treatment such as endocrine therapy for luminal subtypes as these make up the majority of estrogen receptor (ER) positive tumors. Subtypes with hormone receptor activity, which make up about 80% of breast cancers, should avoid systemic hormone therapy. On the other hand, hormone therapy is not theoretically linked with a higher risk of recurrence in women with hormone receptor negative tumors, though data supporting this are scant. Three large studies are typically referenced relating risk of hormone therapy in breast cancer. The first, the Women’s Health Initiative (WHI) study, showed that combined estrogen and progestin HT increased the risk for primary invasive cancer by 8 per 10,000 person-years in healthy postmenopausal women after 5.2 years. Long term follow up has
revealed a lower risk of breast cancer in women taking estrogen alone for 7.1 years, with a hazard ratio 0.79 in estrogen users compared to placebo (95% CI 0.65–0.97). The second two studies are two randomized trials looking specifically at breast cancer survivors, which demonstrated conflicting results. In the Hormonal Replacement Therapy After Breast Cancer—Is It Safe? (HABITS) trial, breast cancer survivors with menopausal symptoms were randomized to HT or placebo. The relative hazard for breast cancer recurrence was 3.3 (95% CI 1.5–7.4) at median follow up of 2.1 years, with 26 women in the HT group and 7 in the non-HT group diagnosed with a new breast cancer during the trial. The trial was stopped during accrual due to unacceptable risk. The Stockholm trial, which also randomized breast cancer survivors to hormone therapy versus placebo, showed no difference in breast cancer recurrence risk at a median of 4.1 years, or after 10.8 years in a follow-up study. Given both HABITS and the Stockholm trial were prematurely closed due to the preliminary findings from the HABITS trial, the ultimate determination of risk in this population remains unclear. However given the concern for increased risk in the breast cancer survivor population, systemic hormone therapy is not recommended.

Endometrial cancer is estrogen sensitive in 90% of cases, thus concern regarding risk of recurrence with HT is understandable; however, studies do not support this claim. Barakat et al. initiated a randomized trial of estrogen versus placebo after surgery in early stage endometrial cancer, however the study did not reach accrual due to the concomitant publication of WHI trial results. Recurrence rates were not significantly different, with 2.3% in the HT group (with 1.3% developing a new malignancy), compared to 1.9% recurrence in the placebo group (1.6% developed new malignancy). Due to early closure, no conclusions could be made, though the low rate of recurrence and diagnosis of new malignancy was highlighted. A meta-analysis that included nearly 900 endometrial cancer survivors receiving HT compared to over 1000 nonusers found no increased risk of recurrence in the HT versus control group. There is a paucity of data regarding HT use in less common uterine cancers such as endometrial stromal sarcoma and uterine leiomyosarcoma. Studies indicate prolonged survival with hormone suppression in hormone responsive endometrial stromal sarcoma, and one case series found that patients withdrawn from HT responded with disease stabilization and experienced a partial response when aromatase inhibitors were provided. Thus systemic HT is avoided in these cancer types. Uterine leiomyosarcomas often overexpress estrogen and progesterone receptors, however studies have found oophorectomy at the time of hysterectomy did not improve 5 year overall survival and, in a Surveillance, Epidemiology, and End Results review, was associated with significantly lower survival rates. However, given the lack of definite data in this aggressive subtype, many recommend caution in providing systemic hormone therapy to this group.

When considering ovarian cancer, the predominant histological subtype is serous which has been found to have no correlation with worse survival outcomes in patients taking systemic HT. Randomized studies in ovarian cancer survivors found equivalent disease free intervals and overall survival, with one multi-center randomized study of pre- and postmenopausal patients finding an improvement in overall survival in the HT arm at median follow-up of 19.1 years (HR: 0.63, 95% CI 0.44–0.90, p=0.011) as well as relapse free survival (HR: 0.67, 95% CI 0.47–0.97, p=0.032). As such, systemic hormonal therapy for symptomatic ovarian cancer survivors is not only safe but is associated with a survival benefit, and should be recommended to premenopausal, and certainly at least offered to symptomatic postmenopausal patients. Ovarian germ cell and sex-cord stromal tumors are rare and thus data is further limited. However
HT for germ cell tumors is generally considered safe. However, ovarian granulosa cell tumors are hormonally active; patients with a history of this ovarian cancer subtype are typically advised to avoid systemic HT.

Most cervical, vulvar and vaginal cancers, are not considered hormonally sensitive. In a study using systemic HT in cervical cancer patients, no significant increased risk of recurrence or decreased 5 year survival were seen, with significant improvement in post-radiation rectal, bladder and vaginal effects (17% vs 45% in control arm), indicating the benefits of HT use. HT use is acceptable in these patients if no other contraindications to use exist. Vaginal and cervical clear cell adenocarcinoma is exceedingly rare, however there is a near 40-fold increased risk of development of this type of cancer in women who were exposed to diethylstilbestrol (DES), a synthetic estrogen used during pregnancy fifty years ago. Given the rarity of this cancer, no conclusions can be drawn regarding effects of HT, thus recommendations for use of systemic HT in cervical and vulvovaginal adenocarcinoma are limited.

Selective estrogen receptor modulators

Ospemifene is a selective estrogen receptor modulator (SERM) that is approved for the treatment of GSM. Similar to other SERMs, it has shown antioestrogenic effects on the breast in preclinical studies, though it appears to be less potent than tamoxifen or raloxifene. It has favorable effects on bone turnover and breast density, without any data on fracture risk. Studies suggest endometrial safety, but only have one year of follow up. It is not FDA-approved for use in women with or at high risk for breast cancer (though is not contraindicated in Europe for women who have completed their breast cancer treatment). Similar to other SERMs, it may increase hot flashes and risk of thrombosis.

Clinical guidelines

Five major consensus recommendations help guide the treatment of GSM in cancer survivors. There is agreement that nonhormonal treatments should be offered first, including counseling, pelvic floor relaxation techniques and vaginal dilator use. When nonhormonal measures fail to adequately relieve symptoms, local vaginal hormones may be considered after shared decision making with the patient and her oncologist. All recommendations suggest caution regarding the use of vaginal estrogen in women with breast cancer on AI therapy given that the goal of treatment is to maximally suppress estradiol levels. Because tamoxifen exerts its effects by competitively binding to the estrogen receptor, an increase in serum estradiol is less likely to affect patient treatment response. Some of these medical society expert recommendations make specific points that may be helpful in guiding clinical practice. The American College of Obstetrics and Gynecology and the NAMS/ISSWSH guidelines note that women on AIs with severe GSM symptoms may consider discussing a trial of tamoxifen with their oncologist (with or without vaginal hormone treatment). The International Menopause Society endorses the importance of starting therapy early prior to development of irreversible genitourinary changes. The National Comprehensive Cancer Network released survivorship guide updates in 2019 stating that if local estrogen-based treatment is necessary, rings and suppositories are preferred over creams. Local vaginal DHEA...
preparations can also be used with caution in survivors with a history of estrogen-dependent cancers, with limited safety data. There are insufficient data to recommend vaginal estrogen versus DHEA. Checking estradiol levels in those on vaginal hormone treatments is discouraged.

**Special considerations: Contributors to sexual dysfunction**

While GSM can have a significant impact on the sexual health after cancer, other factors are important to consider. In women undergoing gynecologic surgeries requiring resection of a portion of the vulva or vagina, scarring and shortening of the vagina can occur. Radiation therapy may result in vaginal fibrosis, stenosis, and vulvar or clitoral pain sensitivity. Women with cervical cancer may develop dyspareunia after radiotherapy, as well as difficulty with sexual desire and arousal; limited data suggest that orgasm using a clitoral suction device may help symptoms. Other comorbid conditions include endocrine disorders (diabetes, metabolic syndrome, hypo- and hyperthyroidism) and medication effects, which include antihypertensives, narcotics and SSRIs (effects on sexual desire and orgasm). Addressing each of these potential contributors to sexual dysfunction is important to fully address a woman’s sexual health concerns.

The diagnosis and treatment of cancer is a stressful life event which can lead to challenges with mood, intimacy and decreased sexual desire and arousal. Chemotherapy can result in loss of hair, weight changes, and associated issues with body image. Body image issues may also arise when patients require surgery, including removal of breasts, ovaries, genitalia, and placement of ostomies with radical surgery. Additionally, breast sensitivity is lost with mastectomy resulting in a lost erogenous zone for many women. Given the complex and multifactorial nature of sexual health concerns, support for a multidisciplinary treatment approach, including medical providers, sex therapists, and pelvic floor physical therapists, continues to grow. Women are often hesitant to report sexual health concerns and specifically GSM to their healthcare providers due to embarrassment, shame, and/or a mistaken belief that treatment options do not exist. Many suffer for years with sexual pain and resulting avoidance of intimacy and relational distress. Even when medical treatment has been established, shame-based emotions can negatively impact treatment adherence (e.g., women who report embarrassment or even outright disgust about their vulva may struggle to apply local hormonal treatments to the genitals).

Sex therapy is a specialized form of psychotherapy designed to help patients with a wide variety of sexual and relationship concerns. Using cognitive behavioral theories, sex therapists work with patients to address the avoidant cycle of sexual interaction within which many find themselves trapped (especially in the presence of dyspareunia). Sex therapy often involves psychoeducation and skills-building related to sexual communication, identifying one’s own sexual likes, dislikes, and fears, as well as helping patients to identify and alter links between problematic thoughts, emotions, behaviors, and their sexual symptoms. Building skills for relaxation and mindfulness can further improve symptoms of avoidance and anxiety that many patients may have developed around sexual situations. Certified sex therapists can be found on the website of the American Association of Sexuality Educators, Counselors, and Therapists (AASECT.org).
Pelvic floor physical therapy applies the knowledge and skill of specialized physical therapists to evaluate and treat patients with pelvic floor dysfunction. With individually focused assessments, therapists can provide education, exercises in both strengthening and relaxation, manual therapies (such as massage), and pelvic floor biofeedback. Manual physical therapy techniques can markedly or completely relieve up to 80% of patients’ musculoskeletal pelvic pain. Pelvic floor rehabilitation improves sexual pain disorders in up to 77% of women, and increases sexual desire and orgasm. A careful exam to diagnose concomitant pelvic floor dysfunction is recommended to identify individuals who would benefit from referral to a pelvic floor physical therapist. Specialized therapists can be found at the American Physical Therapy Association website (www.womenshealthapta.org).

Conclusion

Women with a history of breast and gynecologic cancers often suffer from symptoms of GSM. Guidelines agree that nonhormonal therapies are first-line treatment, though in many women these options will not adequately control symptoms. Hormonal therapies must be used with caution in women with estrogen-dependent cancers. For many cancer survivors, local vaginal estrogen or DHEA therapy can be considered with informed shared decision making. Clinicians should consult the woman's oncologist when considering these therapies. These discussions and management decisions can be complex, but are of paramount importance to the quality of life of cancer survivors with GSM.
References


Table 1

Factors to consider prior to prescribing vaginal hormones in breast cancer patients

<table>
<thead>
<tr>
<th></th>
<th>More desirable candidates</th>
<th>Less desirable candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of disease</td>
<td>Stage 0-2, or metastatic with limited life expectancy</td>
<td>Stage 3, or metastatic with extended life expectancy</td>
</tr>
<tr>
<td>Grade of disease</td>
<td>Low-intermediate grade</td>
<td>High grade</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hormone receptor status</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>Tamoxifen</td>
<td>Aromatase inhibitors</td>
</tr>
<tr>
<td>Risk of recurrence</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>Remote</td>
<td>Recent</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Nonhormone therapies</td>
<td>Failed</td>
<td>Effective</td>
</tr>
<tr>
<td>Effect on quality of life</td>
<td>Severe</td>
<td>Mild</td>
</tr>
</tbody>
</table>

Adapted from NAMS/ISSWSH Consensus Recommendations
Table 2

**Characteristics of the local vaginal hormonal treatments**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Brand name</th>
<th>Generic Available</th>
<th>Usual Clinical Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-Dose Vaginal Estrogen</strong> (serum estradiol &lt;20pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mcg estradiol insert</td>
<td>Imvexxy</td>
<td>No</td>
<td>1 insert daily for 2 weeks, then 1 insert twice weekly</td>
<td>Formulated as a medium-chain triglyceride</td>
</tr>
<tr>
<td>7.5 mcg estradiol ring</td>
<td>Estring</td>
<td>No</td>
<td>1 ring per vagina every 90 days</td>
<td>Should not be confused with Femring, which is a systemic vaginal estrogen ring</td>
</tr>
<tr>
<td>10 mcg insert and tablet</td>
<td>Imvexxy and Vagifem</td>
<td></td>
<td>1 insert daily for 2 weeks, then 1 insert twice weekly</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate-Dose Vaginal Estrogen</strong> (serum estradiol &gt;20pg/ml, intermittently)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5g (0.3mg) CEE cream</td>
<td>Premarin vaginal cream (0.625 mg/g)</td>
<td>No</td>
<td>0.5-1g 1-3 times per week</td>
<td>FDA approved frequency includes daily for 21 days then off 7 days, but may lead to higher systemic absorption</td>
</tr>
<tr>
<td>≥ 1 gm (0.625mg) CEE cream</td>
<td>Premarin vaginal cream (0.625 mg/g)</td>
<td>No</td>
<td>0.5-1g 1-3 times per week</td>
<td>FDA approved dose is up to 2g which may lead to higher systemic absorption</td>
</tr>
<tr>
<td>≥ 0.5 gm (50 mcg) estradiol cream</td>
<td>Estrace cream (100mcg/gm)</td>
<td>Estradiol</td>
<td>0.5-1g daily for 2 weeks, then twice per week</td>
<td>FDA approved dose: 2-4g daily, then 1g 1-3 times per week</td>
</tr>
<tr>
<td><strong>Vaginal DHEA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.5mg (0.5%) DHEA insert</td>
<td>Intrarosa, Prasterone</td>
<td>No</td>
<td>1 insert daily</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from ACOG Committee Opinion #659, Santen et al, Faubion et al.
CEE = conjugated equine estrogen
Table 3
Recommendations for local hormone therapy based on female cancer type and characteristics

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommendation</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Guidelines</td>
<td>Individualize therapy (see Table 1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use nonhormonal therapy first-line</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Involve treating oncologist in decisions regarding HT use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avoid off-label medications (vaginal testosterone, estriol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider laser therapy, with appropriate counseling regarding limited data on use</td>
<td></td>
</tr>
</tbody>
</table>

Further recommendations after above general guidelines have been considered and nonhormonal therapies have failed:

**Breast Cancer**

<table>
<thead>
<tr>
<th>ER+ breast cancer, on tamoxifen</th>
<th>If favorable factors (see Table 1), local HT* is an option</th>
<th>Tamoxifen is an ER antagonist in breast tissue, any absorbed estrogen may be blocked</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+ breast cancer, on aromatase inhibitor (AI)</td>
<td>Caution in considering local HT; review with oncologist, consider switching to tamoxifen</td>
<td>AIs block conversion of androgen to estrogen, goal is very low serum estradiol levels; GSM symptoms often severe</td>
</tr>
<tr>
<td>Triple-neg breast cancer</td>
<td>Local HT is an option, counsel on limited data</td>
<td>No known negative effects, data limited</td>
</tr>
</tbody>
</table>

**Uterine Cancer**

<table>
<thead>
<tr>
<th>Type I (estrogen-dependent) endometrial cancer</th>
<th>Local HT is an option, counsel on limited data</th>
<th>Prematurely closed randomized trial with HT vs placebo showed no increased recurrence risk, small sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II (estrogen-independent) endometrial cancer</td>
<td>Local HT is an option, counsel on limited data</td>
<td>Hormonally active tumor, data limited</td>
</tr>
<tr>
<td>Uterine carcinosarcoma</td>
<td>Caution in considering local HT, counsel on limited data</td>
<td>No known negative effects, data limited</td>
</tr>
<tr>
<td>Endometrial stromal sarcoma</td>
<td>Caution in considering local HT, counsel on limited data</td>
<td>Hormonally active tumor, data limited</td>
</tr>
<tr>
<td>Uterine leiomyosarcoma</td>
<td>Caution in considering local HT, counsel on limited data</td>
<td>Tumor is often ER/PR+, data limited</td>
</tr>
</tbody>
</table>

**Ovarian Cancer**

<table>
<thead>
<tr>
<th>High Grade Serous</th>
<th>Local HT is an option. Consider systemic HT if premenopausal or postmenopausal with symptoms.</th>
<th>Survival benefit and improved relapse-free survival seen in symptomatic pre- and postmenopausal patients on systemic HT after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>Caution in considering local HT,</td>
<td>Hormonally active tumor,</td>
</tr>
</tbody>
</table>
### Sex cord stromal (eg granulosa cell)
- Counsel on limited data
- Data limited

### Germ cell
- Local HT is an option
- No known risks, data limited

### Cervical Cancer

| Squamous cell | Adenocarcinoma | Systemic HT has equivalent recurrence risk and survival compared to control\(^{73}\)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Local HT is an option</td>
<td>No known risks given not hormonally active, no contraindication to HT</td>
<td></td>
</tr>
</tbody>
</table>

### Vulvar/Vaginal Cancer

<table>
<thead>
<tr>
<th>Squamous cell</th>
<th>Adenocarcinoma</th>
<th>No known risks, data limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local HT is an option</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Special Populations

<table>
<thead>
<tr>
<th>Clear cell adenocarcinoma (cervical, vulvar or vaginal)</th>
<th>Caution in considering local HT, counsel on limited data</th>
<th>Possibly hormonally responsive, data limited</th>
</tr>
</thead>
</table>

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927 Adapted from NAMS/ISSWSH Consensus Recommendations\(^{24}\), ACS/ASCO Breast Cancer Survivorship Guidelines\(^{59}\), Deli et al\(^{73}\)
928 HT, hormone therapy; ER, estrogen receptor; AI, aromatase inhibitor; GSM, genitourinary syndrome of menopause; PR, progesterone receptor; DES, diethylstilbestrol.
930 *Local hormone therapies are vaginal estrogen and intravaginal DHEA (prasterone).