

# Genitourinary Syndrome of Menopause in Breast Cancer Survivors: A Common Complication With Effective Treatment Strategies

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Hormone receptor–positive cancer is the most common subtype of breast cancer that we encounter in clinical practice. Endocrine therapy—tamoxifen, aromatase inhibitors, fulvestrant—forms the cornerstone of treatment and has resulted in excellent outcomes for patients with breast cancer in terms of reduced risk of recurrence of disease and improved survival.<sup>1</sup> Although highly effective, it can result in genitourinary syndrome of menopause (GSM) that can adversely affect quality of life.

The term GSM was coined to encompass a constellation of vulvovaginal and genitourinary symptoms—vaginal itching, irritation, dryness, dyspareunia—that result from estrogen loss in postmenopausal patients and the ensuing structural and physiologic alterations in the vaginal mucosa and genital structures. This is also applicable to patients who have these symptoms while receiving endocrine therapy for breast cancer, more often with aromatase inhibitors than tamoxifen or fulvestrant, primarily because of differences in mechanism of action. Aromatase inhibitors reduce peripheral estrogen synthesis, whereas tamoxifen and fulvestrant are selective estrogen receptor modulators. Studies have shown that up to 60% of postmenopausal and 40% of premenopausal breast cancer survivors suffer from GSM.<sup>2</sup> Patients are often skeptical about bringing this up with their oncologist, either because of sexual embarrassment or considering it as part of natural aging. The increased risk of recurrence of breast cancer has swayed oncologists from prescribing estrogen replacement. As highlighted in the accompanying review article by Sussman et al,<sup>4</sup> this is an important complication of endocrine therapy for breast cancer, which has multiple effective and fairly safe treatment options.<sup>3</sup>

The choice of treatment of GSM depends on the severity of symptoms. We treat mild symptoms with nonhormonal therapies, which is in line with the recommendation by the American College of Obstetrics and Gynecology. Vaginal moisturizers and lubricants work effectively by reducing friction and irritation, whereas pH-balancing gels help by reducing the vaginal pH and restoring vaginal mucosa.<sup>4</sup> Hyaluronic acid gel and CO<sub>2</sub> laser therapy are other options, which are still being studied.

Because estrogen depletion is the primary cause of GSM, replacement with systemic estrogen was believed to be an attractive option. Multiple randomized trials investigated their role but found a statistically significant increase in risk of breast cancer recurrence and higher rates of cardiovascular disease, without showing a true benefit in terms of GSM.<sup>5,6</sup> Hence, we have refrained from using systemic estrogen replacement as an option for breast cancer survivors with symptoms of GSM.

Topical estrogen-based therapies have been extensively studied in postmenopausal patients with GSM, but data in breast cancer survivors are not as robust. The dilemma has always been whether there is any systemic absorption and if that translates into a worse outcome in terms of breast cancer recurrence. Some studies showed that intravaginal estrogen did not result in a statistically significant increase in serum estradiol levels, whereas others showed that although the levels of estradiol may increase, they are not sustained for a prolonged period. Importantly, there was no convincing evidence for increased risk of breast cancer recurrence, especially with topical therapy containing estrogen alone.<sup>7</sup> Despite this, given the lack of high-level data, the American College of Obstetrics and Gynecology recommends caution with vaginal estrogen use, especially in breast cancer survivors.<sup>8</sup> It is recommended to reserve this approach for GSM symptoms that are unresponsive to nonhormonal therapies. Estradiol-releasing intravaginal tablets, vaginal inserts, and vaginal rings are reasonable options to discuss with patients. Estradiol-releasing intravaginal tablets at lower doses (4 or 10 µg) for short periods have been our preferred approach for patients with moderate to severe symptoms of GSM.

Post menopause, the ovaries are not producing estrogen from its precursor, androstenedione, but there is still some estrogen production happening in other tissues, with dehydroepiandrosterone (DHEA) being the primary precursor of androgens that get converted to estrogen. This brought up the concept of androgen deficiency being one of the mechanisms for GSM. The limited number of studies of intravaginal DHEA in breast cancer survivors has demonstrated

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that it is highly effective in alleviating symptoms such as dyspareunia and vaginal dryness, without increasing serum estrogen levels. Because of this, intravaginal DHEA, such as the US Food and Drug Administration–approved prasterone, is also an option to be considered.<sup>9</sup>

Ospemifene is a selective estrogen receptor modulator like tamoxifen, but, unlike tamoxifen, it does not affect the endometrial lining. It has estrogenic effects on the vaginal mucosa and bones; therefore, it is approved by the US Food and Drug Administration in postmenopausal women with GSM but is not approved in breast cancer survivors because of lack of specific data in this setting. Given its unique mechanism of action and potential benefits, there is a need to study this drug in breast cancer survivors.<sup>10</sup>

In summary, our initial approach to treating breast cancer survivors with GSM is to offer nonhormonal therapies,

such as vaginal moisturizers, lubricants, or gels. If there is no improvement, we offer intravaginal estrogen preparations, with the aim of using lower doses for the shortest possible time. If patients have apprehensions about using intravaginal estrogen, we discuss the role of intravaginal DHEA and testosterone also. It is important to be up front about GSM with patients and make sure that they are comfortable discussing these symptoms. We also incorporate an interdisciplinary approach and consult with gynecologists at our institution in cases where multiple approaches have failed to improve quality of life. There are multiple effective treatment options for GSM, but most of the high-level data come from studies in postmenopausal patients. Although the outlook for breast cancer survivors with GSM looks promising, there is a need for additional research in GSM specific to this population.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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