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Women's Health Science Journal

ISSN: 2639-2526

GSM: Counseling Points to Discuss with Women Fearful of Vaginal Estrogen

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Review Article

Volume 9 Issue 1

Received Date: May 19, 2025

Published Date: June 11, 2025

DOI: 10.23880/whsj-16000242

Abstract

Genitourinary syndrome of menopause (GSM), affecting both peri and postmenopausal women, is characterized by chronic, and often progressive symptoms that include vulvovaginal atrophy, dyspareunia, dryness, and urinary discomfort. Despite the prevalence and impact of these symptoms, many women remain untreated due to persistent fears about the safety of vaginal estrogen and other interventions as well as not reporting these symptoms to their health care provider. This review addresses the clinical dilemma faced by providers when counseling women who are hesitant to initiate hormone-based therapies. Although concerns about breast cancer, endometrial pathology, and thromboembolic events persist, robust evidence demonstrates that low-dose vaginal estrogen is safe, minimally absorbed systemically, and highly effective in restoring genitourinary tissue integrity and relieving symptoms. Topical preparations offer targeted delivery with favorable safety profiles. For women with contraindications or a preference to non-hormonal options, ospemifene provides a systemic alternative. This review synthesizes the comparative efficacy and safety data, highlights evidence-based counseling strategies, and offers practical guidance for addressing misconceptions that contribute to treatment refusal by women. By confronting misinformation and normalizing GSM treatment, clinicians can help restore quality of life for millions of women living with symptoms of GSM.

Keywords: GSM; Tissue Integrity; Vaginal Estrogen

Abbrevations

GSM: Genitourinary Syndrome of Menopause; EVES: European Vulvovaginal Epidemiological Survey; VMI: Vaginal Maturation Index; and VHI: Vaginal Health Index; SCE-A: Synthetic Conjugated Estrogens A; HRT: Hormone Replacement Therapy; WHI: Women's Health Initiative.

Introduction

Genitourinary syndrome of menopause (GSM) refers to genitourinary tract symptoms that occur due to physical changes caused by the decline in estrogen levels after menopause. Among postmenopausal women, 84% of women report GSM symptoms [1]. Unlike many other menopausal

symptoms that often subside over time, GSM symptoms usually persist throughout a woman's life. It is not uncommon for women to experience numerous GSM symptoms, such as vaginal irritation, burning, itching, dysuria, urinary incontinence, and dyspareunia. A systematic review reported that the prevalence of at least one GSM symptom is 87% and the prevalence of four symptoms is 31.7% [2]. In the European Vulvovaginal Epidemiological Survey (EVES), the study participants experienced an average of five symptoms [3].

However, many women with GSM are fearful of using either vaginal estrogen or clinician prescribed non-hormonal options as well [4]. In addition to estrogen, the non-hormonal option consists of the oral selective estrogen receptor modulator: ospemifene. Low-dose vaginal estrogen is associated with subjective improvement in GSM symptom severity by approximately 60% - 80%, and with improvement in severity by 30% - 50% for oral ospemifene [5].

Yet, the proven efficacy of local hormonal therapy, a persistent clinical dilemma remains: many women are hesitant to initiate vaginal estrogen due to fears of breast cancer, endometrial hyperplasia, and cardiovascular complications. This widespread misconception not only undermines patient care but also places providers in the position of having to reconcile scientific evidence with deeply rooted apprehensions. This article reviews clinician guidelines regarding vaginal estrogen and points to discuss with patients who would benefit from this intervention.

Methods

This review was conducted using OVID as the primary electronic database to identify relevant literature on the treatment of GSM, with a specific focus on vaginal estrogen therapies and non-hormonal alternatives. A keyword-based search strategy was implemented, combining keywords such as "vaginal estrogen", "GSM", "vaginal atrophy", "vaginal dryness", "ospemifene", "vaginal creams", "vaginal ring", and "treatment" using Boolean operators (and/or) to refine results. Included studies were selected based on their relevance to the counseling, pharmacologic management, and clinical outcomes associated with GSM. Preference was given to randomized controlled trials, systematic reviews, and large observational studies that provided data on symptom severity, patient reported outcomes, safety profiles, and provider-patient communication strategies. No geographic limitations were applied, and all included studies were published in English. The search was not limited by year, but priority was given to literature from the last two decades to reflect contemporary clinical guidelines and therapeutic advances.

Vaginal Estrogen

Vaginal estrogen focuses on localized delivery methods that provide symptom relief with minimal systemic absorption. The types of vaginal estrogen are conjugated estrogen creams, estradiol vaginal gels, low dose vaginal estradiol tablets, estradiol containing soft gel capsules, and estradiol vaginal rings.

Traditionally, estrogen has been administered through oral routes. A randomized clinical trial compared the effectiveness of a 10-microgram estradiol oral tablet with a placebo gel versus a placebo tablet with a vaginal moisturizer. After 12 weeks, both groups showed similar reductions in VVA and dyspareunia prevalence, with no significant differences between both groups [6]. The minimal to negligible reduction in symptom severity can be attributed to oral estrogen's systemic distribution and inability to directly target the affected vaginal and urethral tissue. Given these limitations, the clinical focus must shift toward localized therapies that directly target genitourinary tissues and provide more meaningful, lasting symptom relief.

Among the available vaginal estrogen therapies, topical preparations such as conjugated estrogen creams and estradiol vaginal gels are foundational treatment options that allow for targeted symptom relief. These formulations offer advantages in terms of direct application to affected tissue, rapid onset of action, and minimal systemic absorption.

Estradiol vaginal gel provides an effective and well-tolerated approach to managing GSM symptoms. In a randomized control trial, postmenopausal women using a 25-ug estradiol vaginal gel demonstrated statistically significant improvements in vaginal maturation index (VMI), vaginal pH, and Vaginal Health Index (VHI) after eight weeks of treatment compared to placebo. Importantly, there was no associated increase in serum estradiol levels or endometrial thickness, supporting the gel's favorable safety profile.[7] The estradiol gel's hydrophilic properties enhance mucosal absorption, effectively reversing atrophic changes while maintaining systemic estrogen exposure at negligible levels [7]. In counseling women on treatment options, providers should present estradiol vaginal gels as a promising option, particularly for those concerned about systemic effects but desiring robust symptom improvement.

Conjugated estrogen vaginal creams, notably those containing synthetic conjugated estrogens A (SCE-A) and natural conjugated estrogens, have also demonstrated strong efficacy in clinical trials. A double-blind randomized controlled trial displayed that a low dose regimen of 1 g SCE-A cream (containing 0.625 mg estrogen) administered twice weekly significantly improved the severity of the most

bothersome symptom (MBS), VMI, and vaginal pH compared to placebo [8]. Likewise, a large multicenter study evaluating low dose conjugated estrogen cream (0.3mg) administered daily or twice weekly showed sustained improvement in VMI, vaginal pH, and participants reported GSM symptoms over one year, without cases of endometrial hyperplasia [9]. These findings affirm the efficacy of conjugated estrogen creams even at low doses, reinforcing their role as a durable treatment option.

Importantly, the ability of vaginal creams to be topically applied to the vulvar and vestibular tissue offers a therapeutic advantage. This is relevant given that the vulvar vestibule, rather than the deeper vaginal epithelium, is often the primary site of dyspareunia and neuropathic pain [10]. Localized application allows for tailored treatment of the most symptomatic areas, offering greater flexibility than tablets or rings. This approach respects the wide range of GSM symptom distribution and empowers providers to individualize therapy.

Despite their clear benefits, vaginal creams may be perceived by some patients as messy or inconvenient. During counseling, it is essential to balance these practical considerations with the creams' superior ability to restore tissue integrity and alleviate a spectrum of GSM symptoms. Furthermore, reassuring patients that low dose vaginal estrogen delivers symptom relief with minimal systemic estrogen exposure is key to increasing patient compliance [9,11].

Vaginal creams, with their demonstrated efficacy, safety, and flexibility, should be prominently offered as a first-line therapeutic option in this conversation. Despite minimal systemic absorption of estrogen, there is still a fear of side effects from hormone replacement therapy.

The use of analogies can play a critical role in patient comprehension, particularly when addressing the localized action of vaginal estrogen. Providers may associate vaginal estrogen to a topical skin cream for a rash: it treats only the area it touches, not the whole body. This metaphor illustrates the concept of minimal systemic absorption in a relatable way and reduces the perception of vaginal estrogen as a systemic hormone therapy. Research shows that analogical reasoning in healthcare communication can enhance patient recall, reduce decisional conflict, and foster trust in provider recommendations [12]. Such strategies are especially important when addressing misinformation or stigma, allowing providers to reframe the conversation around treatment goals rather than fear.

For osteoporotic women on raloxifene, providers should emphasize that the efficacy of vaginal estrogen creams remains uncompromised. A randomized controlled trial demonstrated that low-dose conjugated estrogen creams significantly improved GSM symptoms, and that concomitant raloxifene use did not diminish this therapeutic response [13]. Importantly, women receiving raloxifene can safely use vaginal estrogen creams to address GSM symptoms without jeopardizing the benefits of their osteoporosis treatment. Concerns about deep vein thrombosis have contributed to hesitancy about combining selective estrogen receptor modulators (SERMs) with any form of estrogen. However, low dose vaginal estrogen is minimally absorbed systemically and has not been shown to elevate the risk of venous thromboembolism, even in conjunction with raloxifene. Highlighting this compatibility can help alleviate patient concerns and reinforce the suitability of vaginal creams as a first line option, even in women with complex medical histories.

While vaginal creams remain a foundational option, the range of vaginal estrogen therapies also includes devices designed for sustained, hands-free hormone delivery. Chief among these is the estradiol-releasing ring, which offers a distinct approach to GSM symptom management through continuous, low-dose estrogen release.

The estradiol releasing vaginal ring, containing 2 mg of micronized 17β-estradiol and delivering approximately 7.6 ug per day over 90 days, offers a continuous, ultra-low dose therapy that maintains stable local estrogen exposure with minimal system absorption [14]. Across multiple randomized trials, use of the estradiol vaginal ring has been associated with significant improvements in vaginal pH, mucosal maturation, and relief of symptoms including dryness, burning, dyspareunia, and urinary urgency [15,16]. A 36-week multicenter trial also demonstrated that the ring significantly prolonged the time to first recurrence of urinary tract infection, further highlighting its utility in managing the broader spectrum of GSM symptoms [16]. Objective measures such as VMI and pH were consistently improved, and endometrial safety was preserved across studies with no unexpected adverse events or significant endometrial stimulation reported [16].

Notably, one comparative trial found that estradiol vaginal ring to be equally effective as conjugated equine estrogen vaginal cream in relieving symptoms of vaginal atrophy, improving cytologic indices, and reducing pH, with equivalent endometrial safety [14]. However, patients reported significantly higher acceptability for the ring, citing improved convenience and comfort, These findings suggest that in the context of long-term use, especially among older women for whom dexterity or concerns about messiness may be limiting, the ring offers a compelling alternative to creams. Vaginal creams provide flexibility in dose titration

and allow targeted application to the vulvar vestibule, an advantage in treating localized dyspareunia, but are often perceived as messy or cumbersome, which may limit long term adherence. In contrast, the estradiol vaginal ring offers sustained, consistent dosing with significantly higher patient-reported acceptability [14].The ring requires only quarterly replacement and does not require daily or weekly application, which may enhance adherence and stratification over time. Women should be instructed on proper insertion, reassured about its retention during daily activities, and offered the option to remove it briefly for intercourse if preferred. Importantly, providers should proactively address common concerns about safety by sharing data on its favorable safety profile and low systemic estradiol levels.

Providers must be prepared to navigate patient concerns regarding estrogen therapy, particularly among those with a history of breast cancer or cardiovascular disease. However, counseling should emphasize that low dose vaginal estrogen carries minimal systemic absorption and has not been associated with increased endometrial hyperplasia, venous thromboembolism, or breast cancer recurrence in large scale studies [17]. To address patient apprehension surrounding the perceived risks, providers should incorporate data-based reassurance that contextualizes its safety profile. Integrating data into counseling allows providers to offer evidence-backed assurances and to contrast the negligible systemic absorption of local estrogen with the higher circulating levels associated with oral hormone therapy. Clearly presenting these comparative risks enables patients to make informed decisions grounded in empirical evidence rather than fear. A conversation grounded in clinical evidence and personalized risk assessment can help overcome hesitation, allowing more women to benefit from proven, effective therapies.

Non-Hormonal Options

While vaginal estrogen therapies offer efficacy and flexibility, there remains a subset of patients for whom hormonal options may be declined or contraindicated. In such cases, non-hormonal treatments, vaginal moisturizer and SERMs, are presented as alternatives. Although these interventions have a role, it is critical that providers counsel patients on their limitations relative to local estrogen therapies, particularly when symptom severity impairs quality of life.

Nonhormonal gels, such as aqueous hypromellose based vaginal moisturizers, are frequently positioned as a first line option due to their accessibility and lack of hormonal activity. In a randomized controlled trial comparing oxytocin gel and a hormone free hypromellose gel, both groups showed statistically significant reductions in the severity of their MBS at 4 and 12 weeks. However, there were no significant differences between the treatment arms at either time point, and neither matched the clinical impact observed with vaginal estrogen.[17,18] These results underscore the relative lack of efficacy of non-hormonal gels in restoring vaginal epithelial integrity or alleviating the full range of GSM symptoms. Although moisturizers can provide transient relief for dryness, they do not stimulate epithelial proliferation or restore vaginal pH. Unlike estrogen based therapies, they lack the pharmacologic activity necessary for mucosal absorption and long term reversal of atrophic changes [17,18]. Consequently, their benefits are typically not as effective. As such, they are best suited for women with very mild symptoms or as adjunctive care, rather than as stand-alone therapy for moderate to severe GSM. Ospemifene, a novel SERM, has emerged as an oral, non-estrogen option for treating moderate to severe dyspareunia and vaginal dryness associated with GSM. In a phase 3 trial, ospemifene 60 mg daily significant improved maturation index (increase in superficial cells, decrease in parabasal cells), lowered vaginal pH, and reduced the severity of dyspareunia compared to placebo [19,20]. These findings were supported by a one year extension study that demonstrated continued safety without clinical significant endometrial stimulation or adverse events related to breast of cardiovascular systems [21]. Notably, ospemifene was found effective in improving vaginal dryness as the MBS, showing significant improvement in both patient satisfaction and sexual function indices after 12 weeks [22].

While ospemifene presents a reasonable option for women who prefer or require oral therapy, data suggest that its efficacy is lower than that of localized vaginal estrogen [19,21]. In comparative analyses, vaginal estrogen products consistently demonstrate superior GSM symptom alleviation with a more direct mechanism of action. Ospemifene may be the best option for women who decline all local therapies or have absolute contraindications to estrogen, or did not get adequate relief from other non-hormonal interventions. While ospemifene offers a non-local, hormone-free option, its costs and accessibility may pose financial barriers to its use. Furthermore, it may not be listed on all insurance formularies and may require prior authorization.

As with all counseling around GSM treatment, the discussion should center individual symptom burden, treatment preferences, and evidence-based risk profiles. When grounded in shared decision making, even complex treatment pathways become accessible and empowering for patients.

Estrogen Use in Women with a History of Breast Cancer

Concerns about the safety of vaginal estrogen in breast cancer survivors, specifically those with estrogen receptor positive disease, remain a significant barrier to care. There

are many studies that have evaluated the role of vaginal estrogen in this population. A pivotal randomized controlled trial evaluated serum estradiol levels in women using vaginal conjugated estrogen creams (0.5 g/day) and found that levels remained below 20 pg/mL, which is well within the postmenopausal range [23]. Similarly, women using the estradiol releasing vaginal ring (Estring®, 7.5 μg/day) did not show a clinically significant increase in serum estradiol, with levels averaging between 4-11 pg/mL, even when assessed during long term use [24]. These levels are markedly lower than those achieved with oral estrogen therapy, which can raise serum estradiol to 40-60 pg/mL and even exceed 100 pg/mL depending on dose and duration [25].

Among breast cancer survivors undergoing treatment with aromatase inhibitors, estrogen suppression is critical to mitigate recurrence risk. However, data suggest that the use of ultra-low dose vaginal estradiol tablets in this population does not significantly increase systemic estradiol, estrone, or estrone sulfate levels [26]. Serum concentrations often remain below the lower detection limit of 5 pg/mL, even with continued use over several months [26]. These pharmacokinetic profiles are reassurance for both oncologists and gynecologists, allowing for symptom relief without compromising systemic estrogen suppression.

Notably, a meta-analysis assessing the safety of vaginal estrogen in breast cancer survivors found no significant increase in breast cancer recurrence or mortality. The analysis included over 3,000 women across multiple studies and highlighted that vaginal estrogen, when used at low doses and for localized relief posed no additional oncologic risk, even in women receiving tamoxifen or aromatase inhibitors [27]. Among vaginal estrogen users, the pooled recurrence rate was approximately 10%, and cancer-related mortality was 2.6% over an average follow-up of seven years, comparable to rates in non-users [27]. Importantly, no statistically significant difference in outcomes was observed between those receiving vaginal estrogen and those not receiving any form of hormone therapy, affirming the oncologic safety of localized, low-dose formulations in this population [27].

In contrast, systemic hormone replacement therapy (HRT) has been associated with increased risk in breast cancer survivors, particularly among those with estrogen receptor–positive disease. The Women's Health Initiative (WHI) reported a 24% increase in breast cancer incidence (HR 1.24; 95% CI, 1.01–1.53) and higher mortality associated with combined estrogen-progestin therapy [28]. Furthermore, recurrence rates in survivors using systemic HRT have reached 15%–20%, especially in the absence of concurrent oncologic monitoring [29]. Systemic HRT has also been shown to elevate serum estradiol levels by as much as 76 pg/mL, a marked contrast to the negligible increases observed with vaginal estrogen formulations [30]. These findings underscore the importance of selecting therapies that avoid systemic hormonal exposure. Therefore, when considering treatment options for GSM in women with a history of hormone-sensitive breast cancer, low-dose vaginal estrogen remains the safer route due to its localized action, minimal systemic absorption, and well-documented safety profile.

It is essential to contextualize estradiol exposure from vaginal estrogen relative to routine physiological fluctuations and other common exposures. The transient serum estradiol increases seen with some vaginal creams are not only markedly lower than those observed with systemic HRT, which can elevate circulating estradiol by over 70 pg/mL, but are also comparable to natural spikes that occur after sexual activity or physical exertion. These exposures remain well below the thresholds needed to stimulate breast tissue, particularly when localized vaginal estrogen is used under oncologic supervision. Framing this information through clear analogies will help improve patient understanding and compliance.

Conclusion

In clinical practice, GSM should be addressed in all peri and menopausal women and those with symptoms offered management. A proactive, evidence-based approach in counseling postmenopausal women, emphasizing that effective, safe, and individualized treatment options are available is advisable. Among these, vaginal estrogen therapies should be presented to symptomatic women due to their localized action, minimal systemic absorption and robust efficacy. Providers should highlight that systemic estradiol levels with low-dose vaginal formulations remain well within postmenopausal ranges, which reinforces their safety, even in women with hormone-sensitive conditions. For women unable or unwilling to use local estrogen, ospemifene is another effective option. Ultimately, counseling must move beyond symptom inquiry to offer therapeutic guidance that affirms a patient's concerns while empowering women with the knowledge to make informed, confident decisions about GSM treatment. In summary, individual counseling should be offered to all women who note GSM symptoms [31-35].

References

1. Angelou K, Grigoriadis T, Diakosavvas M, Zacharakis D, Athanasiou S (2020) The Genitourinary Syndrome of Menopause: An Overview of the Recent Data. Cureus 12(4): e7586.

2. Carlson K, Nguyen H (2025) Genitourinary Syndrome

of Menopause. [Updated 2024 Oct 5]. In: StatPearls. Treasure Island (FL).

3. Palacios S, Nappi RE, Bruyniks N, Particco M, Panay N (2018) EVES Study Investigators. The European Vulvovaginal Epidemiological Survey (EVES): prevalence, symptoms and impact of vulvovaginal atrophy of menopause. Climacteric 21(3): 286-291.

4. Stair SL, Chyu J, Rangwala S, Palmer CJ, Lucioni A, et al. (2025) Experiences With Genitourinary Syndrome of Menopause and Barriers to Vaginal Estrogen Usage Reported by a National Sample of 1500 Women. Urology 196: 115-123.

5. Crandall CJ, Mehta JM, Manson JE (2023) Management of Menopausal Symptoms: A Review. JAMA 329(5): 405-420.

6. Constantine GD, Simon JA, Pickar JH, Archer DF, Kushner H, et al. (2017) REJOICE Study Group. The REJOICE trial: a phase 3 randomized, controlled trial evaluating the safety and efficacy of a novel vaginal estradiol soft-gel capsule for symptomatic vulvar and vaginal atrophy. Menopause 24(4): 409-416.

7. Tanmahasamut P, Jirasawas T, Laiwejpithaya S, Areeswate C, Dangrat C, et al. (2020) Effect of estradiol vaginal gel on vaginal atrophy in postmenopausal women: A randomized double-blind controlled trial. J Obstet Gynaecol Res 46(8): 1425-1435.

8. Freedman M, Kaunitz AM, Reape KZ, Hait H, Shu H (2009) Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy. Menopause 16(4): 735-41.

9. Bachmann G, Bouchard C, Hoppe D, Ranganath R, Altomare C, et al. (2009) Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. Menopause 16(4): 719-27.

10. Goetsch MF, Garg B, Lillemon J, Clark AL (2023) Treating where it hurts-a randomized comparative trial of vestibule estradiol for postmenopausal dyspareunia. Menopause 30(5): 467-475.

11. Biehl C, Plotsker O, Mirkin S (2019) A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause. Menopause 26(4): 431-453.

12. Minkin MJ, Maamari R, Reiter S (2013) Improved compliance and patient satisfaction with estradiol vaginal tablets in postmenopausal women previously treated with another local estrogen therapy. Int J Womens Health 5: 133-139.

13. Parsons A, Merritt D, Rosen A, Heath H, Siddhanti S (2003) Effect of raloxifene on the response to conjugated estrogen vaginal cream or nonhormonal moisturizers in postmenopausal vaginal atrophy. Obstetrics & Gynecology 101(2): 346-352.

14. Ayton RA, Darling GM, Murkies AL, Farrell EA, Weisberg E (1996) A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy. Br J Obstet Gynaecol 103(4): 351-358.

15. Nelken RS, Ozel BZ, Leegant AR, Felix JC, Mishell DR (2011) Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder. Menopause 18(9): 962-966.

16. Eriksen BA (1999) Randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. Am J Obstet Gynecol 180(5): 1072-1079.

17. Fianu Jonasson A, Bixo M, Sundström Poromaa I, Åstrom M (2020) Safety and Efficacy of an Oxytocin Gel and an Equivalent Gel but Without Hormonal Ingredients (Vagivital® Gel) in Postmenopausal Women with Symptoms of Vulvovaginal Atrophy: A Randomized, Double-Blind Controlled Study. Med Devices (Auckl) 13: 339-347.

18. Lima SM, Yamada SS, Reis BF, Postigo S, Galvão da Silva MA, et al. (2013) Effective treatment of vaginal atrophy with isoflavone vaginal gel. Maturitas 74(3): 252-258.

19. Bachmann GA, Komi JO (2010) Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause 17(3): 480-486.

20. Portman DJ, Bachmann GA, Simon JA (2013) Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause 20(6): 623-630.

21. Simon JA, Lin VH, Radovich C, Bachmann GA (2013) Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 20(4): 418-427.

22. Archer DF, Goldstein SR, Simon JA, Waldbaum AS,

Sussman SA, et al. (2019) Efficacy and safety of ospemifene in postmenopausal women with moderate-to-severe vaginal dryness: a phase 3, randomized, double-blind, placebo-controlled, multicenter trial. Menopause 26(6): 611-621.

23. Krause M, Wheeler TL, Richter HE, Snyder TE (2010) Systemic effects of vaginally administered estrogen therapy: a review. Female Pelvic Med Reconstr Surg 16(3): 188-195.

24. Moegele M, Buchholz S, Seitz S, Lattrich C, Ortmann O (2013) Vaginal Estrogen Therapy for Patients with Breast Cancer. Geburtshilfe Frauenheilkd 73(10): 1017-1022.

25. Batur P, Blixen CE, Moore HC, Thacker HL, Xu M (2006) Menopausal hormone therapy (HT) in patients with breast cancer. Maturitas 53(2): 123-132.

26. Kendall A, Dowsett M, Folkerd E, Smith I (2006) Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. Ann Oncol 17(4): 584-587.

27. Beste ME, Kaunitz AM, McKinney JA, Sanchez Ramos L (2024) Vaginal estrogen use in breast cancer survivors: a systematic review and meta-analysis of recurrence and mortality risks. Am J Obstet Gynecol 232(3): 262-270.

28. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, et al. (2002) Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 288(3): 321-33.

29. Col NF, Kim JA, Chlebowski RT (2005) Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. Breast Cancer Res 7(4): 535-540.

30. Santen RJ, Mirkin S, Bernick B, Constantine GD (2020) Systemic estradiol levels with low-dose vaginal estrogens. Menopause 27(3): 361-370.

31. Pinkerton JV, Shifren JL, La Valleur J, Rosen A, Roesinger M, et al. (2003) Influence of raloxifene on the efficacy of an estradiol-releasing ring for treating vaginal atrophy in postmenopausal women. Menopause 10(1): 45-52.

32. Nachtigall LE (1995) Clinical trial of the estradiol vaginal ring in the U.S. Maturitas 22: S43-S47.

33. Danan ER, Sowerby C, Ullman KE, Ensrud K, Forte ML, et al. (2024) Hormonal Treatments and Vaginal Moisturizers for Genitourinary Syndrome of Menopause : A Systematic Review. Ann Intern Med 177(10): 1400-1414.

34. Mitchell CM, Reed SD, Diem S, Larson JC, Newton KM, et al. (2018) Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms: A Randomized Clinical Trial. 178(5): 681-690.

35. Kingsberg S, Kellogg S, Krychman M (2010) Treating dyspareunia caused by vaginal atrophy: a review of treatment options using vaginal estrogen therapy. Int J Womens Health 1: 105-111.