



SUPPLEMENT TO

**OBG**  
**MANAGEMENT**

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# Dyspareunia Associated with Vulvovaginal Atrophy: Innovations in Counseling, Diagnosis, and Management

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## TITLE OF ACTIVITY

Dyspareunia Associated with Vulvovaginal Atrophy: Innovations in Counseling, Diagnosis, and Management

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**Sean T. Barrett** has nothing to disclose.  
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**Robert Schneider, MSW** has nothing to disclose.

## LEARNING OBJECTIVES

After participating in this educational activity, participants should be better able to:

- Define vulvovaginal atrophy (VVA), and genitourinary syndrome (GSM) and their impact on post-menopausal dyspareunia
- Identify the factors, both clinician-based and patient-based, that may inhibit diagnosis of dyspareunia
- Describe clinician counseling approaches to facilitate a discussion with patients about their symptoms
- Discuss the benefits and risks of innovative therapeutic interventions indicated for the management of menopause-related dyspareunia

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## Introduction

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In the United States, there are approximately 64 million women who are postmenopausal. Of these women, it is estimated that 50%—or more than 32 million—have symptoms of vulvovaginal atrophy (VVA) and/or dyspareunia (painful sexual intercourse). These two conditions, along with several others, are components of the Genitourinary Syndrome of Menopause (GSM). GSM is a term introduced in 2014 by the North American Menopause Society (NAMS) and International Society for the Study of Women's Sexual Health (ISSWSH) to describe the constellation of signs and symptoms associated with the decreased levels of estrogen and other sex steroids associated with menopause.

Many women are knowledgeable of the vasomotor symptoms (VMS) that often occur with menopause and seek treatment for these. However, many are less likely to recognize that VVA symptoms such as vaginal dryness and painful intercourse are treatable conditions that occur as a result of the hormonal changes of meno-

pause. Additionally, these women may not be aware that, unlike vasomotor symptoms that spontaneously resolve, VVA is a chronic condition that worsens over time in the absence of treatment. Consequently, VVA often interferes with a woman's sexual functioning, her overall quality of life, and can be the source of partnership issues. Historically, the standard treatment for VVA has been estrogen therapy, administered systemically (oral or patch) or topically (vaginal cream, tablet, ring). Two innovative, non-estrogen therapies – ospemifene and prasterone -- have been approved for the treatment of dyspareunia associated with VVA.

This CME-designated journal supplement is comprised of three articles that will provide information and strategies regarding best practices as to patient counseling, diagnosis, and treatment of VVA, and its associated dyspareunia. The goal is to provide women's health clinicians the knowledge and tools they need to optimize the care they provide to their menopausal patients.

Cover photo: Prof. P.M. Motta/Univ. "La Sapienza", Rome

Post-menopausal vagina. Colored scanning electron micrograph (SEM) of the post-menopausal vagina of a 63-year-old woman. Magnification: x1100 at 6x7cm size.

# Understanding and Resolving Dyspareunia's Distress on Women and Clinicians

**Sheryl A. Kingsberg, PhD**

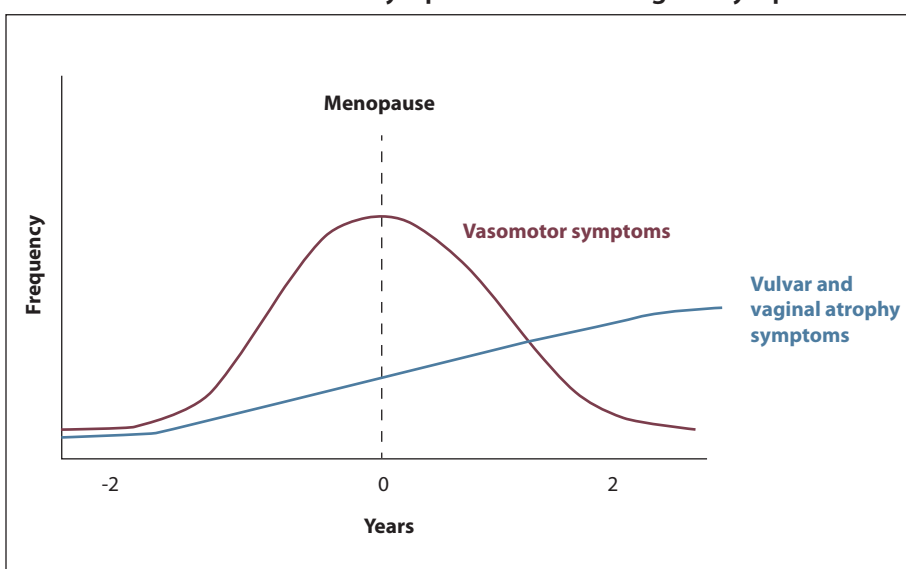
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## INTRODUCTION

Of the approximately 64 million women in the United States who are postmenopausal, at least half—estimated at more than 32 million women—have symptoms of vulvovaginal atrophy (VVA) or dyspareunia, or both.<sup>1</sup> However, many of these women are unaware that the underlying vulvar and vaginal changes can be the direct result of perimenopause or menopause.<sup>1,2</sup> Although these symptoms can be quite bothersome, the majority of women (approximately 93%) fail to seek treatment for them, either owing to embarrassment, lack of knowledge, or negative attitudes/misperceptions regarding hormone therapy.<sup>1,3-5</sup> Furthermore, women who do seek treatment are often dissatisfied with the safety, convenience and/or efficacy of currently approved products.<sup>1</sup> Consequently, VVA and dyspareunia remain underdiagnosed and undertreated.

Unlike vasomotor symptoms, VVA is a chronic condition with symptoms that worsen over time in the absence of treatment (FIGURE 1). Symptomatic VVA is one component of the genitourinary syndrome of menopause (GSM), a term recently introduced by the North American Menopause Society (NAMS) and International Society for the Study of Women's Sexual Health to describe the constellation of signs and symptoms associated with decreased estrogen and other sex steroids associated

**FIGURE 1** Onset of vasomotor symptoms vs. vulvovaginal symptoms<sup>8,9</sup>



with menopause.<sup>6</sup> GSM can involve changes to the labia (majora and minora), vestibule/introitus, vagina, clitoris, urethra, and bladder. Signs include decreased vaginal moisture and diminished elasticity, labial resorption, pallor/erythema, loss of rugae, petechiae, fragility, urethral atrophy, and introital involution. Symptoms include, but are not limited to, vaginal dryness, pain with sex that may lead to subsequent sexual dysfunction, bladder and urethral symptoms (frequency, urgency, dysuria), frequent urinary tract infections, burning, itching, and irritation that are bothersome or distressing. Treatment of symptomatic VVA may improve all components of GSM. A more alkaline (>5) vaginal pH and increased parabasal cells on the vaginal maturation index are supportive signs of GSM.<sup>3</sup>

Dyspareunia is another common component of GSM. As noted by the American College of Obstetricians and Gynecologists, "Recent perspectives suggest that dyspareunia may be characterized as a pain disorder that interferes with sexuality rather than as a sexual

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disorder characterized by pain. Therefore, dyspareunia is believed to be a specific pain disorder with interdependent psychological and biologic contributions.<sup>17</sup> In a study of 500 postmenopausal women with vaginal discomfort, vaginal dryness (85%) and dyspareunia (52%) were the most commonly reported complaints.<sup>5</sup>

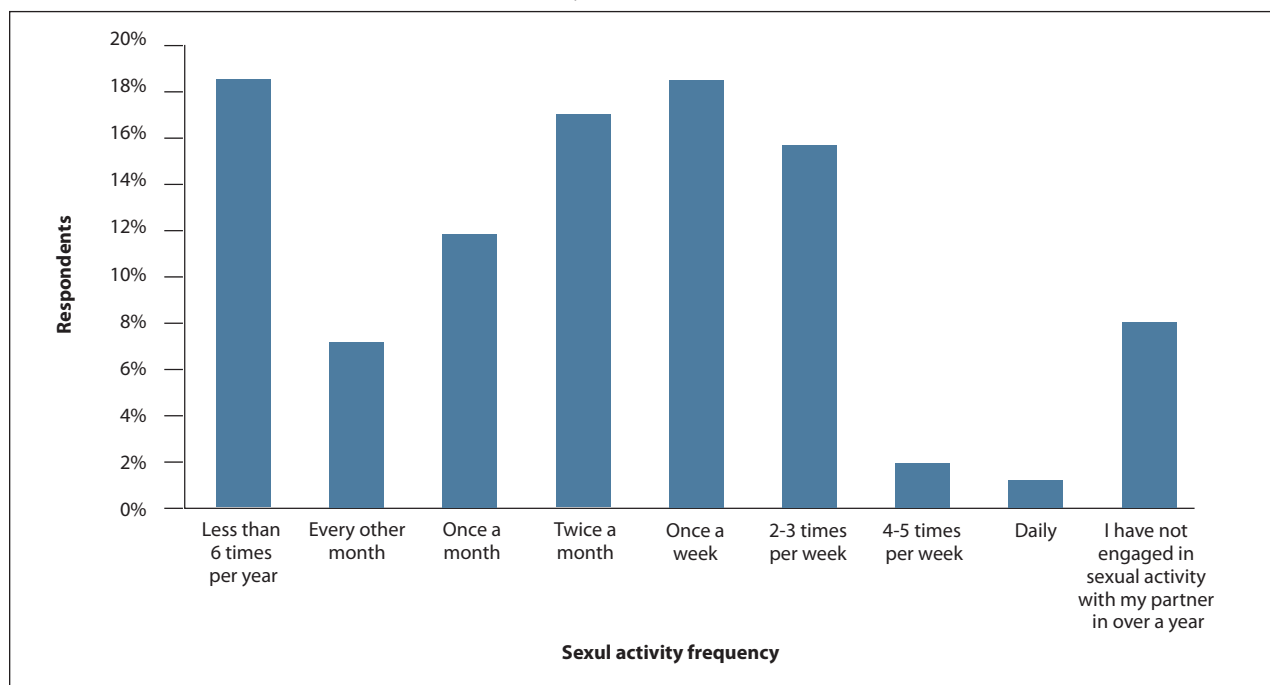
### WOMEN'S EXPERIENCE OF VVA: SURVEY DATA

Recent studies have consistently identified 3 major factors that influence sexuality in older women: age, hormonal insufficiency, and partnership status (TABLE 1).<sup>6</sup> Of these 3 factors, age does not appear to be the most important (FIGURE 2). A random digit dialing survey of

**TABLE 1** Key studies and findings on postmenopausal sexual health<sup>2</sup>

Study title	Survey population	Survey methodology	Key findings
REVEAL <sup>14</sup>	<ul style="list-style-type: none"> <li>• 1006 postmenopausal women (45-64 years)</li> <li>• 602 HCPs who treat postmenopausal women</li> </ul>	Telephone interviews	<ul style="list-style-type: none"> <li>• 25% of women reported dyspareunia</li> <li>• 44% did not discuss symptoms with HCP</li> </ul>
VIVA <sup>5,15</sup> (US data)	<ul style="list-style-type: none"> <li>• 3520 postmenopausal women (55-65 years; 500 women in US)</li> </ul>	International online survey	<ul style="list-style-type: none"> <li>• 93% had ≥1 menopausal symptom               <ul style="list-style-type: none"> <li>– 85% vaginal dryness</li> <li>– 52% dyspareunia</li> <li>– 48% vaginal discomfort</li> </ul> </li> <li>• Fewer than two-thirds associated symptoms with menopause</li> </ul>
REVIVE <sup>1</sup>	3046 women who reported symptoms consistent with VVA	Online survey	<ul style="list-style-type: none"> <li>• 40% of total respondents (n&gt;8000) reported symptoms               <ul style="list-style-type: none"> <li>– 55% had vaginal dryness</li> <li>– 44% had dyspareunia</li> <li>– 37% had vaginal irritation</li> </ul> </li> <li>• 60% reported VVA symptoms interfered with enjoyment of sex</li> <li>• 24% attributed symptoms to menopause, 12% to hormonal changes</li> </ul>
CLOSER <sup>11,16</sup> (North American cohort)	<ul style="list-style-type: none"> <li>• 1000 married/cohabitating women (ages 55-65) with vaginal discomfort</li> <li>• 1000 male partners</li> </ul>	International online survey	<ul style="list-style-type: none"> <li>• VVA negatively affected intimate relationships</li> <li>• Women:               <ul style="list-style-type: none"> <li>– 64% reported dyspareunia</li> <li>– 64% reported loss of libido</li> <li>– 58% reported vaginal discomfort led to avoiding intimacy</li> <li>– 30% cited vaginal discomfort as reason they stopped having sex</li> </ul> </li> </ul>
MIDUS II <sup>12</sup>	2116 women aged 28-85 years	Telephone interviews, self-administered questionnaires	<ul style="list-style-type: none"> <li>• 63% of women (n=1345) were sexually active in prior 6 months</li> <li>• 59% of women ≥60 years were sexually active</li> <li>• Women who have a partner had 8-fold-higher odds of being sexually active</li> </ul>
EMPOWER <sup>17</sup>	<1900 postmenopausal women	Online survey	<ul style="list-style-type: none"> <li>• 77% had vaginal itching/irritation, soreness, burning, pain</li> <li>• Most women fail to recognize signs/symptoms of VVA</li> </ul>

Abbreviations: CLOSER, Clarifying Vaginal Atrophy's Impact On SEx and Relationships; EMPOWER, Women's EMPOWER survey; HCP, health care provider; MIDUS II, Midlife Development in the United States; REVEAL, REvealing Vaginal Effects At mid-Life; VIVA, Vaginal Health, Insights, Views, & Attitudes; VVA, vulvovaginal atrophy.

**FIGURE 2** Postmenopausal women are sexually active<sup>13</sup>


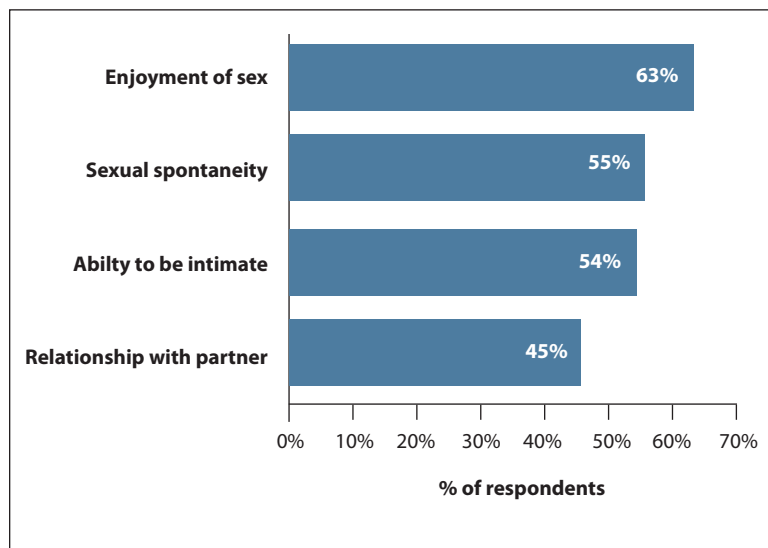
2000 women 18 to 94 years old, published in 2003, noted that older women (defined as >60 years) remain sexually active.<sup>10</sup> In comparison, women are more likely to cite the consequences of hormonal insufficiency (VVA, dyspareunia) and lack of a partner as the most important determinants of their postmenopausal sexual functioning.<sup>1,2,5,11,12</sup> In addition, surveys have consistently noted that women generally have a poor understanding of the symptoms and treatments of VVA and highlight the need for better communication between women and their health care providers (HCPs) regarding VVA and dyspareunia.

The **REvealing Vaginal Effects At mid-Life (REVEAL)** market research survey involved telephone interviews with 1006 postmenopausal women in the United States, aged 45-65 years and not currently on hormonal therapy, along with 602 HCPs who treat such women (**TABLE 1**).<sup>14</sup> More than two-thirds of the participating women were married or living with a partner, and 80% were Caucasian. The majority (87%) reported that sexual health was important to them. However, although 25% of the women reported dyspareunia, nearly half (44%) did not discuss their symptoms with their HCP. Only 10% of the women reported that their HCP initiated a conversation regarding dyspareunia, whereas 44% reportedly initiated the conversation. The majority of women perceived that society is more accepting of discussions around men's sexual problems than women's (74%), that soci-

ety constrains sexual expression of older women more so than older men (75%), that there are no medications to address women's physical sexual problems (71%), and that society would prefer to believe "older" women do not have sex (53%).

The **Vaginal Health, Insights, Views, & Attitudes (VIVA)** survey was an online international survey of 3520 postmenopausal women, including 500 women from the United States, all 55 to 65 years of age (**TABLE 1**).<sup>5,15</sup> Nearly two-thirds of the participants were either married (58%) or living as married (4%). Among the US cohort, 93% of women had experienced at least 1 menopausal symptom, but fewer than two-thirds of them associated vaginal symptoms with menopause.<sup>5</sup> Nearly half of the women had experienced 'vaginal discomfort' (48%), with most reporting vaginal dryness (85%) and dyspareunia (52%). Of note, 82% of women had experienced vaginal discomfort for at least 1 year; however, 37% did not consult any HCP and 40% waited at least 1 year before contacting one. The majority of women (80%) reported vaginal discomfort negatively impacted their lives: 75% reported that it affected their sexual intimacy, 33% noted it had a negative effect on relationships, and 25% believed it led to a lower quality of life.<sup>5</sup> Therefore, while VVA negatively influenced women's lives, the survey found they lack knowledge about the condition and do not consult with HCPs about their symptoms.

**FIGURE 3** REVIVE: Vulvovaginal atrophy symptoms interfere with female sexuality<sup>1</sup>



Just over 8000 postmenopausal women in the United States participated in the **RE**al Women's **V**IEWS of **T**reatment Options for Menopausal **V**aginal **Ch**ang**E**s (REVIVE) online survey (**TABLE 1**).<sup>1</sup> Nearly 40% of the respondents (3046) reported symptoms consistent with VVA—including vaginal dryness (55% of all participants), dyspareunia (44%), irritation (37%). Tenderness and bleeding with sexual activity were also commonly reported. Approximately 60% of participants reported that their VVA symptoms interfered with enjoyment of sex, 55% reported interference with sexual spontaneity, and 45% reported VVA impacted the relationship with her partner (**FIGURE 3**). Twelve percent of women without a sexual partner noted they were not actively seeking a partner because of the discomfort associated with these symptoms. In addition, 1 in 4 participants reported their symptoms also interfered with sleep (24%), general enjoyment of life (23%), and temperament (23%). However, few participants attributed their symptoms to menopause (24%) or hormonal changes (12%).<sup>1</sup> Nearly two-thirds of the women were using over-the-counter (OTC) products to manage their symptoms, and only 27% reported using vaginal estrogen therapies.

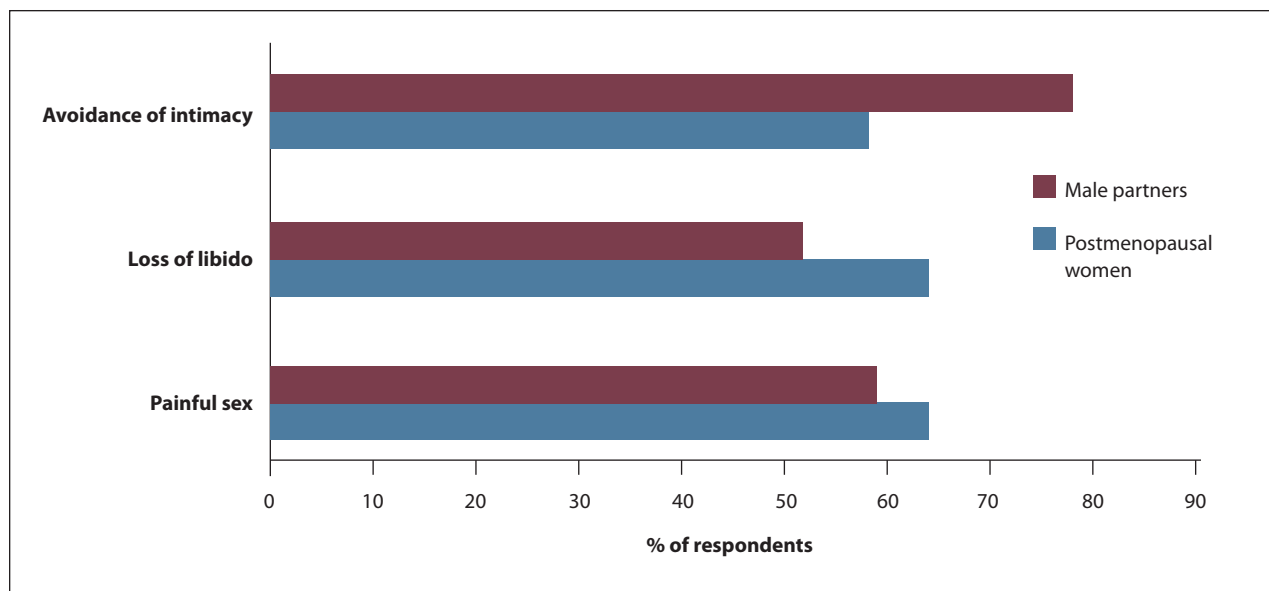
The **CL**arifying Vaginal Atrophy's Impact **ON** **S**Ex and **R**elationships (CLOSER) study examined the physical and emotional impact of vaginal discomfort and local hormone (estrogen) therapy on intimacy, relationships, and self-esteem (**TABLE 1**). The study involved 1000 married or cohabiting postmenopausal women, aged 55-65 years, with vaginal discomfort, and 1000 male partners of

postmenopausal women, aged 55-65 years, with vaginal discomfort, in North America (United States and Canada).<sup>11,16</sup> Survey results demonstrated that vaginal atrophy negatively affected the intimate relationships of postmenopausal women and their male partners. Specifically, among women in the study, 64% reported painful sex, 64% reported a loss of libido, and 58% reported that vaginal discomfort led them to avoid intimacy. At the same time, 78% of male partners said vaginal discomfort caused their partner to avoid intimacy, 52% reported it caused loss of libido in their partner, and 59% believed it caused pain with sex (**FIGURE 4**).<sup>11</sup> Of particular note, 30% of both women and men cited vaginal discomfort as the reason they stopped having sex. The women were more likely to use lubricating gels and creams (77%) and less likely to use hormone therapy—including

vaginal estrogen therapy (9%)—to treat their vaginal discomfort. However, those women who used vaginal estrogen therapy reported less painful sex (56%), more satisfying sex (41%) and an improved sex life (29%). Consequently, these women reported greater optimism about the future of their sex life (34%) and felt more connected to their male partner (31%).<sup>11</sup>

Findings from the Survey of Midlife Development in the United States (MIDUS II), 2004-2006, indicate that, while the percentage of women who are sexually active decreases with age, the best predictor of being sexually active was romantic partner status (**TABLE 1**).<sup>12</sup> This cross-sectional analysis used data from telephone interviews and self-administered questionnaires from women who participated in the original Survey of Midlife Development in the United States (MIDUS), 1995-1996, random-digit dialing sample of more than 7100 adults. Notably, in this survey of 2116 women aged 28-84 years, 63% (n=1345) were sexually active in the previous 6 months. Women who had a partner (married or cohabitating) had approximately 8-times-higher odds of being sexually active compared with those without a partner. Fifty-nine percent of women aged 60 years or older who were either married or cohabitating were sexually active. Among this subgroup of women, higher relationship satisfaction, better communication, and higher importance of sex were all significantly related to higher sexual satisfaction.<sup>12</sup>

Most recently, the online Women's EMPOWER survey evaluated the experience and perceptions of nearly 1900

**FIGURE 4** Impact of symptomatic vulvovaginal atrophy on sexual function: CLOSER survey

postmenopausal women regarding VVA and its symptomatic treatment options (TABLE 1).<sup>17</sup> Results from the EMPOWER survey were generally consistent with results of the above-mentioned surveys. Specifically, 77% of respondents had vaginal itching or irritation; other reported symptoms included vaginal soreness, burning, and pain upon touch. This survey also noted that postmenopausal women generally fail to recognize the signs and symptoms of VVA and are reluctant to discuss such symptoms with their HCPs.<sup>17</sup> Thirteen percent of women in the EMPOWER survey reported a desire to have more sexual activity, but refrained owing to dyspareunia, dryness, or itching. Approximately 30% were satisfied with their current level of sexual activity, but would like it to be more enjoyable or frequent by decreasing/eliminating VVA symptoms. Last, the EMPOWER survey reported that HCPs most often recommended vaginal moisturizers/lubricants for treatment (50%) versus prescription hormone-based (estrogen) therapy (approximately 25%). Only approximately 7% of women selected hormone therapy in the EMPOWER cohort; however, hormone therapy was discontinued owing to concerns about safety/risks (31%) or side effects (17%), and nearly 50% of women currently using hormonal therapy reported concerns regarding a perceived risk of systemic absorption.

#### BARRIERS TO DIAGNOSIS AND MANAGEMENT

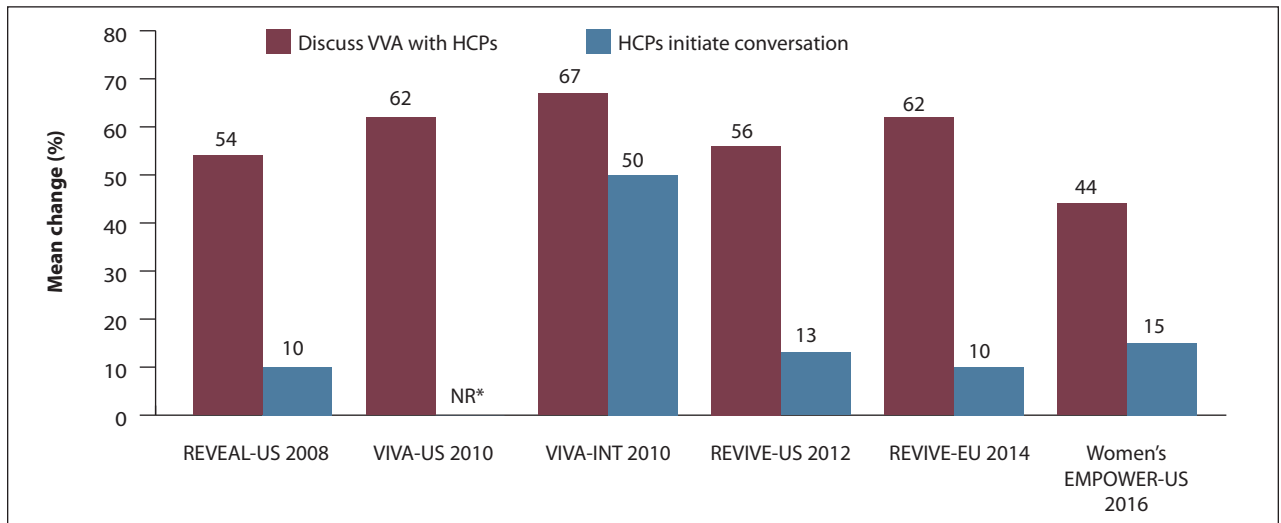
Despite the apparent frequency of postmenopausal vulvovaginal symptoms and their overall negative consequences, VVA and dyspareunia remain underdiag-

nosed and undertreated in the United States. One reason highlighted in the above-mentioned surveys is the lack of patient awareness regarding the underlying cause of their symptoms. Notably, key findings from the REVIVE study demonstrated that most women were unfamiliar with the terms “VVA” and “vulvar and vaginal atrophy”; further, only 25% of respondents knew that menopause or hormonal changes were the cause of their vaginal symptoms.<sup>1</sup> In fact, approximately 50% of the respondents believed the symptoms were a natural, likely unavoidable consequence of aging.<sup>1</sup>

Another significant barrier is the lack of meaningful dialogue between patient and HCP regarding postmenopausal vulvovaginal symptoms and their (sexual) consequences (FIGURE 5). In the REVIVE survey, nearly 50% of women reported never having discussed their VVA symptoms with their HCP; conversely, 40% of women expected that their HCP would initiate the discussion.<sup>1</sup> However, women reported only 19% of HCPs addressed their sexual life, and only 13% of women went to their HCP specifically to discuss VVA symptoms.<sup>1</sup> Among those women who initiated a discussion with their HCP about VVA symptoms, nearly 75% waited until a scheduled exam—and about 50% reported waiting 7 months or more. The most common symptoms of VVA prompting an HCP visit were vaginal irritation (50%), dyspareunia (27%), and vaginal dryness (24%).<sup>1</sup> Similarly, only 44% of women in the EMPOWER survey discussed their VVA symptoms with their HCP; but HCPs initiated a conversation only 15% of the time.<sup>2</sup> The most common rea-



**FIGURE 5** HCPs are reluctant to initiate dialogue with their patients regarding symptoms of vaginal atrophy<sup>2</sup>



Data for individual studies can be found in Krychman.<sup>2</sup>

\*NR, not reported

Abbreviations: EMPOWER, Women's EMPOWER survey; HCPs, health care providers; REVEAL, REvealing Vaginal Effects At Mid-Life; REVIVE, REal Women's Views of Treatment Options for Menopausal Vaginal ChangEs; US, United States; VIVA, Vaginal Health: Insight, Views, & Attitudes; VVA, vulvovaginal atrophy.

sons women did not consult an HCP about their vaginal health were that they considered their symptoms as part of aging (42%), they were uncomfortable discussing the topic (18%), or they were not aware there were available treatments (13%).<sup>2</sup>

Nevertheless, women have expressed a strong desire for accurate medical information about dyspareunia and VVA from their HCPs. In addition, they would like their HCPs to take a proactive role in initiating discussions surrounding the symptoms of VVA. The surveys consistently demonstrate that, regardless of who initiated the conversation, the majority of discussions regarding VVA symptoms occur during the annual exam.

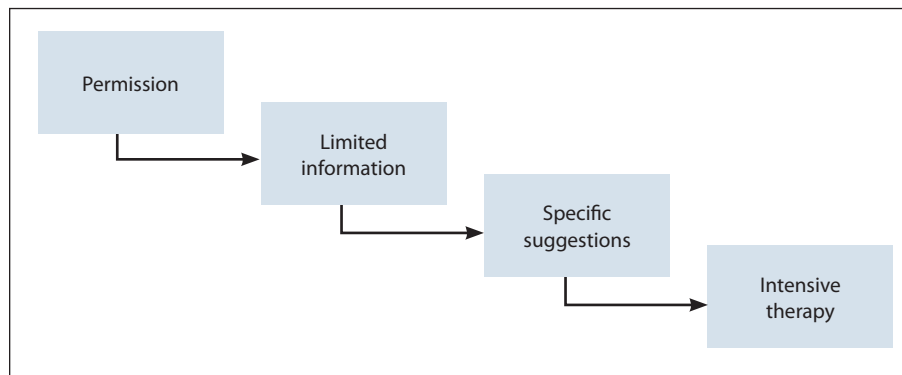
Clinicians often lack training and comfort in discussing sexuality-related topics with patients. Notably, the minimal time traditionally devoted to sexual health education in medical school or PA programs has been diminishing, and predominantly focuses on prevention of unwanted pregnancy and sexually transmitted infections.<sup>18-20</sup> A recent literature review noted that medical education on sexual function/dysfunction and female sexuality is generally "scant or absent."<sup>20</sup> Time limitations, beliefs, and attitudes (of both patient and HCP) also interfere with open and effective dialogue. However, it is important for clinicians to have discussions surrounding the sexual symptoms of VVA to ensure that their patients receive appropriate therapy that will

reduce their symptoms and enhance their sexual/social well-being.

The annual gynecologic exam visit presents an optimal opportunity to initiate a discussion surrounding sexual and vaginal health. Regardless of whether a patient complains of dyspareunia or other VVA symptoms, a clinician can note the presence of specific signs indicative of VVA and inquire about vaginal/urinary/sexual symptoms. This can be followed by a statement such as "I notice that you have some changes in your vaginal tissue that I've seen in many other postmenopausal women. These changes may cause symptoms such as dryness, itching, or pain with intercourse. Have you experienced any such symptoms? If so, I can recommend therapies to help diminish them." Another approach is to "normalize" the symptoms of VVA so that the patient does not feel that she is the only one experiencing them.<sup>21</sup> For example, a clinician can note that "Many women have vaginal changes after menopause, so I ask all of my patients about vaginal and sexual health." This demonstrates that VVA symptoms are common and experienced by many postmenopausal women.

Ideally, clinicians should proactively raise the issue of dyspareunia and VVA symptoms with all perimenopausal and postmenopausal patients.<sup>22</sup> It is beneficial to inform these patients that VVA is a common medical condition in postmenopausal women as a result of reduced levels

**FIGURE 6** PLISSIT: *Permission, Limited Information, Specific Suggestions, Intensive Therapy*<sup>23</sup>



of estrogen and other hormones. Furthermore, patients need to be educated that, unlike vasomotor symptoms such as hot flashes, VVA symptoms worsen over time if not treated. Clinicians can review the physical changes occurring in the vaginal tissue owing to diminishing hormone levels that lead to VVA symptoms such as vaginal dryness and pain with intercourse. In addition, clinicians then have the optimal opportunity to discuss the various treatment options to manage symptoms of VVA—including OTC and prescription therapies.

It is important that clinicians emphasize that, while OTC products might provide immediate symptomatic relief, only prescription medications are able to treat the underlying pathologic cause of the symptoms. OTC products may suffice as an initial course of therapy; a proactive strategy would be to provide a prescription for a hormonal agent should the OTC product prove ineffective.

It is also important to use counseling strategies that engage the patient when initiating and discussing conversations with postmenopausal women regarding sexuality and vaginal health. Specifically, clinicians should use simple, direct language that is appropriate to the age, ethnicity, and culture of the woman and refrain from using overly medical terminology. Women should be encouraged to ask questions; if they are uncomfortable verbalizing questions, they can be given paper to write them down. Clinicians need to maintain eye contact with the patient throughout these conversations, and demonstrate an open, concerned, and non-embarrassed body posture. If necessary, clinicians can practice using sexual terminology to minimize appearing nervous or uncomfortable. General comments can lead to open-ended questions to elicit more information about possible sexual or vaginal health concerns.

The PLISSIT model offers a simple strategy that clinicians can use to initiate sexual health discussions with patients (FIGURE 6).<sup>23</sup> Developed more than 40 years ago, this model involves 4 levels of interaction and information, beginning with Permission; moving on to provide Limited Information and then Specific Suggestions; and, for some patients, referrals for Intensive Therapy.

- During the initial level, the clinician gives the patient *permission* to acknowledge their sexuality, and to talk about sexual issues or concerns. For example, postmenopausal women may be uncomfortable admitting that they are (still) sexually active, or that they have pain with intercourse. Clinicians need to indicate that it is acceptable for their patients to talk with them about their sexual and vaginal health in an objective, non-judgmental dialogue. This can also normalize their concerns, and demonstrates empathy and understanding.
- Many women lack general knowledge about their genital anatomy and, as demonstrated in the various surveys discussed earlier, that many vulvovaginal and sexual symptoms are associated with hormonal changes and aging. In addition, they may not be aware that many of these symptoms are amenable to treatment. Clinicians can provide *limited information* about the aging process, how it affects vulvovaginal and sexual health, and that there are available treatments to address their distressing symptoms. Limited information may be as simple as providing a mirror to demonstrate how their bodies have changed with menopause. Limited information can be provided through dialogue, handouts, or even suggestions for outside reading. For example, clinicians can note that “Many postmenopausal women develop vaginal symptoms that can cause pain with sex – have you noticed any such symptoms?”
- *Specific suggestions* can entail recommendations for lubricants, other OTC products, or prescription medications.
- Patients who do not respond to limited information and specific suggestions, and patients who have additional underlying issues, may require a referral to a specialist for *intensive therapy*, which may encompass psychological and/or sexual therapy.

## CONCLUSIONS

NAMS recommends that “proactive education on vaginal health is recommended for postmenopausal women.”<sup>24</sup> Survey data consistently demonstrate that women prefer that clinicians initiate these discussions. Annual health visits afford an optimal opportunity to educate women about vulvovaginal changes associated with menopause, including potential sexuality consequences and available treatments.

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# Advances in Diagnosing Dyspareunia

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### INTRODUCTION

Three major factors adversely affect postmenopausal female sexuality: anatomic and physiologic changes associated with aging, ovarian and adrenal hormonal insufficiency, and partnership issues.<sup>1,2</sup> In postmenopausal women, the lack of estrogen stimulation in vaginal and vulvar tissue commonly results in involution of these tissues—commonly referred to as vulvovaginal atrophy (VVA). In the United States, it is estimated that there are 64 million postmenopausal women and that as many as 32 million women have been found to suffer VVA symptoms.<sup>3,4</sup> The symptoms may also occur in premenopausal women if they exhibit significant hypoeestrogenemia (eg, postpartum breastfeeding women). Symptoms of VVA include, but are not limited to, vaginal dryness, irritation, burning, dysuria, dyspareunia, and vaginal discharge.<sup>5</sup> Whereas vasomotor symptoms (VMS) associated with menopause diminish over time, VVA is a chronic condition that worsens in the absence of treatment.<sup>6</sup> VVA symptoms can adversely affect a woman's sexual functioning, partnership issues, and her overall quality of life.<sup>7,8,9</sup>

VVA is a component of what is now better referred to as the “genitourinary syndrome of menopause” (GSM): a constellation of signs and symptoms that are the result of hormonal (estrogen and androgen) insufficiency in the urogenital tissues.<sup>10</sup> The term GSM arose from a perceived need by the International Society for the Study of Women's Sexual Health and The North American Menopause Society to find a medically accurate and all-encompassing term to replace the pejorative “vulvovaginal atrophy.”<sup>10</sup> GSM is a more accurate nosology because it refers to the entire genitourinary system and incorporates changes to the labia major/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder. Signs include decreased vaginal moisture and diminished elasticity, labial resorption, pallor/erythema, loss of rugae, pete-

chia, fragility, urethral atrophy, and introital involution. GSM often includes genital symptoms of vaginal dryness, burning, and irritation; adverse effects on sexual function (lack of lubrication, dyspareunia, decreased libido); and urinary symptoms of urgency, dysuria, and recurrent urinary tract infection (UTI).

Dyspareunia, another prevalent component of GSM, has recently been (re)characterized by the American College of Obstetricians and Gynecologists as “a pain disorder that interferes with sexuality rather than as a sexual disorder characterized by pain.”<sup>11</sup> In fact, a recent study of 500 postmenopausal women with vaginal discomfort identified “vaginal dryness” (85%) and “dyspareunia” (52%) as the most commonly reported complaints.<sup>12</sup> Over time, the vast majority of postmenopausal women will develop VVA.<sup>13</sup> For the syndrome to be classified as a *sexual dysfunction*, the symptoms must be *bothersome* to the patient and not better accounted for by another diagnosis, such as cancer, or other major medical or psychiatric disorder.<sup>10,14</sup>

Despite its frequency, GSM and the accompanying sexual dysfunction often go unrecognized, undiagnosed, and therefore untreated. This may stem from embarrassment (on the part of the patient as well as the healthcare provider [HCP]), a misperception that the symptoms are a natural consequence of aging, and/or the erroneous belief that there is no specific therapy for the condition.<sup>15</sup>

Data from the **CL**arifying Vaginal Atrophy's Impact **On** **SE**x and **R**elationships (CLOSER) study revealed that 28% of women did not tell their partner when they first experienced vaginal discomfort because they either associated it with growing older (52%) or were embarrassed (21%).<sup>16</sup> Dr. Sheryl A. Kingsberg (page S2) highlights the lack of communication between patient and HCP as well as the apparent disconnect between GSM symptoms and hormonal changes of menopause.

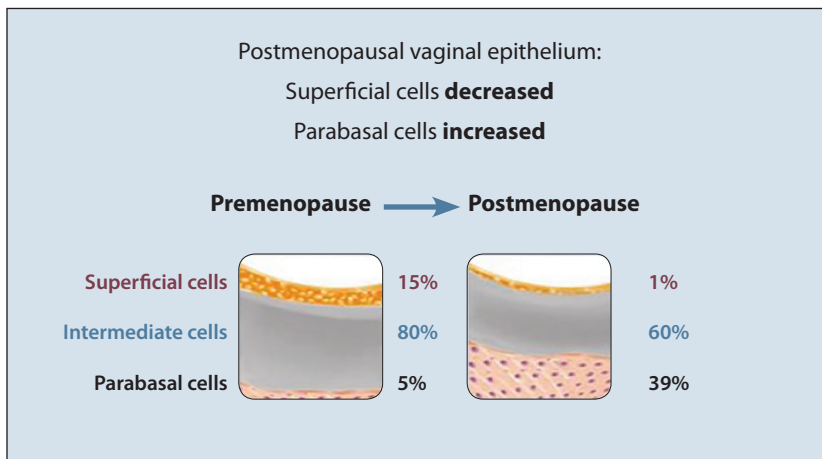
### PATHOPHYSIOLOGY OF THE AGING GENITOURINARY TRACT

Estrogen is a prerequisite for the normal physiology and ecosystem present in the vagina.<sup>1,5</sup> The lower or distal

#### Disclosure:

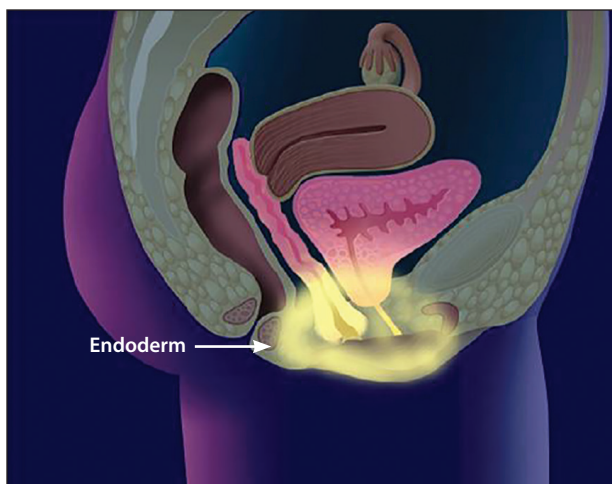
Consulting Fees: AMAG Pharmaceuticals; Commercial Interest Speakers Bureau: Valeant Pharmaceuticals; Contracted Research: Procter and Gamble

**FIGURE 1** Vaginal Maturation Index<sup>1</sup>



urogenital tract is derived from the embryonic urogenital sinus and is endoderm in its origin. In contrast, the upper portions of the vagina and bladder are mesodermal in origin. The vaginal vestibule is also a homologue of the urogenital sinus, whereas the labia majora is of ectodermal origin.<sup>5</sup> The vagina is composed of 3 layers: a superficial stratified squamous epithelium, a middle muscular layer, and an outer fibrous layer. Estrogens, progesterone, and androgens all influence maturation of the 3 types of vaginal epithelial cells: parabasal, intermediate, and superficial (FIGURE 1). The percentage of each “type” of cell is summarized in the Vaginal Maturation Index (VMI). In the presence of adequate estrogenic stimulation, there are approximately 15% or more superficial cells and less than 5% parabasal cells. Conversely, in estrogen-deficient states, there are typically less than 5% superficial cells,

**FIGURE 2** Estrogen-receptor concentration in select adult genital tissues<sup>1</sup>



and there are more than 30% parabasal cells. The VMI simply represents the relative percentage of superficial, intermediate, and parabasal epithelial cells on a vaginal smear taken from the lateral vaginal wall. As will be discussed, the VMI, as well as vaginal pH, is considered a good proxy for adequate levels of circulating estradiol.

In the presence of adequate endogenous estrogen (principally estradiol), the vaginal wall is a thickly stratified squamous epithelium with a rugated surface that is rather elastic. The rich vasculature of the underlying dermis contributes to the epithelium’s moisture and lubrication. The menopausal transition is characterized by diminishing levels of endogenous estrogen; an estradiol level <30 pg/mL can impact the entire lower urogenital tract rather rapidly.

Reduced estrogen levels result in distinct atrophic changes in the vulvovaginal tissues: thinning of vaginal epithelium, vaginal dryness, pruritus, loss of rugae, and loss of considerable vaginal elasticity, as well as thinning of the vaginal wall and, ultimately, shortening of the vaginal vault.<sup>17</sup> The vaginal epithelium becomes friable and is susceptible to injury, resulting in petechiae and occasional bleeding with minimal trauma. Once serum estradiol levels are <20 pg/mL, patients often begin to experience vulvovaginal symptoms such as dryness, irritation and dyspareunia.<sup>6,18</sup> Administration of exogenous hormone can stimulate estrogen receptors and usually alleviates symptoms.

Estrogen receptors have been found throughout the body. The highest concentration of these receptors in the female body is found in the homologues of the urogenital sinus shown in yellow in FIGURE 2.<sup>1,15</sup> Consequently, hormonal insufficiency is also associated with urinary dysfunction: thinning of urethral mucosa, atrophy of the bladder trigone, loss of muscle tone and connective tissue in the urogenital diaphragm, decreased intraurethral pressure, disordered collagen metabolism, and decreased activity of the  $\alpha$ -adrenergic system innervating the bladder neck and urethral sphincter.<sup>6</sup> Symptomatic manifestations include increased urinary frequency, nocturia, urge incontinence, dysuria, and recurrent urinary tract infection (UTI), thereby authenticating a *urogenital syndrome*—a constellation of signs and symptoms—rather than simply VVA.

As shown by the white arrow in FIGURE 2, the atro-

**TABLE 1** Vaginal Health Index<sup>22</sup>

	1	2	3	4	5
<b>Elasticity</b>	None	Poor	Fair	Good	Excellent
<b>Fluid volume</b> (pooling of secretions)	None	Scant amount, vault not entirely covered	Superficial amount, vault entirely covered	Moderate amount of dryness (small areas of dryness on cotton-tip applicator)	Normal amount (fully saturates on cotton-tip applicator)
<b>pH</b>	>6.1	5.6-6.0	5.1-5.5	4.7-5.0	<4.6
<b>Epithelial integrity</b>	Petechiae noted before contact	Bleeds with light contact	Bleeds with scraping	Not friable, thin epithelium	Normal
<b>Moisture</b> (coating)	None, surface inflamed	None, surface not inflamed	Minimal	Moderate	Normal

phy associated with diminished estrogen production is most pronounced initially in the areas with the highest density of estrogen receptors: the vaginal introitus and distal urethra. In contrast, the upper two-thirds of the vagina is spared significant atrophy initially. The vestibule loses much of its concavity and, as the introitus contracts, it begins to lose its elasticity.<sup>1</sup> The involution at the level of the vestibule and hymenal carunculae leads to introital stenosis, which is often associated with dyspareunia. The contraction of the distal vagina at the area of the hymen and transverse perineal membrane can lead to subsequent “reflex” vaginismus, but the pain associated with introital stenosis is at the perineum and hymenal “ring” rather than higher in the vagina at the area of the insertion of the levator muscles.

Hormonal changes also affect the vaginal microbiome across the life cycle. During the reproductive years, lactobacilli metabolize the abundant vaginal glycogen, producing lactic acid and hydrogen peroxide. This leads to the normal acidic pH in the vagina (range, 3.5-4.5) and helps maintain the normal ecosystem of the lower urogenital tract.<sup>1</sup> The acidic pH, along with a healthy stratified squamous epithelium, affords protection against various vaginal pathogens.<sup>5</sup> During the menopausal transition, pH levels usually begin to rise and become more alkaline. Continued declining levels of estrogen are associated with a diminution in vaginal lactobacilli, and vaginal pH rises >5.0 within 12 months of becoming truly hypoestrogenic (defined as serum estradiol <20 pg/mL).<sup>1,18,19</sup> Higher pH levels can also be associated with the overgrowth of pathogens that predispose postmenopausal women to irritation and infection in both the vagina and the bladder.<sup>6,20</sup>

### VULVOVAGINAL ATROPHY AS A CAUSE OF DYSpareunia

The diagnosis of dyspareunia associated with postmenopausal VVA is based on patient-reported symptoms of pain with sex and physical findings of VVA.<sup>6,21</sup> Patients may report vaginal dryness, itching, and burning; pain with sex; bleeding with intercourse or wiping; and/or urinary complaints of frequency, urgency, dysuria, or frequent UTI. It is easy to understand why many women report reduced sexual activity owing to these symptoms.

A careful physical examination should assess the appearance of the epithelium, skin color and elasticity, rugae, moisture, labial fat content, and the morphology of the vaginal introitus.<sup>1,22</sup> In patients with VVA, the vulvovaginal epithelium may appear erythematous initially and then appear pale, dry, and inelastic. (These physiologic changes are illustrated in the section “Diagnostic Considerations.”) Because atrophy typically occurs insidiously, sometimes over years, the contraction of the introitus and changes in the urethra often go unnoticed at the time of the patient’s annual visit.<sup>1</sup>

### DIAGNOSTIC TOOLS

Over the years, a few indices have been developed to aid in the diagnosis of VVA. Most include both quantitative and qualitative assessments of variables associated with the pathophysiologic changes in the genitourinary tract after menopause. The Vaginal Health Index was developed to evaluate vaginal elasticity, fluid secretion, epithelial integrity, pH, and vaginal moisture (TABLE 1).<sup>22</sup> Another index, the VMI (discussed on page S10), indirectly assesses the level of estrogen based on the number of mature and parabasal epithelial cells on a vaginal smear.<sup>23</sup> Other research—for example, that of Minkin and

**TABLE 2** Vaginal pH and atrophy<sup>18</sup>

Therapy	Atrophy	No atrophy
Estrogen therapy (n=992)	14.1%	85.9% (862 of 992)
No estrogen therapy (n=508)	69.5% (353 of 508)	30.1%
No estrogen therapy + pH >5 (n=434)	85.1% (434 of 508)	-

colleagues<sup>21</sup>—focused on general, external, and internal physical signs of VVA.<sup>21,22</sup>

In a recent study of 1500 healthy, asymptomatic postmenopausal women who were seen for their annual well-woman visit, the effect of exogenous estrogen therapy in the prevention of atrophy was evaluated by a single investigator.<sup>18</sup> Vaginal pH and the degree of atrophy (mild, moderate, or severe) were recorded in women treated with various forms of estrogen (oral, transdermal, and injectable) versus untreated patients.<sup>18</sup> Eighty-six percent of the 992 patients (862 of 992) receiving estrogen therapy had no physical signs of atrophy, whereas 70% of the women not receiving estrogen therapy (353/508) had

demonstrable, visible changes of urogenital atrophy (TABLE 2). Notably, among women in the “no-therapy” arm in whom the vaginal pH was >5, 85% exhibited at least “mild” atrophy. Fifteen percent of the untreated women presented with a normal

pH and did not show signs of atrophy. Contraction and loss of elasticity at the introitus and “typical” urethral changes were consistent and prominent features of atrophy, whereas changes inside the vagina (erythema/petechiae, loss of elasticity, vaginal shrinkage, secretions, discharge, etc.) were more variable and usually only seen among women with “moderate”-to-“severe” atrophy.

Findings from this study led to the development of the Vaginal Health Score (VHS) (TABLE 3), which is based on objective, quantifiable variables (vaginal pH and changes in the epithelium at the introitus, the urethra, and morphology of the fourchette/vestibule) rather than on variable subjective findings (moisture, secretions, and tissue friability) found *in* the vagina *per se*. In a more recent study, 20 postmenopausal patients (52-62 years of age) were evaluated for visual signs of atrophy, had vaginal pH measured, and had serum estradiol levels assayed by mass spectrometry [Freedman MA, unpublished data (2018)]. All 10 patients with a serum estradiol <10 pg/mL had a pH >5.5 and severe atrophy, whereas 5 patients in whom serum estradiol values were >10 pg/mL but <20 pg/mL had moderate-to-severe atrophy. None of the 5 whose serum estradiol was >20 pg/mL had significant atrophy on exam, but they were clearly postmenopausal. pH was also very predictive of the degree of atrophy in the previous study of the 1500 patients done by the author [Freedman MA, unpublished data (2018)], but estradiol values, when available, were obtained by radioimmunoassay, not mass spectrometry.<sup>18</sup> The correlation between serum estradiol, pH, and degree of atrophy has been quite consistent when all 3 parameters have been available.

**TABLE 3** Vaginal Health Score\*

Atrophic change	Minimal	Moderate	Severe
<b>pH</b>	<5 -/+	5-5.5 2	>5.5 4
<b>Introital morphology</b>		1	2
Fourchette <sup>†</sup>	-	+	+
Labia	-	+	+
Involution	-	+	+
<b>Urethra</b>		1	2
Meatus	-	+	++
Tunneling/tubular	-	+	++
Externalized	-	+	++
<b>Epithelium</b>		1	2
Rugation	-	+	++
Color/moisture	-	+	++
Elasticity	-	+	++

\*Freedman, unpublished data (2012).

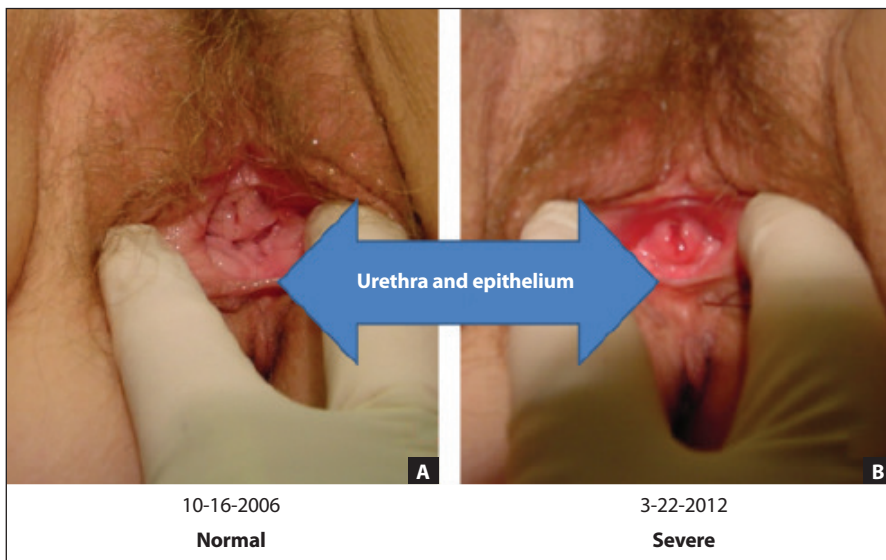
<sup>†</sup>Contour/contraction.

The introital morphology, urethra, and epithelium are each given a score of 1 or 2, depending on whether it reveals “moderate” or “severe” change, respectively. In order for a category to receive a 1 or 2 score, however, 2 of the 3 changes under that category must be affected. Because of its importance and objectivity, pH is weighted more heavily. The numerical scoring system allows for quantitative assessment of the progression (or regression with therapy) of urogenital atrophy. With “severe” atrophy, scores are usually ≥8, whereas “moderate” atrophy scores are usually ≤6.

## DIAGNOSTIC CONSIDERATIONS

It is sometimes challenging to make an accurate diagnosis of GSM in the perimenopause and early menopausal years, particularly among women with mild symptoms. Because most women affected do not report symptoms spontaneously, including those experiencing dyspareunia, HCPs need to initiate the conversation if they observe atrophic change. Establishing the relationship of the onset of symptoms to menopause is often help-

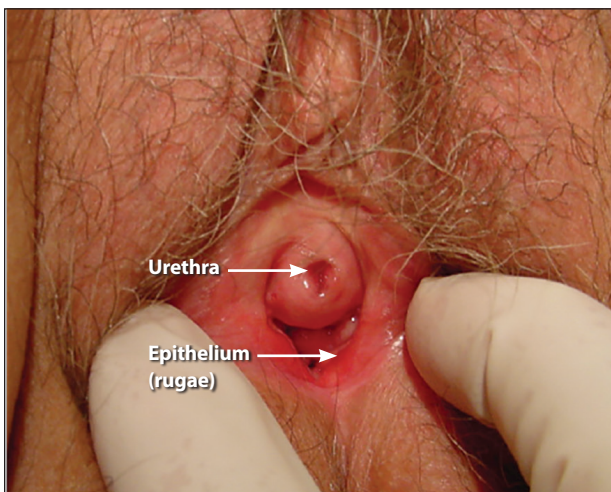
**FIGURE 3** Morphological and color changes



ful in discussing therapy. Patients need to be made aware of the many safe and effective therapies that are available today. It also behooves clinicians to determine the impact that the symptoms have on the patient’s sexual functioning and quality of life.<sup>5,14</sup> It should also be noted that the severity of symptoms does not always correlate with the degree of physical findings.

The most constant feature in the VHS is the correlation between vaginal pH and presence of atrophy. When the pH is >5.5, there is almost always evidence of significant atrophy; therefore, it has greater “weight” than other parameters. The 3 parameters measured in the VHS include the epithelium at the introitus, the urethra,

**FIGURE 4** Morphology, urethral changes, and epithelial changes



and the morphology of the fourchette/vestibule. The epithelium at the hymenal carunculae is particularly noteworthy (FIGURE 3), as is its color and elasticity. The urethral meatus becomes patulous and is relatively exteriorized (secondary to contraction of the surrounding tissues) and thus causes a “tunneling” or “tubular” appearance (FIGURE 4). The stratified squamous epithelium at the meatus is atrophied and exposes the transitional (columnar) epithelium of the urethra. The concavity of the fourchette/vestibule is diminished, the labia undergo involution, and the introitus contracts and

becomes circular rather than oval (FIGURE 5).

**Cases Illustrating the Effects of Hypoestrogenemia and Estrogen Therapy on Vulvovaginal Atrophy**

**Case 1 and Case 2**

Both women were 64 years of age, G2P2002 (FIGURE 6). The woman on the left (A) has been on hormone therapy for years; the woman on the right (B) stopped therapy 4 years previously. The woman on the right (B) has loss of the concavity of the vestibule, and the introitus has become circular in its contraction. The epithelium (B) shows loss of elasticity at the fourchette, whereas the epithelium (A) at the hymenal carunculae is normal and maintains its elasticity.

**Case 3**

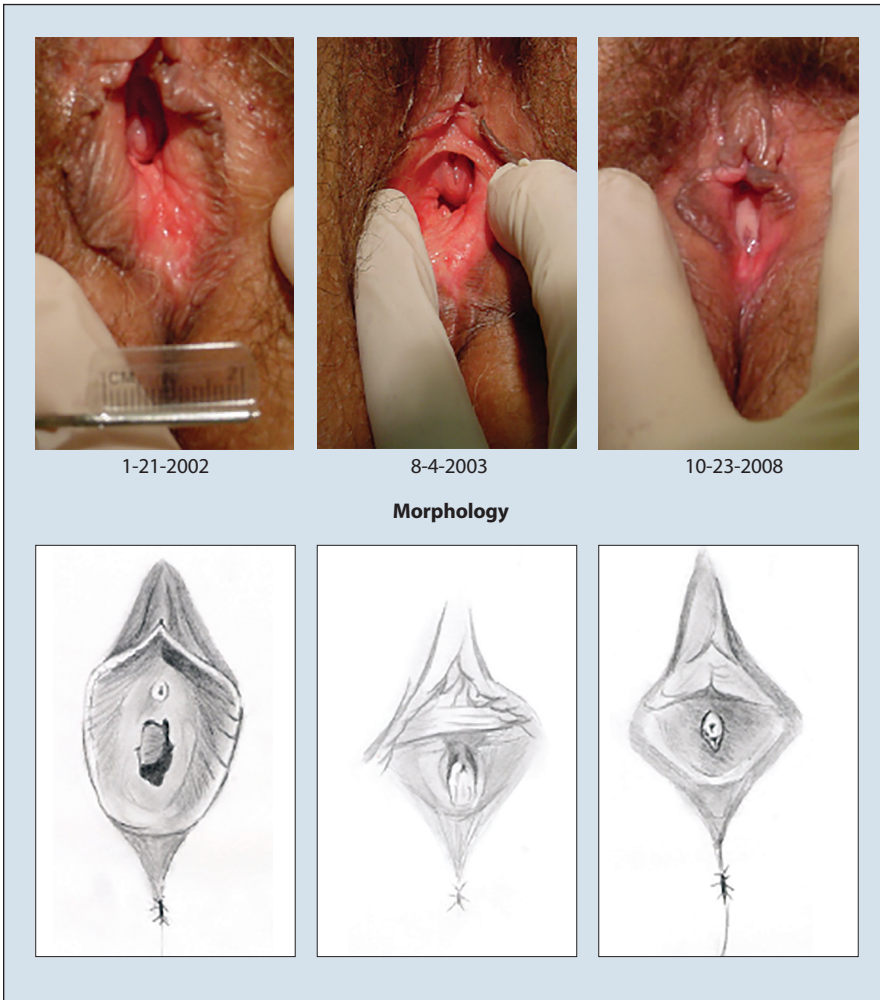
This nulliparous woman was “normal”; her pH was 4.5 in (A). In (B), she demonstrates severe atrophy; pH was 5.5. The changes in the epithelium, urethra, and fourchette are “severe” after 5 years (FIGURE 3).

**Case 4(a)**

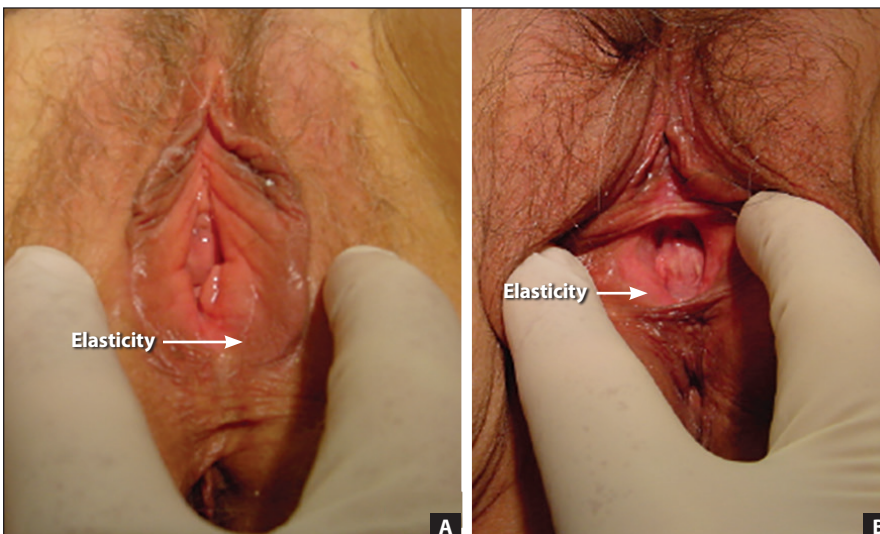
This woman stopped hormone therapy approximately 6 months before this visit (A) (FIGURE 7). She reinstated topical estrogen therapy and returned in 3 months (B). In (A), the change in the atrophic epithelium is particularly apparent in the hymenal carunculae, color, and elasticity; the urethra is obvious because of the everted meatus, revealing transitional epithelium (rather than squamous



**FIGURE 5** Progression of atrophy<sup>1</sup>



**FIGURE 6** Case 1 and Case 2



epithelium), “tunneling,” and exteriorization; and morphology is represented by contraction and loss of considerable concavity, labial resorption and circular dimension.

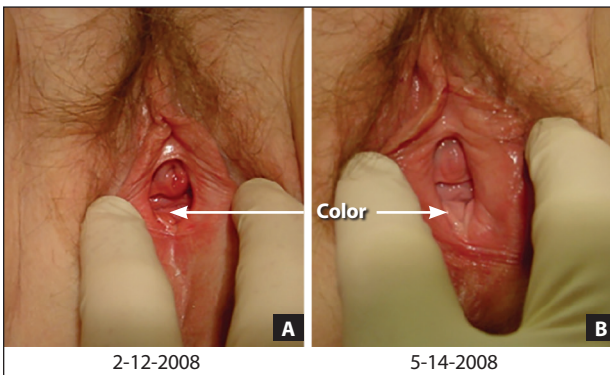
**Case 4(b)**

This is the same woman in Case 4(a) (FIGURE 8). She stopped, then restarted, topical hormone therapy several times over the next few years. The changes in the epithelium, urethra, and morphology were “moderate” in February 2008 and are “severe” in July 2009. This demonstrates the rapidity of atrophy as well as its responsiveness to therapy in truly hypoestrogenemic women. FIGURE 9 shows the changes once again when she discontinued her topical therapy again in 2010.

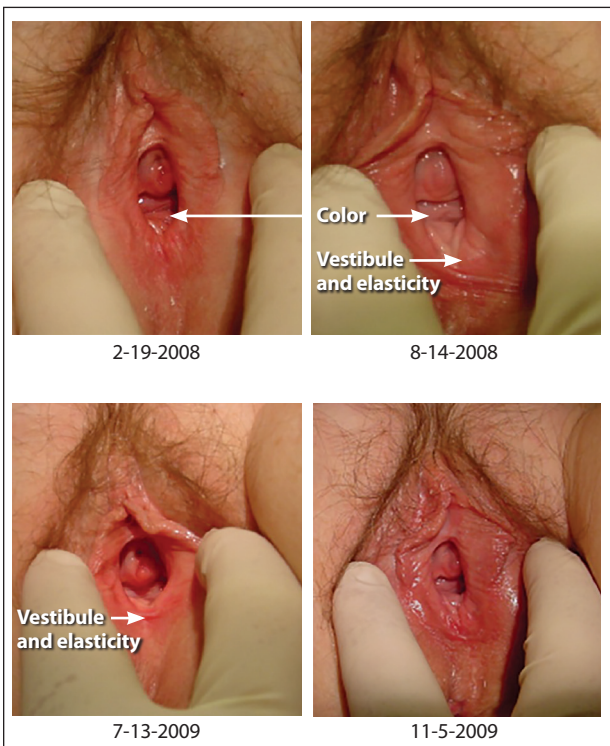
An accurate diagnosis requires elimination of other possible vulvovaginal conditions with similar symptoms.<sup>5</sup> The following conditions should be considered in a differential diagnosis of dyspareunia associated with VVA: candidiasis, bacterial vaginosis, desquamative inflammatory vaginitis, contact dermatitis (irritant or allergic), lichen sclerosis, lichen planus, lichen simplex chronicus, and vulvar neoplasia, as well as other benign and malignant tumors, psychological causes, trauma/foreign body, and vulvodinia.<sup>11,24</sup>

Symptomatic VVA often ensues once the serum estradiol is <20 pg/mL, and is often seen after bilateral ovariectomy, pelvic radiation therapy, chemotherapy, gonadotropin-releasing hormone therapy and premature menopause. Because of the abrupt drop in estrogen and androgen levels

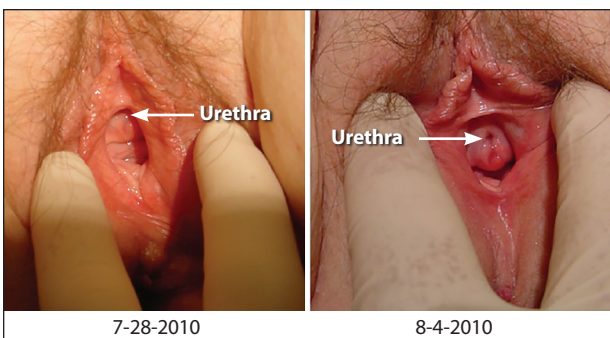
**FIGURE 7 Case 4a**



**FIGURE 8 Case 4b**



**FIGURE 9 Case 4b (continued)**



after bilateral salpingo-oophorectomy, patients may experience significantly greater severity of psychological, vasomotor, and somatic menopausal symptoms, including significantly more sexual dysfunction, compared to women undergoing natural menopause.<sup>5,25</sup>

In the study of 1500 patients referenced above [Freedman MA, unpublished data (2018)], a number of factors were found that can mitigate the degree of postmenopausal atrophy women experience.<sup>18</sup> In addition to the concentration of estrogen *in* the urogenital tissues, there are many factors that impact the degree of atrophy women experience. Some women with diabetes or cardiovascular disease, or who smoke, develop “vasculogenic insufficiency” in the pelvis and may develop GSM despite normal circulating levels of estradiol. A very significant factor in mitigating against atrophy is sexual activity, especially penetrative sex.<sup>26</sup> Obesity (peripheral conversion of androgen to estrogen in adipose tissue) may mollify risk and, similar to osteoporosis, genital atrophy is typically less severe and less prevalent in African-American women as well as women with intact ovaries. Vaginal births also afford some protection, in that the diameter of the introitus is less compromised as compared to nulliparous women.

**CONCLUSION**

Symptoms and consequences of vulvovaginal atrophy associated with menopause, including dyspareunia, are common and frequently necessitate treatment.<sup>27</sup> By observing the changes in the epithelium, urethra, and the morphology of the fourchette/vestibule, urogenital atrophy is easily identifiable. Distinct physical changes combined with vaginal pH measurement provide identification and quantification of VVA. Appropriate treatment requires accurate diagnosis, which, in turn, necessitates open and objective dialogue with all perimenopausal and postmenopausal patients, irrespective of symptoms.

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# Innovations in the Treatment of Dyspareunia

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### INTRODUCTION

The aging of the US population has led to a substantial increase in the number of postmenopausal women. Currently, there are an estimated 64 million women in the United States who are postmenopausal, and that number is estimated to reach 1.1 billion women worldwide by 2025.<sup>1</sup> Diminishing hormonal levels associated with the menopausal transition began years earlier, and can result in vasomotor symptoms (VMS), vulvovaginal atrophy (VVA), urinary symptoms, and dyspareunia. At least two-thirds of menopausal women experience VMS, which are often considered the “cardinal symptoms of menopause.”<sup>2</sup> VMS, which include hot flashes and night sweats, can have a significant effect on quality of life, and lead many women to seek treatment for their symptoms.<sup>3</sup> VMS typically are self-limiting, last for 4 years, on average, before spontaneously resolving, and are readily associated with menopause by both women and their health care provider (HCP).<sup>3,4</sup> However, in a number of women, VMS can last 10 years or longer. In contrast, the symptoms of VVA, which result from thinning and inflammation of the vaginal walls, are chronic and progressive. VVA can cause vaginal dryness, itching, and soreness, and often leads to pain with sex and sexual dysfunction. Although at least 32 million women experience symptoms of VVA and/or dyspareunia, because these symptoms often do not manifest in and around the time of the last menses, a majority of these women are unaware that their symptoms are the result of underlying vulvovaginal and hormonal changes stemming from menopause.<sup>1,5</sup> The overwhelming majority of US women—approximately 93%—fail to seek treatment for VVA or dyspareunia.<sup>1</sup>

### MANAGEMENT CONSIDERATIONS

As discussed in Dr. Sheryl A. Kingsberg's article on page S2, several surveys have examined the impact of VVA on women's sexual well-being, and on their relationships. These studies have consistently shown that effective management of VVA leads to reduced pain with sex, better overall sexual well-being, and better sexual/personal relationships.<sup>1,5-9</sup> Furthermore, as Dr. Murray A. Freedman notes in his article on page S10, HCPs have many opportunities to educate women about VVA and dyspareunia, and to initiate the discussion upon identifying overt signs of vaginal atrophy. Consequently, HCPs have the opportunity and responsibility to also educate women about the numerous treatment options for these common, yet often overlooked, conditions.

Health care providers must consider a variety of factors when helping patients select the most appropriate management approach to dyspareunia, including symptom severity, amount of distress associated with their symptoms, risk of medical complications (such as risk of estrogen-responsive neoplasia), and anticipated patient compliance with the various options. In addition, HCPs' experience with the therapy and patient preference can provide the foundation for patient satisfaction with the chosen therapy, facilitating enhanced patient adherence, leading to improved clinical outcomes.<sup>10-13</sup>

For milder symptoms, nonhormonal therapies, available over the counter (OTC), have limited effectiveness, yet are suitable for women who are not bothered enough by symptoms to seek pharmacotherapy or are at risk of estrogen-responsive neoplasia. For bothersome moderate-to-severe symptoms, several hormonal therapies have been shown to be effective, including systemic and topical estrogens. Two innovative therapies that do not contain estrogen have been approved for the management of moderate-to-severe dyspareunia owing to VVA: ospemifene (Osphena<sup>®</sup>, Shionogi Inc.), a selective estrogen receptor modulator (SERM), and intravaginal prasterone (dehydroepiandrosterone [DHEA] Intrarosa<sup>®</sup> Endoceutics Inc.). Because dyspareu-

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**TABLE 1** Examples of over-the-counter nonhormonal products

Product	Recommendation for Use	Mechanism of Action	Examples
Vaginal moisturizer	Chronic	Replaces secretions	K-Y Liquibeads, Fresh Start, K-Y Silk-E, Moist Again, Replens
Vaginal lubricant	Acute	Reduces friction	<i>Water-based:</i> Astroglide, FemGlide, Just Like Me, K-Y Jelly, Slippery Stuff, Summer's Eve
			<i>Silicone-based:</i> Pink, ID Millennium, Pjur, Pure Pleasure
			<i>Oil-based:</i> Mineral oil, Élégance Woman's Lubricant

nia is a chronic condition, long-term management is essential to prevent recurrence of symptoms.

### NONHORMONAL OTC THERAPIES

There are 2 categories of nonhormonal therapy for the management of dyspareunia: lubricants and moisturizers. Each category is available OTC but offers different benefits. In addition, neither of these topical options treats the underlying pathophysiology and tissue changes causing dyspareunia, and lubricants and moisturizers are therefore most beneficial for women with mild symptoms.<sup>14</sup> Ideally, to achieve significant effects, lubricants and moisturizers should be used as needed in conjunction with systemic or topical hormonal therapy.<sup>15</sup>

Lubricants are considered for short-term relief of vaginal dryness during sexual activity.<sup>16</sup> These agents, which act by reducing friction, have a short duration of action and must be applied prior to or during each sexual encounter. Conversely, vaginal moisturizers are considered for long-term relief of vaginal dryness.<sup>16</sup> They typically are recommended to be used several times a week, and provide continuous therapy; unlike lubricants, they are absorbed into the skin and cling to the vaginal lining in a way that mimics natural secretions.<sup>10,16</sup> Examples of commonly used lubricants and moisturizers are found in **TABLE 1**.

There is a dearth of published scientific research regarding the effects of moisturizers on vaginal physiology, including moisture, fluid volume, and elasticity. An early study compared the efficacy of an OTC nonhormonal vaginal moisturizer (Replens™; Church & Dwight Co., Inc.) versus estrogen vaginal cream, and found the OTC moisturizer was comparable to prescription estrogen cream in demonstrating statistically significant increases in vaginal moisture, fluid volume, and tissue elasticity.<sup>17</sup> However, the majority of recent scientific surveys conducted with patients have demonstrated the inadequacy of OTC treatments in addressing their bothersome symptoms.<sup>1,8</sup>

### HORMONAL THERAPIES

#### Estrogen Therapies

For many years, estrogen therapy was the standard treatment for VVA atrophy and its associated symptoms. Numerous studies have demonstrated the effects of exogenous estrogen on the pathophysiology of VVA, including rapidly restoring vaginal epithelium and associated vasculature, improving vaginal secretions, lowering vaginal pH to enhance the production of healthy vaginal flora, and alleviating overall vulvovaginal symptoms.<sup>18-21</sup> Consequently, women receiving estrogen therapy may experience increased lubrication and improved vaginal elasticity, which may alleviate subjective vaginal symptoms of dryness, irritation, pruritus, dyspareunia, and urinary urgency.<sup>19</sup> In addition, estrogen can improve the vaginal maturation index through a higher ratio of superficial cells to parabasal cells. However, there are potential local and systemic side effects of vaginal estrogen therapy, including breast pain/tenderness, headache, hair loss, mild nausea or vomiting, spotting or breakthrough bleeding, stomach cramps or bloating, increased vaginal discharge, and/or vaginal yeast infection.<sup>22</sup>

Estrogen therapy can be administered systemically (oral or patch) or topically (vaginal cream, tablet, or ring) to address VVA. Estrogen must be administered with progestin in women with a uterus to minimize the risk of uterine cancer. The lowest effective dosage of systemic estrogen therapy should be prescribed in light of the stimulatory effect of high estrogen levels on the endometrium, which can lead to proliferation, hyperplasia, or carcinoma. This is reflected in the US Food and Drug Administration's black-box warning that is a component of the prescribing information for all estrogen therapy. Before publication of the Women's Health Initiative (WHI) study in 2003, hormone therapy, in the form of systemic estrogen (plus progestin) was the prevalent therapy for treating the symptoms of menopause—both VMS and VVA. However, in light of the WHI results demonstrating significant adverse events, including

breast cancer, stroke, myocardial infarction, and venous thromboembolism associated with use of systemic estrogen therapy and estrogen–progestin therapy, these therapies became very unpopular—reflected in plummeting prescriptions—and presented complex counseling challenges for patients and HCPs. To this day, many women (and HCPs) continue to hold an unfavorable opinion of systemic hormone therapy, resulting in its low acceptance and usage.<sup>23</sup> Consequently, local administration of estrogen—through topical vaginal cream, vaginal tablet, or intravaginal ring—is the preferred modality for urogenital-only symptoms. Health care providers need to individualize treatment selection, based on the patient’s preferred mode of estrogen administration, optimal dosage, and risk factors to provide optimal symptom relief while minimizing the risk of potential adverse events.

Vaginal estrogen cream affords flexible dosing and is quite familiar to HCPs.<sup>24</sup> However, it is associated with an increased risk of systemic absorption and a potential for leakage.<sup>11,24</sup> Compared with estrogen cream, estrogen tablets afford enhanced fixed-dosing control, a reduced potential for systemic absorption, and decreased potential for leakage.<sup>25</sup> However, vaginal estrogen tablets may not relieve symptoms that affect the introitus. In addition, the required twice-weekly dosing can be confusing and thus impede optimal adherence. A flexible estrogen ring delivering continuous estradiol, inserted into the upper third of the vagina where it can remain for as long as 90 days, is a convenient option. Compliance issues are therefore eliminated, as is the risk of endometrial hyperstimulation associated with estrogen overtreatment.<sup>26,27</sup> However, not all women are candidates for the vaginal estrogen ring, particularly women with pelvic organ prolapse. In addition, the ring can become dislodged during sexual intercourse, and some women prefer not to have a foreign body retained long-term in the vagina.<sup>11</sup> Consequently, women considering estrogen therapy for management of VVA symptoms should be sufficiently counseled regarding all the vaginal estrogen delivery modalities and their potential advantages, risks, and benefits.

### Prescription Non-Estrogen Therapies

Two non-estrogen agents were approved in the past few years for the treatment of dyspareunia associated with VVA. The first was ospemifene, an oral SERM approved in 2013. The second agent is prasterone (DHEA), an intravaginal steroid transformed into androgens and/or estrogens locally in peripheral tissues, which was approved in 2016.

**Ospemifene.** In working on the development of anti-estrogens, scientists made a surprising discovery: specifically, some drugs that block the action of estrogen in certain tissues can actually mimic the action of estrogen in other tissues. Such selectivity is made possible by the fact that the estrogen receptors of different target tissues assume unique conformational shapes, depending on the ligand binding to the receptor. These differences allow estrogen-like drugs to interact in different ways with the estrogen receptors of different tissues, recruiting co-repressor and coactivator proteins to varying degrees, thus allowing the ligand–receptor complex to either stimulate or block protein synthesis and cell proliferation. Such drugs are called selective estrogen receptor modulators because they selectively stimulate or inhibit the estrogen receptors of different target tissues. For example, a SERM might inhibit the estrogen receptor found in breast cells but activate the estrogen receptor present in uterine endometrial cells. A SERM of this type would inhibit cell proliferation in breast cells, but stimulate the proliferation of uterine endometrial cells.

Ospemifene (Osphena®, Shionogi Inc.) was approved for treatment of moderate-to-severe dyspareunia. It is the first nonhormonal alternative to estrogen-based products for this indication. Unlike other SERMs (including the breast cancer drugs tamoxifen and toremifene), ospemifene exerts a strong, nearly full estrogen agonist effect (thereby mimicking estrogen effects) in the vaginal epithelium, making it well suited for the treatment of dyspareunia in postmenopausal women.<sup>28,29</sup> Ospemifene also acts as an antagonist—inhibiting estrogen effects—in other tissues.<sup>28,29</sup>

Results of 5 phase III clinical trials, involving 2171 postmenopausal women, showed that ospemifene, 60 mg/d, significantly improved the vaginal maturation index (decreased parabasal cells and increased superficial cells), decreased vaginal pH, and decreased severity of the self-identified most bothersome symptom of dyspareunia compared to placebo. For most-bothersome moderate-to-severe dryness, ospemifene numerically, but not statistically, separated from placebo. (TABLE 2).<sup>30-32</sup> The ospemifene trials encouraged the use of vaginal lubricants on demand, which may have made dryness as a subjective endpoint difficult to discern for women in the studies. Hot flashes were the most prevalent adverse event, experienced by approximately 7.5% of patients; vaginal discharge was the second-most common adverse event (3.5%).<sup>33</sup> Similar to estrogen therapy, ospemifene increases the incidence of VTE. Contraindications include estrogen-dependent neoplasia, active or prior VTE, prior

**TABLE 2** Ospemifene efficacy summary<sup>30,32,34,37,38</sup>

	Parabasal cells (%Δ) <sup>a</sup>	Superficial cells (%Δ) <sup>a</sup>	Vaginal pH (Δ) <sup>a</sup>	Most bothersome symptom (Δ) <sup>a</sup>
<b>Overall</b>	-30.1 <sup>b</sup>	10.8 <sup>b</sup>	-1.01 <sup>b</sup>	-1.26 <sup>b</sup>
<b>Dyspareunia ITT</b>	-40.2 <sup>c</sup>	12.3 <sup>c</sup>		-1.19 <sup>d</sup>
<b>Dyspareunia PP</b>	-42.1 <sup>c</sup>	13.2 <sup>c</sup>	-0.94 <sup>c</sup>	-1.5 <sup>c</sup>
<b>Vaginal dryness ITT</b>	-31.7 <sup>b</sup>	7.0 <sup>b</sup>	-1.10 <sup>c</sup>	-1.6 <sup>e</sup>
<b>Vaginal dryness PP</b>	-36.6 <sup>b</sup>	8.0 <sup>b</sup>	-0.95 <sup>b</sup>	-1.3
<b>Long-term safety</b>	-40.0 <sup>c</sup>	5.0 <sup>c</sup>	-0.99 <sup>b</sup>	-1.4 <sup>f</sup>

<sup>a</sup>Calculated from baseline to 12 weeks.

<sup>b</sup> $P < .001$ , compared to placebo.

<sup>c</sup> $P < .0001$ , compared to placebo.

<sup>d</sup> $P = .023$ , compared to placebo.

<sup>e</sup> $P = .0004$ , compared to placebo.

<sup>f</sup> $P = .014$ , compared to placebo.

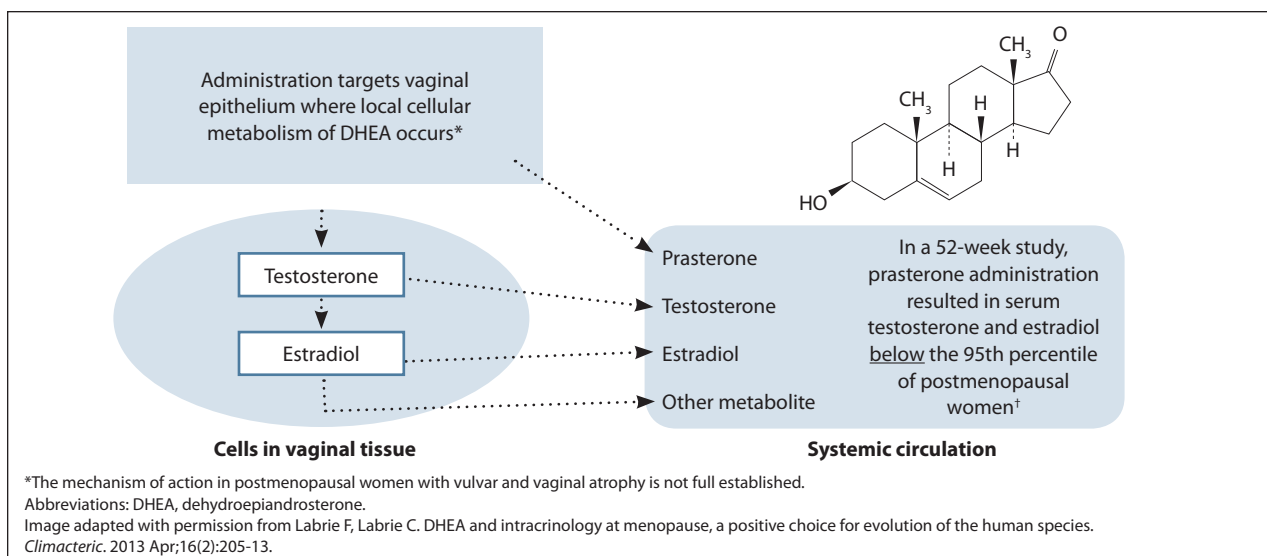
Abbreviations: ITT, intent to treat; PP, per protocol.

stroke, active or prior myocardial infarction, and severe hepatic impairment. Long-term safety studies revealed that 60 mg of ospemifene, given daily for 52 weeks, was well tolerated and was not associated with any endometrium or breast-related safety concerns.<sup>34</sup> There were no cases of endometrial cancer and <1% of patients experienced endometrial hyperplasia with treatment.<sup>35</sup>

The safety of ospemifene has been assessed in 9 phase II and III trials in approximately 1900 patients, with dosages ranging from 5-90 mg/d.<sup>36</sup> The duration of treatment in these studies ranged from 6 weeks to 15 months, with an average duration of exposure of 182 days. In these clinical studies, no clinically significant changes

in routine safety assessments, including hematology, chemistry, and urinalysis, were observed. The most common treatment-emergent adverse events included hot flashes (7.5%, vs. 2.6% for placebo), vaginal discharge (3.8%, vs. 0.3% for placebo), muscle spasms (3.2%, vs. 0.9% for placebo), and hyperhidrosis (1.6%, vs. 0.6% for placebo). Discontinuation rates due to any treatment-emergent adverse event were 7.6% with ospemifene and 3.8% with placebo.<sup>36</sup>

**Prasterone.** Prasterone (DHEA) (Intrarosa<sup>®</sup>; Endoceutics, Inc.) is an endogenous steroid hormone, and is the most abundant circulating steroid hormone in humans. It functions predominantly as an inactive metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids (FIGURE). Active hormones made in peripheral tissues are inactivated at their site of synthesis before being released outside the cells as inactive metabolites.<sup>39</sup> Prasterone is transformed into androgens and/or estrogens locally in peripheral tissues (FIGURE). Prasterone has no stimulatory effect on the endometrium because enzymes, especially aromatase, that are able to transform DHEA into estrogens are absent in the normal human endometrium.<sup>39</sup> Published literature suggests *the absence of aromatase in the normal human endometrium* as the rationale for lack

**FIGURE** Prasterone vaginal inserts: localized effect<sup>42</sup>

**TABLE 3 Prasterone: efficacy summary**<sup>39,44</sup>

Trial* (measure)	% Parabasal cells		% Superficial cells		Vaginal pH		Dyspareunia	
	Placebo	Prasterone	Placebo	Prasterone	Placebo	Prasterone	Placebo	Prasterone
Trial 1 (mean change in severity [SD])	-1.62 (28.22)	-47.40 (42.50)	0.91 (2.69)	5.62 (5.49)	-0.21 (0.69)	-1.04 (1.00)	-0.87 (0.95)	-1.27 (0.99)
Trial 1 (difference from placebo)	—	-45.77	—	4.71	—	-0.83	—	-0.40
Trial 1 (P value)	—	<.0001	—	<.0001	—	<.0001	—	.0132
Trial 2 (mean change in severity [SD])	-11.98 (29.58)	-41.51 (36.26)	1.75 (3.33)	10.20 (10.35)	-0.27 (0.74)	-0.94 (0.94)	-1.06 (1.02)	-1.42 (1.00)
Trial 2 (difference from placebo)	—	-29.53	—	8.46	—	-0.67	—	-0.35
Trial 2 (P value)	—	<.0001	—	<.0001	—	<.0001	—	.0002

\*Two pivotal phase 3 trials (12 weeks) with postmenopausal women with symptomatic vulvovaginal atrophy randomized to placebo or prasterone, 0.50%. Trial 1: n= 158; Trial 2: n= 482.

Abbreviation: SD, standard deviation

of endometrial stimulation.<sup>39-41</sup> Prasterone also exerts no significant changes in systemic estrogen and androgen levels.<sup>42</sup>

Prasterone received FDA approval in 2016 for treatment of moderate-to-severe dyspareunia. One vaginal insert (0.50%; 6.5 mg of prasterone) is inserted once daily at bedtime, using a provided applicator.<sup>43</sup>

Efficacy of prasterone was established in two 12-week, placebo-controlled clinical trials in approximately 400 postmenopausal women, who identified moderate-to-severe pain during sexual intercourse as their most bothersome symptom of VVA.<sup>39,44</sup> Prasterone demonstrated statistically significant superiority over placebo on all 4 co-primary objectives (TABLE 3): reduction of the percentage of parabasal cells; increase in the percentage of superficial cells; decrease in vaginal pH; and reduction in pain associated with sexual activity (dyspareunia). In the prasterone dyspareunia studies, use of the vehicle every night—similar to using a vaginal moisturizer—would provide a certain amount of lubrication in and of itself to placebo subjects, and the significant statistical separation of active prasterone from this robust vehicle effect is quite notable. Moderate-to-severe dryness, present in 80% of women in the pivotal dyspareunia trial, significantly improved. A most-bothersome-symptom-of-dryness study look-

ing at twice-weekly prasterone showed improvement numerically but not statistically, compared to placebo.<sup>45</sup> Women in the placebo group also likely had the emollient effect noted above from the lubricating vehicle, making dryness a challenge for subjects to quantify in a trial setting. Safety of prasterone was established in several 12-week, placebo-controlled trials.<sup>39,44</sup> The most common adverse reactions were vaginal discharge (5.71%, vs. 3.66% for placebo) across the 12-week studies involving 1129 women.<sup>44</sup> In a noncomparative study involving 521 women using prasterone vaginal inserts for 1 year, 14.2% of women reported vaginal discharge and 2.1% had an abnormal Pap smear, including 1 case of low-grade squamous intraepithelial lesion and 10 cases of atypical cells of undetermined significance.<sup>39</sup>

The endometrial effects of prasterone were assessed in an open-label, 52-week trial in which prasterone was given daily to more than 400 women.<sup>40</sup> A total of 389 patients had an endometrial biopsy upon entry into the trial, then again at its conclusion (TABLE 4). Three hundred and eighty-five patients had samples classified as “atrophic”; no patients had a “proliferative” or “hyperplastic” specimen. The scientific literature suggests the absence of aromatase in the normal human endometrium as the rationale for lack of endometrial stimulation.<sup>39,40</sup>

It should be noted that the prescribing information



**TABLE 4** Open label study on endometrial safety<sup>40</sup>

Open-label study on endometrial safety (N=422)	
Endometrial samples taken	N=389
Atrophic	n=385
Inactive	n=4
Proliferative	0
Hyperplastic	0
No tissue/insufficient tissue	n=33

for prasterone does not include the black-box warning for endometrial and cardiovascular risk required of conventional estrogen-containing formulations. It should also be emphasized that the use of prasterone in women with breast cancer or a history of breast cancer has not yet been evaluated; as such, no statements can be made about potential safety concerns regarding prasterone. Prasterone is contraindicated in women with undiagnosed abnormal genital bleeding, with warnings/precautions for its use in women with current or a history of breast cancer.<sup>43</sup>

## CONCLUSIONS

Approximately 50% of postmenopausal women experience symptoms of VVA and/or dyspareunia, yet few connect these symptoms with the underlying vulvovaginal and hormonal changes associated with menopause.<sup>1,5</sup> Unlike VMS, which are hallmark symptoms of menopause and often spontaneously resolve, VVA is a chronic

progressive condition that can substantially interfere with sexual function and quality of life. However, the overwhelming majority of US women do not seek treatment, and those who do are likely to use less effective, OTC, non-estrogen-related options.<sup>1</sup> Both women and HCPs have lingering fears stemming from WHI findings regarding the risks of systemic estrogen, and are therefore reluctant to consider hormonal therapy. Recently, 2 innovative therapies that do not contain estrogen have been added to this armamentarium: ospemifene and prasterone (DHEA). Healthcare providers can review the benefits and disadvantages of all available prescription options, as shown in **TABLE 5**, when helping postmenopausal women select the most appropriate treatment for their VVA and dyspareunia.

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**TABLE 5** Approved prescription therapies for vulvovaginal atrophy<sup>11,24-27,33</sup>

Type (route)	Advantages	Disadvantages
Estrogen cream (vaginal)	<ul style="list-style-type: none"> <li>• Flexible dosing</li> <li>• Familiar to HCPs<sup>1</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Increased risk of systemic absorption</li> <li>• Potential for leakage<sup>1,2</sup></li> </ul>
Estrogen tablet (vaginal)	<ul style="list-style-type: none"> <li>• Compared with estrogen cream, enhanced control of specific dose</li> <li>• Reduced potential for systemic absorption</li> <li>• Decreased potential for leakage<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>• May not relieve symptoms affecting introitus</li> <li>• Twice-weekly dosing schedule</li> </ul>
Estrogen ring (vaginal)	<ul style="list-style-type: none"> <li>• Facilitates compliance</li> <li>• Eliminates risk of endometrial hyperstimulation owing to overtreatment<sup>4,5</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Can be difficult to insert in some women (eg, pelvic organ prolapse)</li> <li>• May be felt by partner during coitus</li> </ul>
Ospemifene (SERM) (oral)	<ul style="list-style-type: none"> <li>• Nonhormonal</li> <li>• Oral</li> </ul>	<ul style="list-style-type: none"> <li>• Increased risk of vasomotor symptoms<sup>6</sup></li> </ul>
Prasterone (DHEA) cream (vaginal)	<ul style="list-style-type: none"> <li>• Metabolized locally to estrogen and androgens intracellularly</li> <li>• No black-box warning</li> </ul>	<ul style="list-style-type: none"> <li>• Daily dosing, applicator</li> </ul>

Abbreviations: DHEA, dehydroepiandrosterone; HCP, health care provider; SERM, selective estrogen receptor modulator.

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# Dyspareunia Associated with Vulvovaginal Atrophy: Innovations in Counseling, Diagnosis, and Management

## CME Instructions for Claiming Credit

The posttest and evaluation of this activity may be taken online by visiting [www.omniaeducation.com/dyspareunia](http://www.omniaeducation.com/dyspareunia).

CME credit may also be claimed by faxing the posttest/evaluation to 215.358.0556. A copy of the posttest/evaluation may also be mailed to Omnia Education 500 Office Center Drive, Suite 300 Fort Washington, PA 19034.

Time spent on this activity: Hours \_\_\_\_\_ Minutes \_\_\_\_\_  
(includes reading articles and completing the learning assessment and evaluation)

This information MUST be completed in order for the quiz to be scored.

**THE MONOGRAPH AND TEXT EXPIRE APRIL 27, 2019**

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LAST NAME FIRST NAME DEGREE

MAILING ADDRESS

CITY STATE ZIP CODE

DATE OF BIRTH (USED FOR TRACKING CREDITS ONLY)

PHONE NUMBER FAX NUMBER

E-MAIL ADDRESS

1. Approximately how many postmenopausal patients do you see every week? \_\_\_\_\_

2. With what proportion of these patients do you discuss sexual health concerns and management options for post-menopausal dyspareunia?

- a) 0%      b) 25%      c) 50%  
d) 75%      e) 100%

3. Whereas vasomotor symptoms associated with menopause (VSM) diminish over time, VVA is a chronic condition that worsens in the absence of treatment.

- a) True      b) False

4. Post-menopausal women cite which of the following as the most important determinant(s) of their postmenopausal sexual functioning?

- a) Lack of available sexual partners  
b) Vaginal dryness, dyspareunia, irritation  
c) Age  
d) Both A and B  
e) All the above

5. Which is true about prasterone, a vaginal insert to manage dyspareunia? (Portman)

- a) It has no stimulatory effect on the endometrium  
b) It reduces the percentage of parabasal cells and superficial cells  
d) Itching is the most commonly reported adverse event  
c) None of the above

6. How would you rate your ability to apply what you learned to improve the following areas of your practice:

- |   | Significantly improved | About the same        | I need more information |
|---|------------------------|-----------------------|-------------------------|
| a) Open a dialogue with patients regarding sexual health concerns                   | <input type="radio"/>  | <input type="radio"/> | <input type="radio"/>   |
| b) Describe the components of a comprehensive sexual history                        | <input type="radio"/>  | <input type="radio"/> | <input type="radio"/>   |
| c) Accurately diagnose vulvovaginal atrophy and genitourinary syndrome of menopause | <input type="radio"/>  | <input type="radio"/> | <input type="radio"/>   |
| d) Provide appropriate treatment options  | <input type="radio"/>  | <input type="radio"/> | <input type="radio"/>   |

7. How often will you now:

- |  | Much more often than before | About the same        | I already do this     | I need more information |
|--|-----------------------------|-----------------------|-----------------------|-------------------------|
| a) Ask your post-menopausal patients about symptoms of GSM/VVA   | <input type="radio"/>       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/>   |
| b) Engage patient in a shared decision-making process when considering treatment options for VVA/GSM                 | <input type="radio"/>       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/>   |
| c) Discuss innovative treatment options (eg, ospemifene, prasterone) for the management of dyspareunia with patients | <input type="radio"/>       | <input type="radio"/> | <input type="radio"/> | <input type="radio"/>   |

8. Based on this activity, please select the changes you are committed to make when you return to practice (select all that apply).

- a) Acquire more training/knowledge regarding the diagnosis and management of dyspareunia  
b) Educate patients on the benefits and risks of current management strategies for dyspareunia  
c) Engage postmenopausal patients in discussion regarding symptom of VVA, their sexual health and quality of life  
d) Educate colleagues on innovative treatment options for dyspareunia  
e) No change, I am already comfortable with applying the content presented  
f) Other, please specify \_\_\_\_\_

9. What barriers do you meet in practice impede your efforts to manage dyspareunia in your postmenopausal patients? (Select all that apply)

- a) Internal policies and processes  
b) Confusion about the guidelines  
c) Too many agents to choose from  
d) Patients' fear about safety  
e) My concerns about safety  
f) Patients' adherence to therapy  
g) I need more information  
h) Others \_\_\_\_\_  
i) I have no barriers

