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REVIEW

Review of current and emerging estrogen receptor agonists for vaginal atrophy

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ABSTRACT

Introduction: Vulvovaginal atrophy (VVA) predominantly affects postmenopausal women due to hormonal decline but can also occur in premenopausal women with conditions such as primary ovarian insufficiency or exposure to anti-estrogen medications. Contributing factors include smoking and certain medical treatments. Symptoms like dyspareunia and loss of sexual function affect many women but are underreported due to stigma and lack of awareness. Current treatments range from over-the-counter lubricants to hormonal therapies like estrogen receptor agonists, which improve vaginal elasticity and moisture with minimal systemic absorption.

Areas covered: This review evaluates current and emerging estrogen receptor agonists for VVA treatment. A comprehensive search was conducted using PubMed between August and September 2024, supplemented by snowball sampling from key references.

Expert opinion: Despite its prevalence, VVA remains underdiagnosed, with increasing recognition due to longer lifespans and focus on quality of life. Diagnosis involves comprehensive symptom assessment, including sexual history, urinary tract infection frequency, and clinical exams, with vaginal pH measurements and smear microscopy to determine the condition's severity. Treatment usually involves estrogen, but not all women can safely use it, and preferences toward estrogen must be respected. Alternatives like selective estrogen receptor modulators (SERMs) such as prasterone and ospemifene show promise but need more long-term safety data. Emerging options like E3 and E4 demonstrate efficacy and safety in low doses. Future treatments will emphasize convenience and adherence, making timely diagnosis and management of VVA routine in women's health care.

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1. Introduction

Vulvovaginal atrophy (VVA) is a chronic condition that predominantly affects postmenopausal women and is caused by the natural physiological reduction of female sexual hormones [1]. Equally, premenopausal women may encounter a decrease in female sexual hormones due to conditions such as primary ovarian insufficiency, ovarian failure, taking anti-estrogen medication, breastfeeding, and treatment consequences of breast cancer [1]. External factors such as smoking and alcohol abuse can contribute to the development of VVA [2,3]. It is estimated that 15% of premenopausal women experience overt symptoms of VVA, while at least 50% of postmenopausal women suffer from both urinary and vulvovaginal symptoms [1,2,4]. Presumably, the prevalence of the syndrome is significantly underestimated due to physicians' limited interest or awareness, women attributing these symptoms to natural aging, and the social taboo surrounding discussions about vulvovaginal discomfort and pain [5–7]. VVA leads to changes in the vaginal mucosa, resulting in loss of sexual enjoyment, dyspareunia, and sexual dysfunction [1,7,8]. The loss of elasticity in the vagina, thinning of vulvovaginal tissues, and reduced lubrication make women more vulnerable to micro fissures, vaginal bleeding, and even insufferable pain [1,9]. Sexual intercourse was previously thought to be a protective factor against VVA, but it is not determined whether women who can have sexual intercourse without pain have less atrophy or cause less atrophy by intercourse [9]. Although various terms are used to describe the signs and symptoms of VVA, including atrophic vaginitis, genitourinary syndrome of menopause (GSM), postmenopausal vaginitis, and vaginal atrophy, for clarity and consistency, this publication will use the term 'vulvovaginal atrophy' to refer to this specific set of symptoms. If treatment of vulvovaginal atrophy with over-the-counter lubrication and moisturizers is not effective, non-hormonal and hormonal therapies are considered. One common hormonal option is the use of estrogens or estrogen agonists, which act to alleviate symptoms by exerting or mimicking the effects of estrogen in the vaginal tissues, promoting moisture and elasticity. Estrogen agonists can be administered locally through vaginal creams, tablets, or rings, which target the affected area directly while minimizing systemic absorption. These treatments are often considered for patients who experience more severe symptoms, do not find relief with non-hormonal methods, or have contraindications for systemic use of hormones. To further understand the advancements in this area, this article aims to review the current and emerging estrogen receptor agonists for VVA.

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Article highlights

- Vulvvovaginal atrophy (VVA) should be diagnosed and its severity assessed before treatments are installed. Phase conrast microscopy of fresh vagina fluid is the most indicated technique to achieve this goal.
- Cornerstone of VVA treatment is maintenance therapy with estrogens.
- Very low dose, low potency estrogens like estriol (with or without probiotic lacto-bacilli) , applied locally, are very safe and efficient treatments for VVA, even in breast cancer patients
- Estetrol is a new drug probably suitable for treatment of VVA but requires further testing.
- Alternative treatments with Dehydroepiandrosterone sulfate and ospemifene are promising and safe alternatives for use in women with absolute contraindications for estrogen use or not willing to use estrogens.
- Given the safety, efficacy, variety and multiciply of existing treatments for VVA, currently there is no reason to apply potentially dangerous and expensive treatments like laser therapy of the vaginal mucosa.

2. Methods

This narrative review focuses on current and emerging estrogen receptor agonists for the treatment of VVA. Two independent reviewers conducted comprehensive searches in the PubMed database between August and September 2024, using the following keywords: 'Genitourinary Syndrome of Menopause' (GSM), 'Vulvovaginal atrophy,' 'Vaginal atrophy,' 'Estrogen,' 'Estrogen receptor agonists,' 'Estrogen modulators,' and 'Treatment' or 'Management.' Additionally, the snowball sampling method was applied by reviewing the references and citations of relevant articles to identify supplementary literature. All articles included, both original and review, were in English. Non-English language papers were excluded.

3. Treatment with current and emerging estrogen receptor agonists

In the treatment of vulvovaginal atrophy with estrogen receptor agonists, we can differentiate local and systemic treatments (Table 1). Local treatments contain limited doses of estrogen distributed directly into the vaginal, mainly addressing local symptoms. Systematic therapy commonly contains higher doses of estrogens enabling systematic action and may cause endometrial hyperplasia and breast tissue activation [10].

Besides systemic treatment, for VVA without generalized menopausal symptoms, local estrogen and SERM treatment are available in several formulations such as creams, gels, tablets, and vaginal rings [4]. Estrogen agonists are used for cases that don't respond to lubricants and moisturizers. Dosages and treatment periods are mostly patient-adjusted and can be differentiated among clinicians [10]. Although local estrogen therapies are commonly used to alleviate VVA in postmenopausal women, the efficacy of new estrogen agonists is enormous, and their safety has been examined extensively, with a focus on reducing systemic absorption and minimizing general side effects and risks.

3.1. Estrone (E1)

Previous research from the 1960s indicated that estrone was briefly available, but subsequently withdrawn from the market due to a lack of sufficient clinical studies [11].

3.2. Estradiol (E2)

Estradiol is the natural hormone synthesized by the ovaries through the aromatization of the 'A' ring of testosterone [12]. It is the most potent type of estrogen present during the reproductive years, playing a crucial role in the regulation of the menstrual cycle, cardiovascular function, nervous systems, skeletal systems, and vascular system [13]. Postmenopausal women encounter a higher risk of diseases, such as cardiac infarction, stroke, hip fractures, and possibly dementia.

In a previous review, we highlighted that estradiol hormonal replacement therapy (HRT), whether administered systemically or locally, represents the cornerstone in the treatment of VVA [11]. A comprehensive review of 30 randomized controlled trials involving 6235 women indicates that the extent of symptom relief is consistent across different application forms [14]. It has been established that estrogen therapy containing 25 µg of 17β-E2, represents an ultra-low effective dose for relieving symptoms of VVA [15]. Even more striking, Vaginal tablets of a dose as low as 10 µg of E2 have been demonstrated to be equally effective [15]. Furthermore, a previous study found that there was only a very minimal absorption of estradiol at both dosage levels, not resulting in any systemic impact [16].

An evaluation of the safety and effectiveness of estradiol vaginal cream in low-dose formulations 15 µg and 50 µg has demonstrated its efficacy in the management of VVA in postmenopausal women [17]. In the use of 50 µg vaginal 17-β-estradiol (E2) cream no significant differences were observed in

Table 1. Overview of pathophysiology, spectrum of activity and warning signals of available drugs with estrogen agonist activity for treatment of vulvovaginal atrophy (VVA). SERM: selective estrogen receptor mechanism, CI: contra-indication, VA: vaginal application, TD: transdermal, BC: breast cancer, TEE thrombo-embolic events, EMP: endometrium proliferation.

Name of product	Mode of action	SERM activity EM BR BN	VVA efficacy	Oral/vaginal dose	Side effects /warnings	Use in estrogen CI
Estradiol (E2)	aER	++ ++ ++	++	Oral 1-2 mg dd, TD 25–50 ug dd VA 10 ug-1 mg 2/w	BC, TEE, EMP	No
Estriol (E3)	aER	± + -	++	VA 0.05 – 2 mg/wk	BC ±	No
E3 + lactobacilli	aER + synergism	- - -	++	VA 0.03 mg 2×/wk	-	yes
Estretol (E4)	aER/SERM	+ - +	+	Oral 10 mg dd	EMP	No
Dehydro-epi-androsteron (DHEA)	Androgenic + estrogen conversion	-? -	++	VA 6.5 mg dd	BR (?), TEE (?)	No
Ospemifeen	aER/SERM	+(?) - -	++	Oral (30)-60 mg dd	EMP(?), TEE (?)	?

serum E2 levels (pg/mL), and biomarker staining for TGF-β, NFKB, iNOS, eNOS, or TSP did not show any significant changes at any point. Both studies found a significant improvement in the self-reported symptom of vaginal dryness and an increased percentage of superficial cells, and decreased percentage of parabasal cells. The most common side effect observed in the 15 µg vaginal 17-β-estradiol (E2) cream was vulvovaginal mycotic infections.

According to research, the use of 10 µg of E2 vaginal tablets for 12 weeks (one vaginal tablet daily for 14 days, subsequently one tablet twice a week) significantly improves the cellular subtypes toward a premenopausal vaginal epithelium [17]. Similarly, they found a significant decrease in vaginal pH levels and self-reported symptoms such as dyspareunia and vaginal dryness. Common side effects of 10 µg E2 vaginal tablets include vulvovaginal mycotic infection; back pain; vulvovaginal pruritus infection. In 0,5% of participating women endometrial adenocarcinoma stage II, grade 2 was diagnosed [18].

3.3. Estriol (E3)

Estriol (E3), initially identified in the human placenta, has been linked to pregnancy outcomes, particularly as a marker of adverse pregnancies. E3 promotes the proliferation and maturation of the vaginal epithelium, leading to the release of glycogen. Lactobacilli then convert the glycogen into lactic acid, which lowers the vaginal pH. Due to its brief interaction with vaginal receptors, E3 is associated with minimal or no systemic effects, making topical administration preferable to oral administration [11]. Recent studies suggest that ultra-low doses of estriol (30 µg per application) can effectively reduce symptoms. This efficacy is comparable to that of higher-dose estradiol formulations, including estradiol rings, tablets, estriol ovules, creams, and tablets. Despite its lower estrogenic activity compared to estradiol, and despite being administered at a dose 10 times lower than other estriol products, this ultra-low dose has shown effectiveness in reversing vaginal epithelial changes in postmenopausal women [3].

When administered in standard doses (oral: 2–10 mg daily; vaginal: 0.5 mg or less), E3 has shown minimal or no proliferative effects on the endometrium, unlike estradiol (E2). A systematic review and meta-analysis concluded that intravaginal E3 at doses of 0.5 mg or less is effective in treating VVA without inducing endometrial hyperplasia [19]. Even at lower doses (0.2 mg and 0.03 mg), significant improvements in VVA symptoms have been observed. After 12 weeks of treatment, ultra-low dose estriol gel 0.005% E3 (50 µg per dose) effectively alleviated most vulvovaginal symptoms, including dryness and dyspareunia, thereby enhancing sexual function. The application of ultra-low dose estriol gel has been demonstrated to be both safe and effective in improving symptoms related to estrogen depletion, such as vaginal pH and epithelial maturation. The minimal impact on estrogen, FSH, and LH levels further supports its safety as a treatment option for VVA. In comparison to E2, E3 exhibits no or only weak proliferative effects on the endometrium with single daily doses of 2–10 mg orally or 0.5 mg or less vaginally. Systematic reviews confirm the effectiveness of such low doses in treating VVA without causing endometrial hyperplasia. Further, ultra-low doses of 0.2 mg and 0.03 mg have shown a substantial impact on VVA parameters in both tested formulations [2,19].

An intravaginal gel containing ultra-low 0.005% E3 (50 mcg per dose) was also tested in a Phase 2 RCT involving breast cancer patients on aromatase inhibitors (AIs). The primary safety outcome was the FSH level, with the gel causing minimal changes, which were neither statistically nor clinically significant [19]. The study demonstrated significant improvements in the maturation index, vaginal pH, dryness, and overall symptom scores in the treatment group compared to placebo, along with improvements in the FSFI score, though not all domains reached statistical significance within the 3-month treatment period. While further research is warranted to confirm these findings in larger cohorts, current data support the efficacy and safety of estriol in treating VVA, even in breast cancer patients [19].

The addition of probiotic lactobacilli to low-dose E3 results in a synergistic action, yielding superior improvements for both vaginal atrophy (VVA) and urinary incontinence [27, 28, 20, 21]. A product containing 10^8 lyophilized Lactobacillus KS400 bacteria combined with an ultralow dose of 0.03 mg of estriol (E3) (10 to 30 times lower than in other vaginal products containing 0.5–1 mg of estriol) has been found to be safe and effective in reversing VVA in menopausal women, as well as restoring abnormal vaginal microflora in other cases [29–32, 22, 23, 24, 25]. The safety and efficacy of this combination were evaluated in breast cancer (BC) patients suffering from severe VVA and treated with non-steroidal aromatase inhibitors (AIs) [33 26]. In a pharmacokinetic phase I study, 50% of participants exhibited a small, short-lived increase in serum E3 levels (168 pg/ml 2–3 hours post-insertion). However, serum estrone (E1) and estradiol (E2) remained below detectable limits, even when using the most sensitive tests available globally [33, 26]. Importantly, this E3 level is significantly below the threshold (288 pg/ml) required to stimulate mitogenic activity in breast cancer cells in vitro [34 27]. Furthermore, this serum increase occurred only in the first 12 to 24 hours after application and disappeared completely thereafter. This brief increase was only observed after the initial dose, while the vaginal epithelium was still very thin. After one month of treatment, the serum E3 increase was no longer detected, as the vaginal mucosa had returned to its normal thickness [33 26]. Efficacy-wise, the treatment dramatically improved VVA and microbial dysbiosis, with 88% of women regaining normal lactobacilli levels within just two weeks [35 28]. Additionally, there was a notable reduction in the prevalence of moderate to severe aerobic vaginitis (msAV) and a significant decline in parabasal epitheliocytes and vaginal leukocytes in smear samples, indicating successful treatment ($p < 0.001$) [35 28]. The product was well tolerated, and no adverse side effects were reported. All participants continued the treatment and reported improved sexual activity and quality of life based on adapted questionnaires [36 29]. Although further phase III trials are warranted, it appears that the vaginal use of ultralow doses of E3 combined with lactobacilli is equally effective but safer compared to estradiol (E2), offering a viable alternative therapy for VVA in breast cancer patients undergoing anti-hormonal treatment [34 27].

3.4. Estetrol (E4)

E4 is a natural estrogenic steroid, characterized by its four hydroxyl groups, and is uniquely synthesized in the human

fetal liver by the enzymes 15- and 16 alpha-hydroxylases [31 30]. During late gestation, maternal plasma and urine levels of E4 significantly increase, reaching concentrations of 1 ng/mL or higher. After birth, the neonatal liver ceases E4 production as these enzymes are no longer expressed [31 30]. E4 possesses distinct pharmacokinetic, pharmacological, and safety profiles, notably with low or no thrombogenic activity, a favorable lipid profile, and an antiestrogenic effect on breast tissue in the presence of estradiol [31]. Recent studies in patients with advanced, therapy-resistant breast cancer have demonstrated that E4 not only maintains a high safety and tolerability profile but also induces tumor regression in 9 out of 12 patients [31, 32]. Consequently, E4 has been investigated for use in hormone replacement therapy (HRT) and contraception and is being considered for treating VVA in breast cancer patients, pending further safety studies [32,33].

The effect of E4 on vaginal cytology was evaluated by comparing oral doses of 2 mg and 10 mg of E4 with oral 2 mg of estradiol (E2) over a 28-day treatment period. The 10 mg E4 group showed superior improvements in the vaginal cell maturation index (VCMI) compared to the 2 mg E2 group, while the effect in the 2 mg E4 group was less pronounced [34]. This suggests that E4 may have potential not only in contraception and the management of vasomotor symptoms but also in the treatment and prevention of VVA [35]. However, it is important to note that at the 10 mg dose endometrial proliferation occurred, a side effect not observed at lower doses. In preclinical studies, E4 was shown to activate the alpha estrogen receptor, enhancing the quality of vaginal mucosa in ovariectomized mice [35]. Different oral doses of E4, ranging from 2.5 to 15 mg per day, were compared with a placebo in women experiencing severe hot flashes. The 15 mg dose led to a significant reduction in hot flushes, although additional progestin was required to prevent endometrial proliferation. While further research is necessary, E4 is increasingly viewed as a promising and safe option for treating VVA and other menopausal symptoms, including the prevention of osteoporosis and cardiovascular complications [35].

3.5. Ospemifene

Ospemifene (OSP) is a selective estrogen receptor modulator (SERM) with a range of effects on target tissues. It acts as an estrogen receptor agonist in the vaginal epithelium and bone, while functioning as a partial agonist in the uterus [36]. Ospemifene is uniquely approved for the oral treatment of vaginal dryness and moderate to severe dyspareunia, as clinical studies have demonstrated its effectiveness in significantly alleviating dyspareunia and providing substantial relief from vaginal dryness [32,35]. As a triphenylethylene derivative, ospemifene's chemical structure is similar to that of tamoxifen and toremifene, which are SERMs used in anti-hormonal therapy for hormone-sensitive breast cancer [34,36–38]. Unlike these agents, ospemifene does not produce proliferative effects on the endometrium or breast tissue, making it suitable for managing VVA. Clinical research has shown that oral administration of ospemifene increases the VCMI and promotes vaginal alpha estrogen receptor expression [37]. A Phase III study with postmenopausal women treated with 30 mg or 60 mg of Ospemifene for 12 weeks demonstrated significant improvement in the VCMI by week 4 ($p < 0.001$) and a reduction in vaginal dryness at both doses. The 60 mg dose was particularly effective in reducing dyspareunia [36]. The study also noted increases in endometrial thickness (a mean of 0.4 mm for the 30 mg dose and 0.7 mm for the 60 mg dose) compared to a decrease of 0.02 mm in the placebo group. While these changes in endometrial thickness are not clinically significant, they highlight the importance of ongoing monitoring [36]. Although no thromboembolism cases have been reported with ospemifene, potential risks associated with SERMs – such as thromboembolism, increased breast cancer risk, and hot flashes – necessitate further investigation. A post-hoc analysis of five randomized, placebo-controlled trials found that ospemifene did not adversely affect lipid profiles, with increases in HDL and decreases in LDL levels observed over 3, 6, and 12 months [39].

Preclinical studies suggest that ospemifene may have a neutral or inhibitory effect on breast carcinogenesis. In an in-situ mouse model, it was found to reduce breast cell proliferation in animals with ductal carcinoma [40]. Despite these findings, the Endocrine Society Clinical Practice Guidelines do currently not recommend ospemifene for women with a history of breast cancer [41]. Ospemifene has also shown potential in other areas. A retrospective analysis revealed that postmenopausal women taking 60 mg daily for six months experienced fewer recurrent urinary tract infections (UTIs) [35]. Additionally, in vitro studies indicate that ospemifene positively impacts osteoblasts and reduces bone loss in ovariectomized rats, showing activity similar to raloxifene [42]. A randomized, double-blind study involving 118 healthy postmenopausal women compared ospemifene (30 mg, 60 mg, and 90 mg) with 60 mg of raloxifene, finding that the 90 mg dose of ospemifene had a superior response [43].

In terms of safety, a meta-analysis confirmed that ospemifene does not increase the risk of osteoporosis, cardiovascular events, or venous thromboembolism compared to placebo. Analysis of the MarketScan database from 2013 to 2017 supported these findings, showing a threefold lower incidence of VTE among ospemifene users compared to those using other SERMs [44].

Despite its superior efficacy in clinical trials, overall satisfaction with ospemifene was moderate, with only a 15% higher satisfaction rate compared to placebo and overall satisfaction not exceeding 50%. Discontinuation rates were higher in the ospemifene group (7.6% vs. 3.8% for placebo), primarily due to increased incidence of hot flashes and UTIs. However, these adverse effects were less significant after 52 weeks of treatment [45].

3.6. Dehydroepiandrosterone (DHEA)

In postmenopausal women, reduced testosterone levels contribute to decreased lubrication, vaginal atrophy, and sexual dysfunction. These symptoms can be effectively treated with high doses of intravaginal testosterone, which converts to estrogen through the action of 5α-reductase enzymes. DHEA also promotes vaginal and sexual health by locally converting androstenedione and testosterone into estrone (E1) and

estradiol (E2). After menopause, the ovaries cease estrogen production, leading to serum estrogen levels that are too low to be biologically active. In this context, DHEA becomes the primary source of estrogens and androgens, which are converted in peripheral tissues. However, the body lacks a feedback mechanism to increase DHEA production when its levels drop, so to address this deficiency it can only be restored by replacement therapy [2,10]. DHEA functions as an endogenous precursor steroid hormone, with its effects on the vagina likely due to its local metabolism into androstenedione, testosterone, E2, and E1. While DHEA can be administered orally – for instance, to treat hypoactive sexual desire disorder – its vaginal application is considered safer and more effective for treating vulvovaginal atrophy (VVA) and dyspareunia. This has led to FDA approval of its use in these conditions. However, due to its short-lived action, daily application is required, unlike vaginal estrogens (E2 or E3), which may be applied less frequently. DHEA has been incorporated into treatment guidelines in several countries, including the U.S., Canada, Switzerland, and Poland [2,11].

Pharmacokinetic studies indicate that intravaginal administration of 6.5 mg DHEA does not increase serum levels of estradiol, estrone, testosterone, or DHEA, suggesting that its effects are localized within the vaginal tissues. In clinical trials, daily application of 0.50% DHEA (6.5 mg prasterone cream) has demonstrated superior outcomes in improving vaginal pH, cell maturation, and reducing dyspareunia compared to placebo, without causing significant changes in serum steroid levels, which remain within normal postmenopausal ranges. Additionally, this dose of prasterone cream has shown similar efficacy in alleviating VVA symptoms as 0.3 mg conjugated estrogens (CE) or 10 µg estradiol applied locally. This equivalence in clinical activity to low-dose vaginal estrogen has been supported by a review of 14 studies [2]. In a phase III trial, DHEA clinical benefits were sustained over 52 weeks, with slight increases in serum estrogenic and androgenic metabolites, though still within normal postmenopausal limits. While DHEA appears to result in a lower serum estradiol increase than low-dose vaginal estrogen, the requirement for daily application is a disadvantage, as twice-weekly dosing has proven less effective in managing VVA [2,11].

As an alternative to vaginal estrogen therapy, DHEA has gained FDA approval for the treatment of genitourinary syndrome of menopause (GSM). This steroid hormone plays a critical role in the biosynthesis of androgens and estrogens without causing harmful endometrial stimulation [10]. Importantly, studies have shown that intravaginal DHEA does not raise blood levels of sex steroids such as estradiol, DHEA, DHEAS, androstenedione, or testosterone. The key advantage of intravaginal DHEA is its dual action through both estrogenic and androgenic pathways, which has proven effective across all three layers of vaginal tissue: the epithelium, lamina propria, and muscularis. By enhancing the VCMI, vaginal elasticity, and lubrication, this treatment offers substantial benefits for menopausal women. Despite these benefits, there is limited data on the long-term safety of vaginal DHEA, particularly concerning cardiovascular disease and breast cancer risk. Prasterone has not been studied in breast cancer survivors and is hence not indicated for individuals with current or past breast cancer [10].

4. Conclusion

Several safe and effective therapies are available for the treatment of VVA, both hormonal and non-hormonal. The cornerstone of treatment is intravaginal estrogen therapy, which is highly effective and safe when administered at the lowest possible dose directly in the vagina. For women with contraindications to estrogen, or those preferring non-hormonal options, alternatives such as non-hormonal moisturizers can be effective if symptoms are limited to vaginal dryness or discomfort during intercourse. In cases involving sexual dysfunction, additional benefits may be achieved with intravaginal androgens like DHEA or oral ospemifene, although the latter is more expensive and not widely covered by insurance. Also, larger, longer-term studies would be valuable to confirm the safety of these treatments with estrogen receptor agonists for VVA, especially on breast and endometrium. For women, unable to use systemic estrogen, like in breast cancer patients, ultra-low dose estriol, potentially combined with probiotic lactobacilli, offers a safe and effective alternative.

5. Expert opinion

Even today, VVA (Vulvovaginal Atrophy) remains an underdiagnosed and neglected condition affecting millions of women, despite its increasing prevalence due to prolonged longevity and the desire to maintain a high quality of life. Proper diagnosis involves a comprehensive assessment of symptoms, including an in-depth sexual history, inquiries about the frequency of UTIs, and a clinical exam. Ideally, the examination should conclude with a measurement of vaginal pH and microscopy of a vaginal smear to assess the severity of VVA by composing the Vaginal Cell Maturation Index (VCMI) or evaluating the proportion of parabasal epithelial cells. This approach significantly enhances the quality of follow-up visits, allowing timely adjustments to treatment as needed. While the treatment of VVA is essentially straightforward, primarily involving the reintroduction of estrogen either systemically or locally in the vagina, caution is necessary. Not all women can safely use these products and may require alternatives. Additionally, the preferences and beliefs of women who choose not to use estrogen after menopause should be considered and respected. Therefore, ongoing research to expand the range of non-estrogenic treatment options is essential. In recent decades, significant advancements have been made in developing innovative, safe, and effective products to treat VVA and prevent its complications. Notably, alternative estrogens with selective effects on different estrogen-sensitive tissues, such as the endometrium, breast, and bone – like E3 and E4—have been increasingly studied in various clinical settings. These studies have demonstrated that both E3 and E4 possess unique properties, with E3 proving to be safe in ultra-low doses when combined with probiotic lactobacilli, even in breast cancer patients. The potential uses of E4, including for VVA treatment, are still being explored. However, its risk of endometrial stimulation at doses necessary for alleviating hot flashes may limit its future application for VVA. Still, with lower doses, the addition of progestins, or the use of low-dose intravaginal applications, E4 could hold significant potential

as a future VVA treatment option. Non-estrogenic treatments such as prasterone (DHEA-SO4) and ospemifene with its promising profile as a Selective Estrogen Receptor Modulator (SERM) are likely to play an increasing role in the treatment of VVA. However, due to a lack of long-term safety data, these products are currently not recommended (or should be used cautiously) for women with contraindications to hormone therapy, such as those with an elevated risk of endometrial proliferation, breast cancer, or thromboembolic disease. Long-term studies are needed to establish not only the lasting efficacy of these treatments but also their safety, to expand their indications to a broader population. In the next 5 to 10 years, beyond addressing efficacy and safety, convenience and ease of use will become important factors. Products that require less frequent applications – such as weekly, biweekly, or even monthly – will be favored to ensure comfort and compliance. In my opinion, timely diagnosis, prevention, and treatment of VVA should become as routine and necessary as managing high cholesterol or brushing your teeth.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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