Position of the Spanish Menopause Society regarding vaginal health care in postmenopausal women

Rafael Sánchez-Borrego a,∗, Montserrat Manubens b, María Concepción Navarro c, Mª Jesús Cancelo d, Estanislao Beltrán e, Magda Duran f, Teresa Orte g, Laura Baquedano h, Santiago Palacios i, Nicolás Mendoza j

a Clinica Diatros, Barcelona, Spain
b Instituto Dexias, Barcelona, Spain
c Department of Farmacology, University of Granada, Granada, Spain
d Hospital de Guadalajara, University of Alcalá, Guadalajara, Spain
e Hospital San Cecilio, Department of Obstetrics and Gynecology, University of Granada, Granada, Spain
f Hospital Clinic, Department of Obstetrics and Gynecology, University of Barcelona, Barcelona, Spain
ɡ Parc de Salud Mar, Barcelona, Spain
h Hospital Universitario Miguel Servet, Zaragoza, Spain
i Instituto Palacios, Madrid, Spain
j Clinica Margen, Department of Obstetrics and Gynecology, University of Granada, Granada, Spain

A B S T R A C T

Vaginal health, defined as the vaginal state in which the physiological condition remains stable, being protected from the onset of symptoms and facilitating a satisfying sex life, is one of the most common and less valued concerns in postmenopausal women. Many of the conditions that affect the vagina are related to its tropism and susceptibility to infection by unusual germs, which are phenomena strongly influenced by estrogen impregnation and the microbiota composition, ultimately affecting sexuality and the quality of life. An expert panel of the Spanish Menopause Society met to establish criteria for diagnosing and treating the processes that affect overall vaginal health and to decide the optimal timing and methods based on the best evidence available.

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1. Introduction

We define “vaginal health” as the vaginal state in which the physiological condition remains stable, being protected from the onset of symptoms and facilitating a satisfying sex life. The vagina is a target organ for estrogens, which affect its moisture, pH, blood flow, and bacterial microbiota. This fact explains why postmenopausal hypoestrogenism causes the vagina to become thin, losing elasticity and rendering it more vulnerable to pain and infection, which affects sexuality and the quality of life [1].

Because a high percentage of women report disorders related to vaginal health during menopause, a panel of experts from the Spanish Menopause Society (SMS) met to review the conditions that determine vaginal pathophysiology and the recommendations for preventing or treating the possible diseases. The SMS considers it appropriate to develop its own recommendations based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system to elaborate clinical practice guidelines and to classify the quality of the evidence and the strength of the recommendations [2].

2. Vaginal microbiota

Vaginal microbiota refers to the community of microorganisms that colonize the vagina in healthy women. We differentiate indigenous or resident microbiota from transient microbiota. The former is composed of microorganisms that colonize the vagina over a long period and participate in its physiological functions, although their balance depends on factors such as age, phase of the ovarian cycle, sexual activity, pregnancy, and the use of contraceptives,
antibiotics, or hygiene products [3]. During the reproductive years, the indigenous microbiota is mainly composed of various species of \textit{Lactobacillus}, accompanied to a lesser extent by bacilli and anaerobic Gram-positive cocci, streptococci, enterococci, staphylococci, anaerobic actinomycetes, \textit{Ureaplasma}, and \textit{Mycoplasma hominis}. Isolated in much smaller quantities are bacilli and anaerobic Gram-negative cocci, anaerobes of the genus \textit{Mobiliuncus}, \textit{Gardnerella vaginalis}, and \textit{Escherichia coli} [4].

The main components responsible for maintaining the balance of the vaginal microbiota are lactobacilli, which constitute a genus of Gram-positive, anaerobic, and aerotolerant bacteria known for their ability to convert lactose and other monosaccharides into lactic acid. This characteristic causes the vaginal habitat to have an acidic pH, slowing the growth of other potentially pathogenic microorganisms [5]. Some Lactobacillus species isolated in the vagina are also found in our digestive flora, in the digestive flora of other animals, and in various foods (e.g., meat, fish, fresh produce, beer, or wine). The predominant species in the indigenous vaginal microbiota are \textit{L. crispatus}, \textit{L. jensenii}, and \textit{L. gasseri}, followed by \textit{L. iners}, \textit{L. saliva varius}, and \textit{L. vaginalis} and to a lesser extent by \textit{L. rhamnosus}, \textit{L. casei}, and \textit{L. plantarum}. In a smaller percentage of women, other bacteria (\textit{Atopobium}) are predominant and are responsible for the microbiota balance, involving the production of antimicrobial substances (e.g., organic acids, hydrogen peroxide, surfactants, or bacteriocins) [6].

Although it is not entirely clear whether the reduction or disappearance of these protective organisms, mainly lactobacilli, is the cause or the effect of the proliferation of other pathogenic microorganisms, we now know that the disruption of the balance of the indigenous microbiota is the pathophysiological basis of vaginitis and vaginosis [7].

As we have discussed, one of the factors that regulate microbiota balance is the pH of the vagina, which is hostile to invasion by other germs when it is acid and thwarts the growth of lactobacilli when it is alkaline. Thus, \textit{Gardnerella} and \textit{Trichomonas vaginalis} are some of the opportunistic pathogens isolated in most cases of vaginitis, displaying a potent enzymatic activity that raises the pH, which favors their own expansion and inhibits the growth of lactobacilli. The same pathophysiological reasoning applies to infections caused by other opportunistic pathogens such as \textit{Candida} spp. or those of the urinary or digestive tract [8].

Similarly, the role of estrogens is relevant to the maintenance of vaginal microbiota, as these hormones regulate vaginal tropism and the composition of its exudate, which is rich in glycogen and other monosaccharides that cause the pH to become acidic, by being metabolized by lactobacilli. Before puberty, the vaginal microbiota is composed of microorganisms from the skin and gastrointestinal tract and is colonized by lactobacilli or other protective species when estrogens begin to exert their effects on the vagina. The parallel between estrogen levels and the vaginal microbiota composition explains why the lactobacilli density is greater in the first phase of the cycle and descends to lower levels during menstruation, when alkalinization of the vaginal microbial habitat occurs due to bleeding and the “drag” effect of hygienic products. In an analogous manner, during intercourse, apart from introducing other germs, semen also increases the vaginal pH, temporarily modifying the microbiota [9].

Furthermore, postmenopausal hypoestrogenism causes thinning of the vaginal epithelium, and there is a smaller contribution of glycogen; consequently, the lactobacilli population is reduced, and the pH rises, favoring colonization by other opportunistic microorganisms. While the microbiota of these women change to consist of intestinal and skin bacteria, as occurred during childhood, almost one-half of these women retain a substantial population of lactobacilli, particularly if they use any type of estrogen treatment [10,11].

3. Atrophic vaginitis

The vagina is the organ with the highest expression of estrogen receptors, which explains why the postmenopausal depletion of this hormone causes progressive hypotrophism, and why this process is often accompanied by some discomfort. The pathognomonic, clinical picture of this period is atrophic vaginitis (AV) (also called vaginal or urogenital atrophy), and unlike other symptoms of menopause that tend to diminish or disappear with the passage of time, AV worsens with age and compromises sexuality and the quality of life of the sufferer. AV affects up to 40% of postmenopausal women, although only a small percentage seek medical attention [12].

In AV, thinning of the mucous membranes of the genital area is observed, with loss of vaginal roughness and elasticity, as well as decreased blood flow, sensory perception, and responsiveness to sexual stimulation. All these factors combined cause itching, dryness, bleeding, vaginal discharge, dyspareunia, inflammation, and urinary symptoms (e.g., dysuria and incontinence), as well as microbiota composition changes that predispose to infection [13]. The reduction of collagen secondary to hypoestrogenism affects the support mechanisms of the pelvic floor and the occurrence of genital prolapsed [14].

Although the diagnosis of AV is confirmed by cytology, it is readily detected during inspection of the external genitalia and vagina by the lack of pubic hair; decreased elasticity, turgor, and moisture of the vagina; scratch marks; thinning of the labia majora, and disappearance of the labia minora and clitoral hood. Sometimes tissue appears prominently in the urethral meatus (urethral caruncle), in addition to polyps and urethral prolapse. Therefore, it can be argued that symptoms of AV are common and can adversely affect quality of life.

Recently a questionnaire for measuring vulvovaginal symptoms in postmenopausal women has been developed: the Vulvovaginal Symptoms Questionnaire is a 21-item written questionnaire with four scales: symptoms, emotions, life impact, and sexual impact [15].

4. Treatment of AV

Conventionally, to relieve the symptoms of AV or dyspareunia, it is recommended to begin treatment with lubricant/moisturizer creams, using topical estrogen therapy only when lubricants provide no relief or do not meet the expectations of the patient, reserving systemic hormonal therapy (HT) for women with other menopausal symptoms [16,17]. However, between 10 and 20% of HT users complain of vaginal dryness [18]. It is also recommended to maintain sexual activity or the use of vaginal dilators because in both cases, the vaginal blood flow is increased, improving the elasticity and lubrication [19].

In addition to other advantages for overall health, it is recommended to quit smoking because this practice worsens vaginal health by reducing the blood perfusion and the bioavailability of estrogens [20].

5. Topical estrogen therapy (TET)

TET is the most effective measure for relieving symptoms arising from AV by normalizing the pH, enhancing vascularization/lubrication, and improving the sexual response. The TETs that are available in our setting are listed in Table 1. In 2012, an EMAS clinical guide stated that the effectiveness of these TETs is similar regardless of the application form (creams, pessaries, ring or tablet) [21]. This guide updates the Cochrane review of 2006 [22] and adds recommendations on TETs use in breast cancer survivors.
Although it has been suggested that absorption is greatest during the first days of application, precisely because of the atrophy, sensitive analytical methods have not demonstrated increased plasma levels of estrogen with ultra-low-dose of TETs [23].

As defined by other societies, we accept that low dose is less than 50 mcg per application. These formulations exhibit minimal systemic effects, and the plasma estrogen levels are maintained in the normal postmenopausal range [24,25]. Regarding safety, some women have experienced irritation, itching, or increased vaginal discharge, but this treatment has not been associated with hyperplasia or endometrial adenocarcinoma; therefore, following the EMAS recommendations, it is not necessary to control the endometrium in these patients, nor is it advisable to use progestogens [26]. Moreover, there are no data available reporting an increased risk of thrombosis or recurrent breast cancer [27]. With regard to duration of use, AV is a chronic condition and will recur on cessation of treatment, so it is advisable to individualize and would be prudent an annual review [22].

6. Promestriene

Among the different TET formulations available in Europe, estriol semisolid formulations or promestriene are the most used. Promestriene is a diethyl-ether of estradiol, an effective TET without systemic estrogenic effects available as a vaginal cream or ovules.

In a pilot study, vaginal promestriene was tested in 17 gynecological cancer patients who suffered from severe vaginal dryness and dyspareunia. The level of circulating estrone sulfate was not significantly affected by vaginal promestriene treatment overall, but a wide range of levels was noted pre and post treatment in individual patients [28].

In clinical studies was show to be devoid of systemic estrogenic effects at therapeutic dose administered for up to 4–6 months. Furthermore, dosages of 2–9 times those recommended administered for shorter periods (single dose 2 weeks) did not produce significant changes in estradiol or gonadotrophic hormones [29].

A recent review about its long-term shows its effectiveness to relieve AV and its very rarely side effects. Thus, it could be a first-line option for those who necessitate a minimal or ideally no vaginal absorption, particularly in symptomatic cancer patients. Thus, to further improve promestriene safety in estrogen-sensitive cancer patients, a very low dose is used from the beginning, which could reduce its already minimal vaginal absorption [28].

7. Ospemifene

Ospemifene is a selective estrogen receptor modulator (SERM) with estrogen agonist action in the vagina. Although it has not yet been approved by the European Medicines Agency, the FDA approved it in February 2013 for the treatment of moderate-to-severe dyspareunia secondary to AV. In randomized clinical trials (RCT), compared with placebo, ospemifene has improved the maturation and the pH of the vaginal mucosa, thus reducing dyspareunia. Although it has a slight effect on the endometrium, and a small increase in its thickness (between 0.4 and 0.7 mm at 12 weeks) has been noticed, there has been no atypical hyperplasia or adenocarcinoma in studies after 1 year of use; therefore, it is not recommended to add progestogens, but it is advised to monitor the endometrium in long-term users and to evaluate any vaginal bleeding. The most frequently observed side effects were flushing (7.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.3%), and muscle cramps (3.2% vs. 0.9%) [28,29]. A recent 52-week study confirms tolerance and efficacy of ospemifene in the treatment of AV previously reported in short- and long-term studies [30].

Although preclinical data and those from animal experiments suggest that ospemifene has a neutral or inhibitory effect on mammary carcinogenesis, further studies are necessary to evaluate its safety in women with breast cancer. No thrombotic events have been reported either, although more data are necessary to rule out this complication that occurs with other SERMs. However, ospemifene use is contraindicated in women with breast cancer, endometrial cancer, venous thromboembolism, stroke, or myocardial infarction [30–33].

8. Natural products for vaginal health

Traditionally, natural products have been used for vaginal health, but we do not have a sufficient number of RCTs to demonstrate their effectiveness. Essential oils, probiotics, and propolis have been used to prevent vaginitis, whereas lipid lubricants, pectins, medicinal plant extracts with phytoestrogenic activities, and other extracts with moisturizing effects have been used for AV [34].

- **Essential oils** and their components are complex and volatile mixtures from aromatic plants, which are used to prevent genitourinary infections, due to the presence of phenolic groups (e.g., thymol and carvacrol) or hydroxyl groups (e.g., terpinen-4-ol, geraniol, linalool, and menthol), all with antimicrobial effects. Most formulations contain thyme (Thymus vulgaris), which is rich in thymol and carvacrol; sage (Salvia officinalis), which is rich in linalool; and tea tree oil (Melaleuca alternifolia), which contains terpinen-4-ol. All of these essential oils have data supporting their antimicrobial effects and thus may be recommended as an adjunct in the treatment of infectious vaginitis [35,36].

- **Probiotics**: Despite the limited evidence available for postmenopause, we recommend using probiotics with lactobacilli (e.g., L. gasseri and L. rhamnosus) as an adjunct for treating recurrences of genitourinary infections. Except in immunosuppressed patients, probiotics with lactobacillus have no pathogenic effects [37–39].

- **Lipid lubricants** (e.g., olive oil, evening primrose oil, burdock oil, and rosehip oil): These preparations are rich in unsaturated fatty acids and contribute to improved hydration or vaginal epithelial repair, without causing side effects or changing the vaginal microbiota [40].

- **Pectins** are naturally occurring hydrocarbon products with high hydrophilic capacity and no side effects [41].

- **Phytoestrogens** are nonsteroidal compounds of plant origin, which are capable of binding to estrogen receptors, preferably β receptors. Isoflavones are prominent (present in soybean and red clover seeds) and improve dryness and AV when administered topically alone or combined with other compounds (e.g., hyaluronic acid, liposomes, and vitamin E) [42,19].

- Other natural, topical extracts with moisturizing effects are marigold, purple loosestrife, helichrysum, and chamomile.
9. Management of AV in patients with hormone-dependent cancers

Secondary hypoestrogenism caused by cancer treatments in patients with breast or endometrial cancer causes greater intensity, frequency, and duration of AV symptoms [43]. Although few studies concerning these problems exist, it is believed that maintaining the vaginal lubrication and pH is the key to preventing and alleviating these conditions [44].

The recommended first step is the use of estrogen-free vaginal moisturizers [21,45]. The most commonly used are gels of polyacrylphil polymers, pectin, or hyaluronic acid, which improve moisture, elasticity, and pH even at similar levels to those obtained with TETs [46].

Although we have no data on the safety of TETs, they may be hazardous in these patients because of their possible absorption and theoretical effect on hormone-sensitive cells. The 10-µg tablets or 7.5-µg rings are much less absorbed, although their safety has not been established in these patients. Similarly, vaginal estradiol does not increase the plasma estrogen levels, although it most likely presents certain systemic effects, specifically, decreasing FSH and LH [47].

Other weak TETs with no systemic absorption (e.g., promestriene) and isoflavones have demonstrated their effectiveness on AV without causing endometrium thickening and without being detected in plasma or altering gonadotropins, although their safety is unknown in these patients [48].

In a small RCT with topical oxytocin, AV symptoms were improved [49]. Others RCT with gel or olive oil reduce improved the AV symptoms in patients with breast cancer [40,50].

As we have generically recommended, the maintenance of sexual activity, self-stimulation, the use of dilators, and the practice of exercises to strengthen the pelvic floor are associated with reduced AV symptoms [44].

10. Recommendations

10.1. Atrophic vaginitis

- Regular sexual activity helps to maintain vaginal health.
- It is recommended to quit smoking because of the health benefits and because smoking participates in the effects of hypoestrogenism.
- It is advisable to initiate treatment with vaginal moisturizers, complemented with the use of lubricants during intercourse (Grade 2B).
- In women for whom vaginal moisturizers and lubricants are insufficient and who show no other symptoms of menopause, TET use is recommended rather than systemic HT (Grade 1B).
- In women with associated vasomotor symptoms, we recommend low-dose systemic HT.
- The formulations for TET administration have the same efficacy for treating AV. These formulations should be administered at the lowest effective dose, for the necessary period required to control the symptoms, and in the most convenient formulation for each woman.
- Women who use low-dose TET do not require therapy with progestins (Grade 2C).
- We suggest ospemifene instead of TET in women with difficulty of application (e.g., in severe arthritis, obesity, or vulvodynia) or who would prefer a route of administration other than vaginal (Grade 2B). The safety of ospemifene has not been demonstrated in women with a history or risk of breast cancer or thrombosis.

10.2. Behavior of women with estrogen-dependent cancer when dealing with AV symptoms

- Assess the severity of symptoms and their impact on sexuality and the quality of life and exclude other causes of vaginitis (e.g., infections, irritants, and allergies).
- We recommend quitting smoking due to its anti-oestrogenic effect.
- It is advisable to practice pelvic floor exercises.
- Treat any underlying psychological factors (e.g., anxiety or depression) that may worsen clinical symptoms.
- It is advisable to maintain sexual activity because it improves the vaginal circulation and elasticity.
- The first-line treatment of AV symptoms or dyspareunia in women with breast cancer includes non-hormonal lubricants/moisturizers (Grade 2B).
- For women with breast cancer who present a low risk of recurrence or who are taking tamoxifen, as well as in cases where moisturizers/lubricants are not effective, we recommend TETs at extremely low doses or with no absorption, as promestriene, with a prior analysis of the risk/benefit ratio and having treatment consent from the patient and her oncologist (Grade 2B).
- We do not recommend any TETs in women treated with aromatase inhibitors (Grade 2C).
- The use of vaginal testosterone therapy in women with breast cancer is under investigation.

Contributors

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