CLIMACTERIC 2010; Early Online, 1–14

Recommendations for the management of postmenopausal vaginal atrophy

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Key words: POSTMENOPAUSE, VAGINAL HEALTH, VAGINAL ATROPHY, UROGENITAL ATROPHY, MANAGEMENT, RECOMMENDATIONS

ABSTRACT

Unlike hot flushes and night sweats which resolve spontaneously in time, atrophic symptoms affecting the vagina and lower urinary tract are often progressive and frequently require treatment. The prevalence of vaginal dryness increases as a woman advances through the postmenopausal years, causing itching, burning and dyspareunia, and sexual activity is often compromised. But, despite the various safe and effective options, only a minority (about 25% in the Western world and probably considerably less in other areas) will seek medical help. Some of this reluctance is due to the adverse publicity for hormone replacement therapy (HRT) over recent years that has suggested an increased risk of breast cancer, heart disease and stroke. But, regardless of whether these scares are justified, local treatment of vaginal atrophy is not associated with these possible risks of systemic HRT. Other reasons for the continued suffering in silence may be cultural and an understandable reluctance to discuss such matters, particularly with a male doctor, but the medical profession must also take much of the blame for failing to enquire of all postmenopausal women about the possibility of vaginal atrophic symptoms.

Vaginal dryness can be helped by simple lubricants but the best and most logical treatment for urogenital atrophy is to use local estrogen. This is safe, effective and with few contraindications. It is hoped that these guidelines and recommendations, produced to coincide with World Menopause Day 2010, will help to highlight this major cause of distress and reduced quality of life and will encourage women and their medical advisers all over the world to seek and provide help.

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INTRODUCTION

The female menopause and accompanying ovarian failure result in many changes affecting almost every organ system in the body. While hot flushes and night sweats are universally recognized as the most common features in the Western world, other symptoms may be more prevalent elsewhere. The urogenital tract is particularly sensitive to the decline in estrogen and about half of all postmenopausal women will experience symptoms related to urogenital atrophy, affecting sexual function and quality of life.

Vaginal atrophy becomes clinically apparent 4–5 years after the menopause and objective changes as well as subjective complaints are present in 25–50% of all postmenopausal women.

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RECOMMENDATIONS

DOI: 10.3109/13697137.2010.522875

VAGINAL PHYSIOLOGY RELATED TO ESTROGEN DEFICIENCY

Serum estradiol levels in the premenopausal woman range from 147 to 1468 pmol/l (40–400 pg/ml) and fall to less than 73 pmol/l (20 pg/ml) post menopause[1]. This change in circulating estrogens is reflected in vaginal physiology and symptoms (Figure 1). The vagina is an accessible and sensitive biological indicator of the declining and low circulating estrogen levels in postmenopausal women. The loss of ovarian estrogen production is associated with vaginal atrophy, a progressive condition, but the vaginal response to estrogen therapy is rapid and sustained.

Sexually active postmenopausal women are reported to have fewer symptoms and less physical evidence of vaginal atrophy and slightly higher serum levels of androgens[2].

The loss of vaginal rugal folds and the thinning of the epithelium become apparent 2–3 years postmenopause and the onset of these physical findings is variable. The loss of rugosity is due to the breakdown of the collagen support of the vaginal epithelium. Collagen turnover is increased in aging women without hormone therapy, and these changes may be of importance in vaginal prolapse[3–5].

Dryness of the vagina occurs early in the postmenopausal period and is most apparent in sexually active women in whom it is associated with pain or dyspareunia with intercourse[1,6]. Postmenopausal women have a total estimated volume of vaginal fluid of 0.0825 g per 15-min collection, compared to 0.214 g in fertile women. The majority of vaginal fluid in postmenopausal women appears to be secreted from the vaginal epithelium[7].

The vaginal pH in premenopausal women is less than 4.5, which reflects the production of lactic acid by lactobacillus organisms. The vaginal pH increases to over 6 in postmenopausal women, due to a reduction in the colonization of the vagina by lactobacillus, secondary to a decrease in superficial cells and hence decreased glycogen, and the vaginal epithelium is thinner[1,8]. For these reasons, the postmenopausal vagina is at risk of infections and inflammation, though the evidence for an increased incidence of vaginal infections is limited[8–10]. The female urethra and urinary bladder are associated with the developing vaginal anlage in the embryo. The urethra has high levels of estrogen receptors because it is derived from the same embryonic origin as the distal vagina[1]. Atrophy of the urethra with a relative increase in urethral epithelial transitional cells, and a corresponding decrease in intermediate and superficial

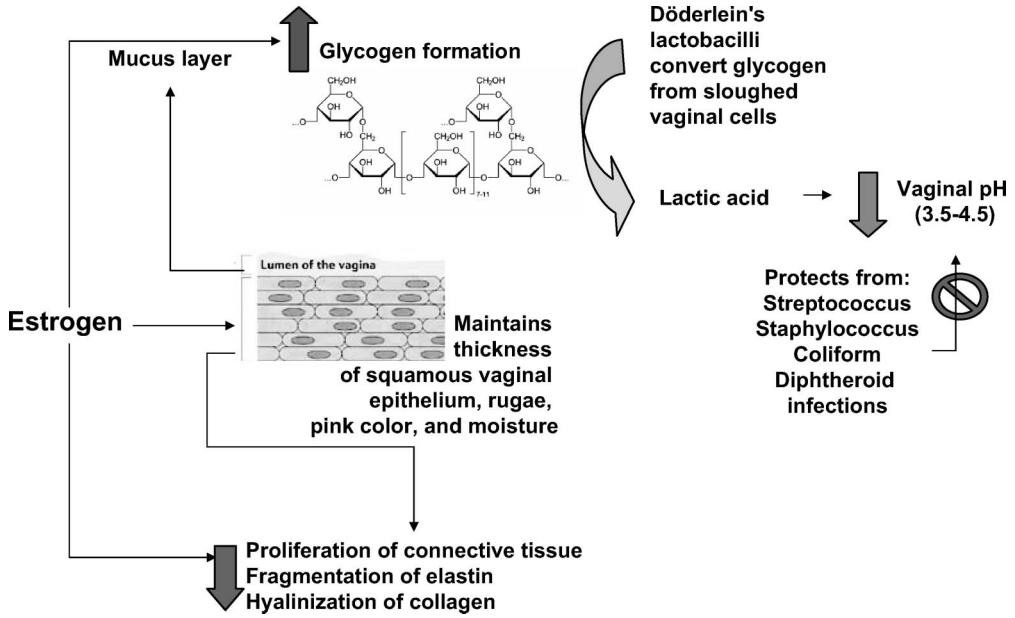

Figure 1 Schematic depiction of the effects of estrogen on the vaginal epithelium. Estrogen promotes glycogen formation in the squamous epithelium. Döderlein's lactobacilli, part of the normal vaginal flora, depend on the glycogen as a source of fuel and convert the glycogen into lactic acid, thus keeping the vaginal pH acidic. The acidic pH serves to reduce pathogen infestation. Estrogen also helps maintain the thickness of the multi-layered squamous vaginal epithelium, which imparts its normal pink color, rugae and moisture. Without estrogen present, connective tissue proliferation increases, elastin becomes fragmented, and collagen is subject to hyalinization. Cartoon created from information reviewed by Ballagh[65] and Bachmann and Nevadunsky[9]. Reproduced with permission from Archer DF. Efficacy and tolerability of local estrogen therapy for urogenital atrophy. *Menopause* 2010;17:194–203

squamous cells, occurs after menopause[11]. The smooth muscle in the lower urogenital tract atrophies gradually as a result of aging, with an abrupt decline during the menopausal transition. The abrupt change with the onset of menopause affects the superficial muscle layers of the trigone, the proximal and distal urethra and vagina, and the lamina propria of the trigone and proximal urethra[12].

- The decline in circulating estrogen associated with the menopausal transition is closely correlated with: decreased vaginal lactobacillus, increased pH, altered epithelial morphology, reduced vascular flow and reduced fluid secretion in the vagina.

SEXUAL FUNCTION, HEALTH OF THE URINARY TRACT, AND QUALITY OF LIFE

Vaginal health plays a crucial role for sexual health, and estrogen modulates the hemodynamic process involved in the sexual response cycle. When vaginal atrophy is evident, menopausal women may complain of vaginal dryness and, when they are sexually active, may experience sexual pain disorders, e.g. dyspareunia. During coital and non-coital activity, women may report changes in genital sensation, vasocongestion and lubrication, which are likely to cause other sexual symptoms, such as reduced sexual desire, poor arousal and orgasm, and impaired sexual satisfaction. In addition, the health of the urinary tract is strongly interrelated with symptoms of the vaginal tract, especially in the absence of estrogen. Urinary symptoms, such as frequency, urgency, nocturia, dysuria, incontinence and postcoital infection, are more often reported when some vaginal atrophy is present[13].

Women experiencing sexual and urinary symptoms as a consequence of vaginal atrophy should be diagnosed and treated without delay in order to avoid a cascade of events which do not resolve spontaneously. However, the experience of sexual symptoms is unique to each woman and is influenced not only by age and the menopause but also by a complex interplay of personal factors affecting the quality of life and the relationship of the couple[14].

It is not only the hormonal changes but also the loss of reproductive function that lead to a redefinition of the feminine role[15]. This results in varying perceptions of body image and self-esteem. In addition, the experience of climacteric symptoms and complaints may negatively affect the sense of physical and mental well-being, together with contextual changes in relationship, family and social life. The partner's physical, mental and sexual health and the presence of a satisfactory relationship may determine the level of distress associated with sexual symptoms and the motivation to consult a physician for conditions associated with vaginal atrophy.

- Vaginal atrophy is one of the most important determinants of sexual function and urogenital health, with a significant impact on the quality of life.

GLOBAL VARIATIONS IN ATTITUDE TO VAGINAL ATROPHY

As most of the data presented are from the Western world (predominantly, North America, Australia and the UK), in order to provide a more global perspective, relevant data from other regions are presented in this section.

Europe

The vaginal health of postmenopausal European women has been studied as part of a large European survey to investigate opinions, attitudes and perceptions of postmenopausal women on the menopause in general and treatment of menopause symptoms[16]. The women included were between 45 and 59 years of age ($n = 4201$). The prevalence of vaginal pain/dryness over the past 5 years was 29%, varying from 19% in Germany to 40% in Spain. A UK survey of women aged 55–85 years ($n = 2045$) found that, in response to a question on vaginal dryness, 42% of women did not seek treatment as it was not important, 36% sought non-prescription preparations, 13% considered it was 'something to put up with', and 10% were too embarrassed to discuss the problem with their doctors[17].

In another European survey[18], mental and sexual well-being interfered with self-worth and enjoyment of life, as did vaginal discomfort. In this survey, the data suggested that European middle-aged women experience the menopause as a process that brings about mood and sexual changes that may impair their sexual life.

- European women deserve better information and education on the implications of vaginal atrophy on their quality of life.

Asia

It is well acknowledged that Asian women are more shy in expressing their opinions and needs compared to Western women. This is particularly true with respect to problems related to genital organs and sexual function. Vaginal atrophy is one of the inevitable changes among postmenopausal women and, as a result, causes frequent vaginitis and sexual dysfunction. A recent multinational survey[19] identified that most postmenopausal Asian women do not complain of vaginal problems to their doctors, although they suffer from sexual dysfunction. In contrast, when postmenopausal women were asked about the reasons for seeking treatment, 17% and 13% indicated reduced sex drive and vaginal pain, respectively. These numbers are

higher than those in a European survey[16], which indicated 7% and 8%, respectively. In the Asian survey, 71% of women had reduced sexual functioning and/or libido and 75% of women had discomfort during sex; 68% and 64% were satisfied with their current sexual relationship and sexual functioning, respectively; 63% indicated that they did not seek treatment as they thought vaginal problems were natural after menopause. The majority of women believed that improving vaginal health may improve their quality of life and would have liked to discuss the problem if their doctors had initiated the discussion.

- Health-care providers in Asia should appreciate women's perspectives and needs in vaginal health.

India

In India, psychological issues and a negative attitude towards vaginal atrophy are quite prevalent. Problems associated with vaginal atrophy, especially sexual dysfunction, are under-reported by women with a low level of education and ignorance with regard to menopausal symptoms, combined with a strong self-conceived notion about their problems. Even the educated urban women are culturally inhibited. They do not admit to these issues and fail to seek help with their sexual problems. However, these women, while hesitant in discussing their sexual problems, are relieved if their doctor initiates a discussion and offers help.

As vaginal atrophy is not an inevitable consequence of menopause, early diagnosis and intervention can prevent atrophic vaginitis. In India, estrogen replacement therapy is offered as appropriate to the individual, in addition to alternative strategies. Women are encouraged to improve their personal hygiene for better vaginal health and are advised to remain sexually active as an important non-pharmacological option for preventing vaginal atrophy and shrinkage. Additionally, this helps to improve psychological and physical well-being, both in rural and urban groups, leading towards a positive attitude.

- Indian women need greater awareness of the implications of vaginal atrophy and the benefits of early treatment.

Latin America

In Latin America, there is a negative cultural attitude towards menopause as it is associated with aging and loss of femininity. Women frequently express concern on how menopause might change their sexual life and, although they might seek help for this, they show poor adherence to lubricants or local estrogen treatment.

The Collaborative Group for Research of the Climacteric in Latin America (REDLINC) analyzed the Female Sexual Function Index (FSFI) in 7243 women aged 40–59 years in 11 Latin American countries and described a high prevalence of sexual dysfunction (56.8%). The FSFI evaluates diverse domains of sexual function: desire, arousal, orgasm, pain, lubrication and satisfaction. The most important risk factor for sexual dysfunction in the population studied was vaginal dryness (odds ratio 3.86, 95% confidence interval 3.37–4.43)[20]. A study in native Bolivian Movima women showed that symptoms associated with genital atrophy were amongst the main menopausal complaints: dyspareunia (40%), genital itching (40.8%) and loss of libido (51%). Hot flushes were prevalent in 45% of the women studied[21].

- In Latin American women, vaginal atrophy is an important cause of menopausal symptomatology, impairing sexual function and quality of life.

Sub-Saharan Africa

Any discussion of menopausal health in Africa should be seen in context of the 2010 population statistics of the Republic of South Africa[22], probably the most developed country in the region. The total population of 50 million people includes only 2 million women above the age of 60 years; whereas the age of menopause for African women in South Africa is comparable to Europeans at about 50 years[23], the life expectancy at birth is only 55 years. The overall HIV/AIDS prevalence rate is 10.5%. In terms of health priorities, this may be an explanation for the lack of peer-reviewed articles on the subject of menopause in general and vaginal health in particular in black African women.

Although the myths and traditions regarding the menopause in African women are largely unknown and expected to differ along ethnic lines, there is no reason to believe that the symptoms of menopause, including vaginal atrophy, should be significantly different. The age of menopause may be earlier in other parts of Africa as a result of multiple parity in a short period of time[24]. Perceptions of menopause may differ between a welcome end to fertility with an elevated social status, to despair for nulliparous, infertile women. No specific reference could be found to the attitude of African women to oral hormone replacement therapy (HRT) or vaginal application of estrogen for the treatment of postmenopausal vaginal atrophy. Recent experience regarding the use of vaginal microbiocides for the prevention of sexually transmitted disease in younger African women does not reveal any significant cultural opposition to the use of vaginally applied gels.

- Practitioners should not neglect the needs of Sub-Saharan menopausal women and especially vaginal atrophy.

- Research in this area should be a priority but needs to take into account the multi-ethnic composition of this vast area.
- With reduced life expectancy, fewer women will experience postmenopausal vaginal atrophy.

Middle East

Cultural and religious taboos in the Middle East regarding sexual life and related issues inhibit some women, especially those of lower socioeconomic class, from discussing vaginal dryness and sexuality issues with health-care providers. It is very uncommon to have a postmenopausal woman attending an outpatient clinic complaining of dyspareunia or vaginal dryness.

The condition is usually diagnosed when a postmenopausal woman attends the gynecologic clinic for some other complaint, such as urinary stress incontinence or postmenopausal bleeding. At the conclusion of her examination, it is usually possible to start opening up the issue of postmenopausal genital atrophy with these women and most of them respond in a satisfactory manner to questionnaires about their sexual and vaginal health.

Provided that there is no contraindication, they are usually offered short-term local hormone therapy as a treatment, with regular follow-up, but only women of medium/high socioeconomic class are able to continue and maintain this relatively expensive treatment.

PRETREATMENT EVALUATION

Symptoms

Although a clear mechanism for delineation between symptoms of estrogen deficiency and urogenital atrophy and symptoms of aging does not currently exist, an attempt at an 'all inclusive' list of vulvar, vaginal, and urinary tract symptoms is given in Table 1. The most common symptoms of vaginal atrophy include dryness (estimated at 75%), dyspareunia (estimated at 38%), and vaginal itching, discharge and pain (estimated at 15%). While the relative frequency of the two most common symptoms (dyspareunia and dryness) may change, depending upon the frequency of penetrative vaginal intercourse in the sample under study, these two symptoms are usually the two most common. Dyspareunia can adversely affect a postmenopausal woman's sexual quality of life or intensify pre-existing sexual disorders[25]. It should be noted that vaginal dryness in this context is not necessarily associated with sexual activity. It is a symptom unto itself (i.e. the sense that there is 'dryness, even sandpaper between my legs'). Despite the rather extraordinary prevalence and diversity of urogenital atrophy-associated symptoms (Table 1), only about 25% of women suffering from them actually volunteer the information to their health-care

Table 1 Estrogen deficiency-related urogenital symptoms, physiologic and anatomic changes

Vulva
- Loss of the labial fat pad
- Shrinkage and loss of definition of the labia majora and labia minora
- Shortening of prepuce and excessive exposure of clitoris
- Susceptibility to chemical and physical irritants, mechanical injuries and infections
- Pubic hair loss

Vagina
- Dryness and insufficient moistness
- Diminished blood flow
- Dyspareunia
- Itching
- Burning sensation
- Soreness
- Loss of elasticity
- Thinning of the vaginal tissue and alteration of keratinization
- Mucosal defects including petechiae, microfissures, ulceration and inflammation
- Shortening, fibrosis, obliteration of vaginal vault and/or narrowing of vaginal entrance
- Smoothing of fornix, flattening of vaginal rugae
- Susceptibility to mechanical injuries
- Susceptibility to mechanical injuries
- Adverse impact on healing of mechanical and postoperative wounds
- Abnormal vaginal maturation index: decreased percentage of superficial layer cells, increased percentage of parabasal cells
- Decreased glycogen content in vaginal epithelial cells
- Expelling of facultative flora of vagina containing pathogenic microorganisms
- Increase of vaginal pH above 5.0
- Leukorrhea and/or foul secretion
- Infiltration of the submucosal layer by lymphocytes and plasma cells

Urinary bladder and urethra
- Increased urinary bladder retention after micturition
- Decreased storage capacity of urinary bladder
- Decrease of maximal pressure of urinary bladder detrusor muscle contraction during urination
- Decreased sensitivity threshold of urinary bladder to extension (first feeling of urgency)
- Decreased urethral closure pressure
- Decreased perfusion of periurethral venous plexus
- Decreased urethral flow of urine
- Abnormal urethral maturation index: decreased percentage of superficial layer cells, increased percentage of parabasal cells
- Symptoms of dysuria, nocturia and urgency
- Urinary incontinence
- Recurrent urinary tract infections
- Disorders of collagen biosynthesis within periurethral connective tissue

professionals, and 70% say that their health-care professional only rarely or never asks about problems like vaginal dryness[26]. Instead, it would appear that patients and practitioners alike attribute the symptoms to a natural and unavoidable part of the aging process.

Differential diagnosis

While many vulvar dystrophies, infections and malignancies may share some of the symptoms already mentioned or listed in Table 1, a review of these diagnoses is beyond the scope of this document. Other non-menopausal conditions associated with a hypoestrogenic state can also share these symptoms. A short list of these non-menopausal, but estrogen deficiency states and the treatments causing them includes: long-term exclusive breast feeding, hormonal therapies like selective estrogen receptor modulators (SERMs), gonadotropin releasing hormone agonists/antagonists, aromatase inhibitors and long-standing high-dose/potency progestogens. Women with diabetes can experience decreased vaginal lubrication and associated vaginal dryness, probably related to diabetic neuropathy and microvascular disease.

Physical signs

With declining estrogen, the mucosa of the cervix, the epithelium of the vagina and vulva thin and become susceptible to injury (Figure 2). The vaginal rugae diminish, leading to a smoother appearing vaginal wall which is accompanied by diminished blood flow. Together, these changes result in a pale appearance which may contain small petechiae and/or other signs of inflammation. While the normal acidity of an estrogenized vagina is usually in the moderately acidic range (normal range of pH 3.5–5.0, favoring lactobacilli), this normal pH increases with falling estrogen concentrations (range of pH 6.0–8.0, favoring pathogenic organisms, including yeast and bacteria, i.e. coliforms). This more alkaline pH leads to a shift in the vaginal flora toward more coliforms and, together with the other atrophic changes, is responsible for increased susceptibility to and frequency of infections and odor[27], as well as traumatic bleeding associated with sexual intercourse or secondary to speculum insertion during routine gynecologic examinations. Both micro- and macroscopic ulcerations can appear in the vaginal epithelium spontaneously or with minor trauma. In patients who are not sexually active or those who engage in penetrative vaginal intercourse only rarely, severe atrophy can result in vaginal narrowing, shortening and even obliteration of the vaginal vault[28]. Such extremes may be more common in vaginal nulliparous women where introital stenosis and insertional dyspareunia are more common.

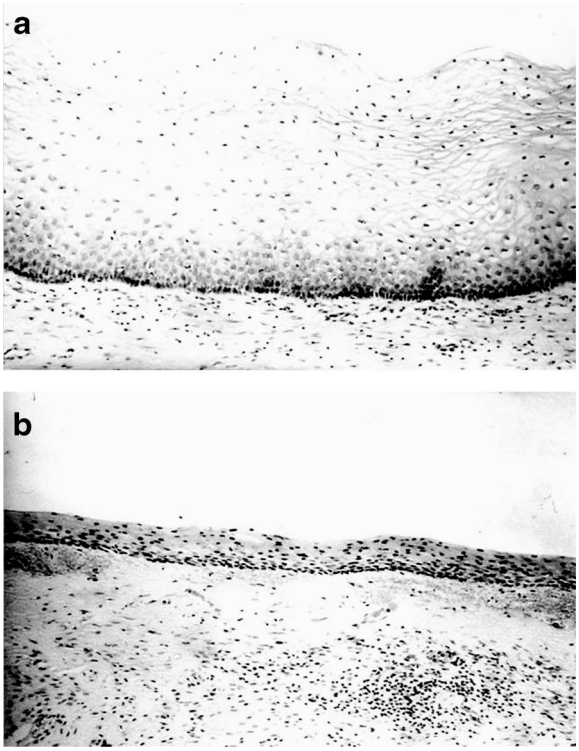

Figure 2 Histological preparations of vagina stained with hematoxylin & eosin (magnification × 10). Premenopause (a), the epithelium is well-estrogenized, multi-layered with a good blood supply, and the superficial cells are rich in glycogen. Postmenopause (b), there is estrogen-deficiency atrophy with marked thinning of the epithelium, the blood supply is reduced and there is a loss of glycogen

Although the physical signs of atrophy in the vulva and vagina are more clearly apparent upon gynecologic examination, estrogen deficiency-related anatomic and physiologic changes within the urinary tract may cause or accentuate dysfunction during micturition, including increased frequency, dysuria, nocturia, as well as urge, stress and mixed forms of urinary incontinence[28]. Estrogen deficiency causes atrophic changes in the bladder trigone, decreased tension of muscular and connective structures of the urogenital diaphragm, disorders of collagen metabolism and decreased activity of the α-adrenergic system innervating both the bladder neck and urethral sphincter[29]. The urethral mucosa, also estrogen-sensitive, becomes thinner along with its submucosal vascular plexus. Taken together, these changes contribute to a decrease in intraurethral pressure, an important mechanism facilitating urinary continence, thereby allowing urine loss. The same pH and bacterial changes in the vagina (noted above) can impact on the lower urinary tract, increasing the risk for acute and recurrent urethritis and cystitis.

Diagnosis

Although most practitioners diagnose vulvovaginal atrophy using their clinical judgment (combining the patient's symptoms, clinical situation and visual inspection), researchers and regulators have increasingly insisted upon more objective and reproducible measures, including patient-reported outcomes like the severity of the patient's most bothersome symptom[30,31]. Historically, the two primary objective measures for both the diagnosis and the assessment of treatment efficacy have been the vaginal pH, obtained using litmus paper or a similar technology, and the vaginal maturation index (VMI). The VMI is a calculation of the relative percentages of superficial cells compared to intermediate and parabasal cells.

Currently, most systematic investigations and product developments include a patient-reported outcome as part of the evaluation. The US Food and Drug Administration requires this approach. Symptomatic patients select which of their symptoms is most bothersome (vaginal dryness, dyspareunia, vaginal irritation, dysuria, vaginal soreness, postcoital bleeding) and rates its severity on a three- or four-point scale. Documented therapeutic benefit consists of a statistically significant improvement in three co-primary endpoints: vaginal pH, VMI and most bothersome symptom compared to placebo-treated individuals[31].

- The symptoms of vulvovaginal atrophy are variable and common.
- Other disease entities and the side-effects of medications may mimic the symptoms of vulvovaginal atrophy.
- The physical signs of vulvovaginal atrophy are: diminished vaginal rugae and reduced blood flow leading to a pale appearance; a change in vaginal pH from the moderately acidic range (pH 3.5–5.0) to a neutral range (pH 6.0–8.0), and a shift in the vaginal maturation index.
- Health-care professionals are not asking postmenopausal women about problems such as vaginal dryness.

How to discuss vaginal atrophy with postmenopausal women

While many women embraced the freedoms of the sexual revolution in their youth, paradoxically, with age, some become embarrassed and reluctant to discuss vaginal symptoms. Between 10 and 40% of postmenopausal women report symptoms of vaginal atrophy, whereas in the Western world only one in four seeks medical help[32]. As opposed to knowledge about hot flushes, women may not be fully aware of the link between vaginal discomfort and declining estrogen levels. Some women erroneously attribute vaginal dryness during the perimenopausal transition to infrequent intercourse, loss of interest or difficulties in the relationship, or just another vagary of aging. Thus, the impetus is upon you to raise the topic of vaginal health. Most women express relief and respond positively when you initiate the conversation.

One approach might be to comment, 'Some women notice that they experience vaginal dryness during this time of life. I wonder if you are having any discomfort with intercourse?'. Be sensitive to the presence (or absence) of an able sexual partner and whether she is distressed by her discomfort. Is she bothered by vaginal itching, burning, or discharge? Include questions about vaginal infections, trauma, recurrent urinary tract infections, and attempts at symptom relief. Depending upon the specific population you serve, modify your approach to reflect the woman's culture, nomenclature, and degree of modesty. If she demurs during the history, ask again after the physical examination, especially if you see signs of vaginal atrophy.

Reassure your patient that vaginal atrophy is reversible. The old adage of becoming 'all dried up' after menopause indeed still crosses some women's minds. Counsel her that vaginal dryness/atrophy is not a temporary discomfort similar to hot flushes which usually resolves with time; relief requires specific treatment.

In spite of recent reassurances to the contrary, many women still fear systemic estrogen therapy. Emphasize the option to treat symptoms vaginally[33]. Reassure her about the safety of vaginal preparations if systemic estrogens are contraindicated because of a history of cardiovascular events (heart attack, stroke, or venous thromboembolic event). For a woman with breast cancer, confirm with her oncologist that your recommendations comply with her cancer treatment strategy.

Explore your patient's comfort level with the available options of vaginal estrogen. Anticipate how soon she will start to experience symptom relief, and make her aware that long-term therapy will probably be necessary. Discuss titrating estrogen dose and/or frequency of administration after the first weeks of therapy. Caution about the need to report vaginal bleeding and breast tenderness, as these side-effects of systemic estrogen therapy are not anticipated, especially at the lower doses of vaginal estrogen now recommended.

As a final word, instruct your patient about sensible hygiene when handling estrogen products (hand washing after application, safe storage and disposal) and the rare possibility of secondary estrogen exposure of her partner through oral or genital absorption. Advise her that vaginal estrogens should not be used as supplemental lubricants during intercourse, and suggest other options.

Your conversation about vaginal health can do more to enhance your patient's quality of life than you might realize. So remember, just ask!

- Initiate the discussion about vaginal dryness; your patient may be reluctant.
- Consider that relationship/sexual issues may present as vaginal discomfort.
- Remember that women using systemic estrogen therapy can still develop vaginal symptoms.
- Be mindful that some urinary symptoms occur concurrently with vaginal atrophy and also respond positively to vaginal estrogen therapy.
- Encourage women to select a vaginal therapy most comfortable for them.

TREATMENT OF VAGINAL ATROPHY

Rationale for treatment

The positive impact of treatment of vaginal atrophy on a woman's general and sexual quality of life cannot be underestimated[34]. Up to 50% of women will develop urogenital signs and symptoms at some time in their postmenopausal life; the incidence is probably under-reported and therefore underestimated[35,36].

In view of the virtual absence of risks and side-effects of most low-dose vaginal preparations (although long-term data are lacking), a case could be made for not only intervention, when symptoms are established, but also for the prevention of atrophy before symptoms become troublesome. Establishment of this prevention principle globally would require a formal cost-effectiveness analysis and further research.

The principles of treatment in women with established vaginal atrophy are (1) restoration of urogenital physiology, and (2) alleviation of symptoms. These are summarized below.

Restoration of urogenital physiology

Postmenopausal estrogen deficiency results in a progressive decline of the health of the vaginal and lower urinary tract epithelium. The rationale for treating urogenital atrophy is that the physiological state of these tissues is restored to normality. Estrogen therapy lowers vaginal pH, thickens the epithelium, increases blood flow and improves vaginal lubrication.

Alleviation of symptoms

The restoration of urogenital physiology leads to alleviation of many distressing vaginal symptoms such as vaginal dryness, superficial and deep dyspareunia, vulvodynia, vulvovaginal bleeding, inflammation and discharge. Urinary problems such as sensory urgency and urinary tract infections can also be ameliorated.

The evidence base for the complementary, pharmaceutical and hormonal interventions will now be discussed, to show how these principles can be put into day-to-day practice.

Treatment options

Non-hormonal treatment/lubricants

Lubricants and non-hormonal treatments for vaginal atrophy mainly consist of a combination of protectants and thickening agents in a water-soluble base and non-hormonal substances that have a maturation effect on the urogenital epithelium. Lubricants are primarily used to relieve vaginal dryness during intercourse and therefore do not provide a long-term solution. There are some data suggesting that moisturizers and some other substances may have a longer-lasting effect if used consistently. Non-hormonal options are primarily indicated in women wishing to avoid hormonal therapy or in high-risk individuals with a history of hormone-sensitive malignancy such as breast or endometrial cancer. Most of these products are available without prescription over the counter and can be expensive.

Lubricants Lubricants are non-physiological, giving only a very temporary relief of symptoms, often followed by vaginal irritation. Vaseline can break down the latex of condoms.

Moisturizers Moisturizers are hydrophilic, insoluble, cross-linked polymers. They are bio-adhesive in that they attach to mucin and epithelial cells on the vaginal wall, thus retaining water. They are eliminated by epithelial cell turnover. The beneficial effects on symptoms related to vaginal atrophy are mainly through buffering properties which lead to a reduction in vaginal pH. Cytomorphometric analysis of vaginal smears in 38 postmenopausal women has shown an increase in mean cellular area, indicating a positive effect on the maturation of the vaginal epithelium. However, there is no effect on the overall maturation value/index[37].

The efficacy on vaginal symptoms is lower than that of topical estrogen therapy in the trials published thus far. One of the few randomized, controlled trials comparing the efficacy of a vaginal moisturizer to vaginal estrogen studied a vaginal moisturizer vs. dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women over 12 weeks. Both treatments led to a significant improvement in the vaginal dryness index in the first week of treatment but the dienoestrol was more effective than the non-hormonal preparation[38].

In a recent trial of vaginal moisturizer compared to low-dose vaginal estrogen, 18 patients received estriol cream ($n = 10$) or estradiol tablets ($n = 8$) and eight received a polycarbophilic moisturizer. Both low-dose vaginal preparations were found to be effective on vaginal symptoms and health, whereas the non-hormonal moisturizer provided only transient benefit[39].

Phytoestrogenic preparations There are some data demonstrating beneficial urogenital activity of phytoestrogenic preparations such as soy and red clover isoflavones[40] but these preparations are not really 'non-hormonal' as they have estrogen-type effects. Eight weeks of oral 40 mg red clover isoflavones reduced parabasal cells and increased superficial cells, thus increasing the vaginal maturation index with no significant effect on endometrial thickness[40]. As there are no data regarding the safety of these preparations in women with hormone-sensitive tumors, caution should be exercised in recommending them in these situations.

Vitamins Vitamin E has been shown to increase vaginal lubrication in one trial[41]. Vitamin D also appears to be involved in the regulation of vaginal stratified squamous epithelium[42] but there are no clinical data relating to vaginal atrophy.

Oral pilocarpine This has been shown to stimulate vaginal lubrication. A significant improvement in vaginal dryness was noted in women with atrophic symptoms following chemotherapy[43].

Topical anesthetics Topical anesthetics have been studied in women with vulvar vestibulitis (overnight 5% lidocaine ointment) and in women with vulvodynia (topical gabapentin 6%). These products could theoretically be useful in women with painful atrophy but there are no data.

Other products Complementary therapies such as nettle, comfrey root, dong quai root, motherwort, wild yam, bryonia and acidophilus capsules have not been proven to be efficacious or safe in randomized, controlled trials[44]. Further data are required before any recommendations can be made regarding the use of these herbal products for vaginal atrophy[45].

- Topical and systemic estrogen therapy are the most efficacious treatments for postmenopausal vaginal atrophy.
- For women in whom hormones are unsuitable, vaginal moisturizers provide improved lubrication.
- Phytoestrogens may have some urogenital benefits but safety has not been demonstrated in women with estrogen-sensitive tumors.

Systemic hormone therapy

Since the indications for systemic HRT include urogenital symptoms, it is evident that all these products have been carefully tested and have demonstrated a clear and good efficacy in this respect. Administration of exogenous estrogen restores normal vaginal pH levels, thickens and revascularizes the epithelium and increases vaginal lubrication. As a result, HRT alleviates the vaginal atrophy-related symptoms, which include dryness, irritation, pruritus, dyspareunia and urinary urgency, and may also lower the incidence of lower urinary tract infections. Most of the data are old, as was summarized in 1998 by a meta-analysis of 58 studies (both systemic and local administration), ten of which were placebo-controlled[35]. Of the various HRT preparations, only those containing estriol seem to be less effective. It is noteworthy that very few studies assessed treatment efficacy beyond 6 months, the Women's Health Initiative being one of these: about 10% of women participating in the estrogen + progestin arm (mean age 63 years) complained of vaginal dryness, of whom 74% reported relief at year 1, as compared to 54% in the placebo arm[46]. Thus, 10–25% of women using systemic hormonal therapy will still experience the symptoms of urogenital atrophy. This finding plus the safety concerns about oral/transdermal HRT are the reasons why systemic therapy is usually not recommended in women with vaginal symptoms only[47], and, in many women, a combination of systemic and vaginal estrogen may be necessary initially.

- Systemic HRT relieves vaginal atrophy in about 75% of women.
- Combination of systemic and local therapy may be required initially for some women.

Local estrogen therapy

Although systemic estrogen therapy will treat vaginal atrophy, local vaginal estrogen therapy is preferable, when systemic treatment is not needed for other reasons, because local therapy avoids most systemic adverse events and is probably also more efficacious for vaginal problems.

Local estrogen therapy can be given as tablets, pessaries/vagitories, cream or a vaginal ring. [The terms 'pessaries' and 'vagitories' are synonymous.] Therapy is available as conjugated equine estrogens, estradiol, estriol or estrone.

Estrogen is readily absorbed through the vaginal wall and effects will not only be local unless pharmaceutical formulations are used to prevent absorption. Even so, there is some absorption especially during the beginning of treatment, when the vaginal epithelium is still atrophic. When the epithelium matures as a result of therapy, absorption decreases and, in addition, smaller dosages of estrogen are necessary to prevent recurring atrophy. Only small dosages are normally needed to treat vaginal compared to systemic symptoms, and also low-potency estrogens like estriol can be used, which provides sufficient effect in the vagina with only limited systemic effects in spite of absorption.

According to the United States Pharmacopeia Search Index and Summaries of Product Characteristics,

steady-state plasma levels of estrogen are 7–8 pg/ml for the vaginal ring releasing 7.5 μg/24 h, with peak levels up to 63 pg/ml with insertion of the first ring and a lower peak again with the following changes of the ring. The 25 μg estradiol tablet induces steady-state estradiol values of 5–10 pg/ml, whereas, with the 10 μg tablet, estradiol serum levels in steady state do not exceed 5 pg/ml, while still being more effective than placebo[48]. Considerable absorption of estriol is seen with both vaginal estriol cream and tablets but, since estriol is a weak estrogen, which is not converted to estrone or to estradiol, systemic effects are limited[49]. A 2009 Cochrane review identified 37 trials, including 19 with randomized comparisons of estrogenic preparations administered intravaginally to 4162 postmenopausal women for at least 3 months[50]. Creams, pessaries, tablets and the estradiol vaginal ring appeared to be equally effective in relieving the symptoms of vaginal atrophy and significantly better than placebo and non-hormonal gels. One trial showed significant adverse effects of conjugated equine estrogen (CEE) cream, when compared to estradiol vaginal tablets, which included uterine bleeding, breast and perineal pain.

Despite the fact that the benefits of local estrogen therapy in preventing vaginal atrophy and reducing the incidence of related symptoms are well established, such treatment is contraindicated in some women, such as those with undiagnosed vaginal/uterine bleeding or known or suspected endometrial cancer, and is not an acceptable option for others. Additionally, almost all preparations are effective in decreasing signs and symptoms of vaginal atrophy but they differ slightly in their adverse-event profiles.

The vaginal ring and tablets cause less discharge compared to pessaries and creams, which may be preferable to some women; however, when therapy is needed for sexual dysfunction, the added lubrication from pessaries and creams may be advantageous. Individual patient preference will determine the choice of product.

- All currently available topical estrogens are absorbed, the extent depending on dose and formulation.
- All are effective; individual patient preference should be respected and will determine the form of treatment.

Are progestins required when women use topical estrogens?

The need for concurrent progestin use by women using vaginal estrogen preparations has been evaluated in numerous clinical trials and in a Cochrane review. Preparations studied include estriol cream and pessaries, estradiol vaginal tablets in two doses, 25 μg and 10 μg, CEE cream in two doses and estradiol-impregnated vaginal rings. Whilst topical estriol preparations do not appear to stimulate the endometrium, both conjugated estrogens and estradiol preparations may do so in a dose-related manner.

In the Cochrane review of 2006[50], endometrial hyperplasia was reported in two studies using conjugated estrogen creams and none in another using estriol pessaries.

Two recent studies of 25 μg estradiol vaginal tablets and low-dose CEE cream for 1–2 years found no incidence of hyperplasia, whilst a study of low-dose (10 μg) estradiol vaginal tablets for 1 year also found no incidence of endometrial hyperplasia amongst 284 biopsies or any change in endometrial thickness throughout the study[51].

A 48-week study comparing an estradiol-releasing vaginal ring and 25 μg estradiol vaginal tablets found no change in endometrial thickness for either group, but less bleeding amongst the ring users compared to those using vaginal tablets[52].

In a recent study of low-dose CEE cream (0.3 mg), proliferative endometrium was reported in six of 423 women over 52 weeks of follow-up, with no cases of endometrial hyperplasia or carcinoma[53].

The incidence of hyperplasia seen in these studies is very low and similar to that seen in an untreated postmenopausal population. A 2009 review of topical estrogen concluded that no studies show evidence of endometrial proliferation after 6–24 months of use[54], so the literature thus provides reassurance regarding the safety of low-dose vaginal estrogen preparations and does not support the concomitant use of systemic progestins for endometrial protection.

This evidence has been endorsed in recent clinical practice guidelines issued by The International Menopause Society[55] and The North American Menopause Society[33], with neither body advocating the use of progestins by women who are using topical estrogen preparations appropriately.

Important clinical points to note are that, first, there does appear to be a link between dose and type of estrogen used and endometrial response. Clinicians should prescribe the lowest effective dose and caution patients not to exceed the recommended frequency of use of the chosen product, although an occasional patient may require more frequent usage to obtain a satisfactory response.

Second, there is very little evidence to prove safety beyond 1 year of use for any vaginal products. Clinicians should be aware of the lack of evidence and patients should be counseled that any unexpected postmenopausal vaginal bleeding must be appropriately investigated.

- Conjugated estrogen and estradiol vaginal preparations may stimulate the endometrium in a dose-related manner.

- Appropriate use of topical estrogen does not require additional progestin for endometrial protection, although there are no data on treatment over 1 year.

Role for androgens and DHEA

The vulva and vagina are endowed with both estrogen and androgen receptors. Previous work had suggested the importance of deficiency of androgen receptors/action in conditions such as lichen sclerosis. More recent data have also suggested that, in the vagina, the estrogen receptor α is important in regulating the levels of androgen receptor in the fibrovascular layer, that these levels correlate well with the cellular proliferation index within the vagina, and that levels are low in atrophic vaginitis[56].

It would be logical to assume, therefore, that androgen therapy might play an important role for women with atrophic vaginal complaints. However, there are very few data available on vaginal testosterone therapy. Most data on testosterone in postmenopausal women come from studies using transdermal testosterone for hypoactive sexual desire; in addition, most studies also included the use of estrogen. While most of these data have shown a benefit of therapy when compared to placebo on various parameters of sexual function, these data are not helpful in assessing the effect of testosterone on the vagina. A recent study, however, has compared the effects of estrogen cream 1 g of CEE (0.625 mg) with the same dose of estrogen and testosterone cream (0.5 g of 2% testosterone) and placebo. Over 12 weeks of therapy, compared to placebo, both hormonal groups showed similar and significant improvements in vaginal health parameters. It also appeared that the combination group with testosterone had a greater improvement in sexual function. However, the group receiving testosterone exhibited a significantly higher serum free testosterone, which increased by 154%, suggesting that this is a form of systemic therapy[57]. There is an ongoing trial assessing the effects of an estradiol-releasing vaginal ring or vaginal testosterone cream (1%) in women with breast cancer, but these results are not yet available[58].

A fair amount of data, however, has been generated using intravaginal dehydroxyepiandrosterone (DHEA). Following the concept of steroids being secreted and having a local action on tissues (intracrinology), DHEA has been delivered to the vagina in ovules in a lipophilic base in doses of 0.25% (3.25 mg) to 1% (13 mg DHEA). Phase 3 randomized trials in postmenopausal women have shown that DHEA, estrogen and several metabolites are not increased above the normal postmenopausal range with this vaginal therapy for 12 weeks. Efficacy data have shown significant improvements with all doses compared to placebo in all parameters of vaginal maturation, a reduction in pH, an improvement in clinical symptoms of atrophy, as well as a reduction in pain with sexual activity[59]. Of interest, despite not having any systemic steroid effects, intravaginal DHEA improved various parameters of sexual function, including domains such as sexual desire[60]. We await longer-term studies to confirm these interesting data.

- Topical DHEA may prove to be a useful additional treatment for urogenital atrophy.

Therapy duration, monitoring and adverse events

At present, there are no guidelines pertaining to the length of therapy. The only recommendation is that, if long-term therapy is going to be implemented, then low-dose therapy must be used. Invariably, women will obtain substantial relief from their symptoms after about 3 weeks of treatment, although in some women it may require 4–6 weeks before adequate improvement is observed. About 80–90% of women will obtain subjective improvement, and treatment failure should mandate further evaluation with the view to exclude other underlying conditions, such as dermatitis/dermatoses or vulvodynia. Surprisingly, there is a paucity of data for the use of local estrogen preparations beyond 6 months, even though it is well known that symptoms commonly return when treatment is discontinued. This is because most of the preparations used are licensed for only 3–6 months of continuous use, in addition to the unproven concern that use beyond this may lead to endometrial pathology.

Adverse effects of local estrogen therapy

Serious adverse events are particularly uncommon. All preparations may, however, be associated with lesser adverse events and may cause vaginal irritation or itchiness, vaginal discharge, vaginal bleeding, pelvic pain, breast tenderness and paresthesias. The occurrence of these events varies according to the preparations used and, in general, it appears that the creams may be associated with more of these events than the tablets and the ring. This may be due to the preparation itself, to greater absorption or to higher doses than those recommended being inadvertently inserted into the vagina[61].

The potential effects of local estrogen therapy in causing endometrial hyperplasia have already been discussed. From all studies, there is no evidence of any increase in thromboembolic events or increase in metastases in breast cancer survivors who were using the vaginal tablets for symptom relief.

At present, there is no reason why women with symptomatic vaginal atrophy cannot use low-dose, local vaginal estrogen therapy for as long as they have symptoms. However, it is prudent to investigate fully all

patients who present with any vaginal bleeding to exclude endometrial pathology[62].

- Long-term use of low-dose topical vaginal estrogen preparations is not contraindicated.

Use of local estrogen treatment following breast and gynecological cancers

Cancer therapies, including surgery, irradiation, chemotherapy and/or hormonal manipulation (especially aromatase inhibitors) can impact on sexual functioning. Aromatase inhibitors can cause severe vaginal atrophy. Doctors involved in the management of these women should be sensitive to possible effects of therapy on their sexual life and activity, especially in women experiencing treatment for cancers. In women with breast or gynecological cancers, 30–100% may have sexual dysfunction[63]. While systemic estrogen therapy is the most effective, this may be contraindicated, whereas non-hormonal vaginal moisturizer treatments and lubricants during intercourse can be used without limitation. Vaginal topical estrogens are usually more efficient in the relief of vaginal dryness.

Most gynecological and breast cancers are hormone-responsive. Squamous cell cervical cancers are not hormone-responsive but local radiotherapy may reduce the number of estrogen receptors and the subsequent response to topical estrogen therapy.

An important question is whether vaginal estrogens can be used safely in women with hormone-responsive cancers, namely breast, ovarian and endometrial cancers and adenocarcinoma of the cervix. It is likely that vaginal absorption may vary from one woman to another and increasing administration to one application/day (instead of twice a week, the usual recommended schedule) can be associated with breast tenderness. There is no valuable study to recommend any evidence-based policy. However, in women taking tamoxifen following breast cancer, there is very little concern that the use of local estrogen may compromise the effects of tamoxifen, but rather the efficacy of vaginal estrogen may be compromised by tamoxifen. This situation is different in women treated with aromatase inhibitors, where the production of estradiol is antagonized but not the binding with the estradiol receptor. Only one study has reported on 1472 women with breast cancer and vaginal estrogen use; 23.2% of the women had used a vaginal estrogen, but 4.7% only for vaginal symptoms. About half (47%) were using tamoxifen[64]. No increase in recurrence was observed after a mean follow-up of 5.5 years, but the design of this study does not confirm any absence of risk. Aromatase inhibitors tend to cause more severe estrogen-deficient symptoms than tamoxifen and thus a greater impact on sexual function.

For women with breast cancer, non-hormonal therapies are preferred but, where these are ineffective, vaginal estrogens can be used at the lowest effective dose with appropriate patient counselling.

Following endometrial cancer, the most frequent recurrence occurs at the vaginal vault, thus raising concern of a possible increased risk with vaginal estrogen therapy. There are no data. Following ovarian cancer, although some concerns have been expressed about systemic treatment, there are no data to suggest an increased risk of recurrence with either systemic or local estrogen therapy. Following any gynecological cancer, it may be appropriate to discuss the relative risk of using estrogen with the oncology team as well as the patient.

- Vaginal atrophy is a common result of the treatment of many gynecological cancers.
- There are few data regarding the use of vaginal estrogens in women with gynecological hormone-responsive cancers.
- Following gynecological cancer, the use of local estrogen may not be contraindicated; these women should receive appropriate counselling regarding the risks and benefits, taking into account their individual risk factors.
- Use of local estrogen therapy in women on tamoxifen or aromatase inhibitors needs careful counselling and discussion with the oncology team.

CONCLUSIONS AND RECOMMENDATIONS

Postmenopausal vaginal atrophy is a common cause of distressing symptoms caused by estrogen deficiency, but it remains poorly recognized by health-care attendants and women are often reluctant to consult or complain about it. Treatment with local estrogen is simple, safe and can transform a woman's quality of life.

The key recommendations from the International Menopause Society Writing Group are as follows:

- It is essential that health-care attendants routinely engage in open and sensitive discussion with postmenopausal women about their urogenital health to ensure that symptomatic atrophy is detected early and appropriately managed.
- Treatment should be started early and before irrevocable atrophic changes have occurred.
- Treatment needs to be continued to maintain the benefits.
- All local estrogen preparations are effective and patient preference will usually determine the treatment used.

- Additional progestogen is not indicated when appropriate low-dose, local estrogen is used, although long-term data (more than 1 year) are lacking.
- If estrogen is ineffective or undesired, vaginal lubricants and moisturizers can relieve symptoms due to dryness.

Conflict of interest The Writing Group reports no associations or financial relationships with any pharmaceutical company, other than consultative agreements, honoraria for lecturing at scientific meetings, and research support. Details of all disclosures have been updated and are on file in the International Menopause Society Secretariat.

Source of funding In addition to International Menopause Society funds, unrestricted educational grants have been received from Bayer Schering Pharma AG, Endoceutics, Inc, Lil Drug Store Products, MSD Israel, and Novo Nordisk FemCare AG. The industry had no influence on the choice of contributors, the content and writing of the Recommendations, or the final paper.

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