

Vulvovaginal atrophy: modern approaches to diagnostics and management

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The aim of the review is to analyze the latest data on the current state of diagnosis and management of a common benign vulvar and vaginal disease in postmenopausal women – atrophic vulvovaginitis.

The paper presents an analysis of national and foreign scientific publications on the diagnosis and management of vulvovaginal atrophy and also focuses on the modern nomenclature and terminology of this pathology. Vulvovaginal atrophy is a common and progressive condition affecting on average more than 50 % of postmenopausal women, and its development and severity depend mainly on the duration of hypoestrogenism. Such a hormonal imbalance with a gradually increasing estrogen deficiency leads to atrophic changes in the tissues of the female genital organs and thinning of the vaginal epithelium. Degenerative alterations are accompanied by inflammatory phenomena and disturbances in the vaginal microflora. Atrophic lesions in the genitourinary system induce urinary incontinence aggravation, dysuria, increased micturition frequency, and recurrent urinary tract infections.

Vulvovaginal atrophy is diagnosed based on appropriate clinical assessments as well as with the involvement of validated questionnaires. Differential diagnosis of the vulvovaginal atrophy should include all pathological conditions imitating the clinical symptoms and signs.

Experts of the International Society for the Study of Women's Sexual Health and the North American Society of Menopause have proposed a new nomenclature, namely, the terms "vulvovaginal atrophy" and "atrophic vaginitis" have been supplanted by "genitourinary menopausal syndrome".

First-line therapy for mild symptoms is non-hormonal vulvar and vaginal lubricants, vaginal moisturizers used on a regular basis. Hormonal therapy (both transdermal and oral) remains the most effective choice for the treatment of clinical manifestations, but contraindications to its use should be considered. In women with contraindications to systemic hormonal therapy, it is possible to prescribe estrogens in the form of vaginal suppositories or vaginal cream. 5-Aminolevulinic acid photodynamic therapy can be one of the promising methods in the treatment of this women's clinical group.

Given the serious consequences of vulvovaginal atrophy for the patients' health and quality of life, timely diagnosis of the disease in accordance with its specificity and possible complications is of primary importance for the successful treatment and management of this pathology.

Conclusions. Vulvovaginal atrophy has been shown to be a common disease, especially among women in the postmenopausal period, based on the analysis of national and foreign scientific publications. The pathogenesis of vulvovaginal atrophy is associated with hypoestrogeny which results in structural and functional abnormalities of the genital organs such as mucus thinning, loss of elasticity, changes in microbiota and increased pH. Given the new nomenclature and terminology, it is appropriate to use the term "genitourinary menopausal syndrome" (GMS or GUMS) in lieu of "vulvovaginal atrophy".

Ключові слова:

вувльвовагінальна атрофія, генітоуринарний менопаузальний синдром, менопауза, постменопауза, гіпоестрогенія, діагностика, лікування, фотодинамічна терапія.

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Вувльвовагінальна атрофія: сучасні підходи до діагностики та лікування

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Мета роботи – аналіз найновіших відомостей щодо стану діагностики та лікування поширеного доброякісного захворювання вувльви та піхви у жінок у постменопаузі – атрофічного вувльвовагініту.

Наведено аналіз вітчизняних і зарубіжних публікацій щодо діагностики та менеджменту вувльвовагінальної атрофії, акцентовано на сучасній номенклатурі та термінології цієї патології. Вувльвовагінальна атрофія – доволі поширений стан, що прогресує; в середньому його виявляють у 50 % жінок у постменопаузі. Розвиток і тяжкість вувльвовагінальної атрофії залежать передусім від тривалості гіпоестрогенії. Такий гормональний дисбаланс із дефіцитом естрогенів, що поступово посилюється, призводить до атрофічних змін тканин жіночих статевих органів, потоншення епітелію піхви. Дегенеративні зміни супроводжуються запальними явищами і порушеннями мікрофлори середовища піхви. Атрофічні зміни сечостатевої системи спричиняють збільшення частоти сечовипорожнень, нетримання сечі, дизурію та інфекції сечовивідних шляхів, що рецидивують.

Вувльвовагінальну атрофію діагностують за результатами клінічного оцінювання, а також використовуючи валідовані опитувальники. Диференційний діагноз цієї патології необхідно здійснювати з усіма патологічними станами, що імітують симптоми та клінічні прояви.

Експерти Міжнародного товариства з вивчення жіночого сексуального здоров'я і Північноамериканського товариства менопаузи запропонували нову номенклатуру, зокрема терміни «вувльвовагінальна атрофія» та «атрофічний вагініт» замінено на «сечостатевий синдром менопаузи» і «генітоуринарний менопаузальний синдром».

Терапією першої лінії в разі менш виражених симптомів є негормональні вульварні та вагінальні змазки, вагінальні зволожувальні засоби, що призначені для регулярного застосування. Гормональна терапія (і трансдермальна, і пероральна) залишається найефективнішою під час лікування клінічних проявів генітоуринарного синдрому. Втім, слід враховувати протипоказання щодо її призначення. Якщо є протипоказання до призначення системної гормональної терапії, можливе використання локальних естрогенів у лікарській формі вагінальних супозиторіїв або вагінального крему. Одним із перспективних методів лікування таких пацієнок може стати фотодинамічна терапія з 5-амінолевуліновою кислотою.

Зважаючи на складні наслідки вульвовагінальної атрофії для здоров'я та якості життя пацієнок, для успішного лікування та управління цією патологією першочерговою є своєчасна діагностика захворювання, беручи до уваги його специфіку та можливі ускладнення.

Висновки. Аналіз вітчизняних і зарубіжних наукових публікацій показав, що атрофія вульвовагінального каналу є доволі поширеним захворюванням, особливо в жінок у постменопаузальному періоді. Патогенез атрофії вульвовагінального каналу пов'язаний із гіпоестрогенією, що призводить до змін структури та функції статевих органів, як-от потоншення слизової оболонки, втрати еластичності, зміни мікробіоти, підвищення рН. Враховуючи нову номенклатуру та термінологію, замість «атрофія вульвовагінального каналу» доцільно використовувати термін «генітоуринарний менопаузальний синдром» (ГМС, ГУМС).

In today's modern society, interest in health problems and social adaptation of women who have gone through menopause is constantly growing every day, due to the increased number of this population segment. The menopausal period represents the physiological process of female aging and is defined as a period of gradual decrease in ovarian activity [1].

One of the complications of the postmenopausal period physiological course for women is the development of metabolic disorders in the reproductive system characterized by involuntional changes, namely atrophic, in the cervical, vaginal and vulvar structure [2]. Postmenopausal atrophic vaginitis, along with vasomotor symptoms and sleep disorders, is one of the most unpleasant menopausal symptoms.

Vulvovaginal atrophy (VVA) is a common and progressive condition, but few menopausal women seek medical care for these symptoms [3,4]. VVA is typical for postmenopausal women, but it can affect women of all ages diagnosed with decreased estrogenic stimulation of the genitourinary tissues. A hypoestrogenic state can occur in the postpartum period, be a consequence of prolonged breastfeeding, hypothalamic amenorrhea, or the use of antiestrogens as part of adjuvant therapy for breast cancer [5,6]. More than 50 % of women suffer from a severe form of VVA associated with menopause. The development and severity depend mainly on the duration of hypoestrogenia, which causes changes in the genitourinary tissues, giving rise to the corresponding signs and symptoms. In young women, this clinical problem may occur temporarily while taking various pharmacological drugs or radiation therapy [7,8]. The most common symptom of VVA is vaginal dryness (reported by up to 83 % of postmenopausal women) [9,10], vaginal irritation (37–77 %) and dyspareunia (38–59 %) [11,12]. But at the same time, atrophic changes in the genitourinary system include worsening dysuria, increasing frequency of urination, urinary incontinence, and recurrent urinary tract infections [13]. Patients with breast cancer report that these symptoms reduce their quality of life, occur not only at the age of menopause, but also much earlier [14].

Aim

The aim of the review is to analyze the latest data on the current state of diagnosis and management of a common benign vulvar and vaginal disease in postmenopausal women – atrophic vulvovaginitis.

VVA can occur at any time of a woman's life, although it is more frequent in the postmenopausal period, and it is characterized by hypoestrogenia. Other reasons for hypoestrogenic states are lactation, various breast cancer treatments, and the certain medication use. In other situations, excluding menopause, VVA may resolve spontaneously due to estrogen level restoration.

According to various epidemiological studies, the prevalence of VVA varies depending on the parameters considered for diagnosis and the patients' age, but an average of more than 50 % has been reported among postmenopausal women [15]. VVA is the main factor for the quality of life deterioration in patients with breast cancer as well as a side effect of adjuvant therapy [14].

The reproductive period of a woman's life is characterized by the activity of estrogen receptors in the vagina, vulva and urinary bladder trigone, that modulates physiological cell proliferation and maturation. Low levels of circulating estrogen after menopause lead to physiological, biological, and clinical changes in the genitourinary system tissues [5]. In women, the genital and lower urinary tracts share a common embryological origin and express estrogen receptors extensively. In particular, normal vaginal and vulvar tissue contains estrogen receptors alpha and beta, which "are reduced after menopause [16]. One of the main estrogen effects is to maintain the physiological vaginal microbiome and pH values. Naturally, the vaginal microbiome is formed by the predominance of *Lactobacillus* species, which reduce the pH to the range of 3.5–4.5, metabolizing glucose into lactic and acetic acids, thereby protecting against vaginal infections [17]. Menopausal thinning of the vaginal epithelium results in a decreased number of vaginal squamous cells with reduced glycogen levels. Once vaginal glycogen levels drop, the lactobacilli population decreases and vaginal pH increases [18]. An increased pH, in turn, leads to the loss of lactobacilli and an overgrowth of other bacteria, including group B streptococci, staphylococci, coliform bacteria, and diphtheroids. These bacteria are causative factors for symptomatic vaginal infections and inflammation [19]. Therefore, one of the reasons for the VVA manifestations is a vaginal microbiota perturbation, which is a dynamic formation and plays a decisive role in the pathogenetic interaction of postmenopausal symptoms. This explains the importance of understanding the relationship between the postmenopausal vaginal microbiome and genitourinary syndrome of menopause [20,21].

A hypoestrogenic milieu impairs fine vascular, nervous and muscular mechanisms that regulate sexual function. Having been involved in the natural lubrication of the genital tract, estrogens regulate sexual activity through complex brain networks [22]. The main value of insufficient estrogenic stimulation is the tissue elasticity loss due to the induction of fusion and hyalinization of collagen fibers and elastin fiber fragmentation. The mucosa of labia minora, vagina and vaginal vestibule becomes thinner, pale and less moisturized. The vaginal canal is shorter and narrower due to gradual flattening of the vaginal epithelial folds that provide elasticity. In addition, there is a significant decrease in vascular support, which leads to a reduced volume of vaginal transudate and other glandular secretions [23,24].

Both estrogens and androgens contribute to pelvic nerve-stimulated genital blood flow, tissue response to neurotransmitters, and sensory threshold to stimuli [25].

Clinical symptoms and validated questionnaires are commonly used to diagnose VVA. Based on currently available data, the most commonly used assessment tools for diagnosing GSM are the Vaginal Health index (VHI), the Visual Analogue Scale (VAS) for VVA symptoms and the Female Sexual Function Index (FSFI) [26]. Whilst the VAS is a progressive 10-point scale that asks patients to describe their discomfort, the FSFI assesses general sexual discomfort and dyspareunia using questions about desire, lubrication, orgasm or painful sensation [27]. Both questionnaires consider subjective results and depend on the patient's perception of a disease. In contrast, most authors regard the VHI as an objective indicator [26]. The VHI includes assessment of five elements: vaginal elasticity, discharge, pH, mucosal epithelial integrity, and tissue hydration. The score can range from 5 to 25, with a cutoff of 15, below which the condition is considered as atrophic vaginitis [28]. Given that four out of the five indicators are actually specific to a physician decision, not all authors agree that this tool can be used as an objective indicator [26]. Vaginal pH measurement, which is part of the VHI, is a useful assessment tool and is calculated using a pH indicator strip [28]. Considering the mechanism of postmenopausal pH changes mentioned above, research findings indicate that a value greater than 4.5 is associated with decreased serum estrogen levels, menopause and is correlated with a decrease in FSH [19].

Other tool, according to scientific publications, used to diagnose VVA is the Vaginal Maturation Index (VMI). The VMI is the percentage calculation of parabasal, intermediate and superficial squamous cells in cervical cytological examination [29]. The ratio of these cells is used as a diagnostic means to assess the therapy effectiveness [28]. Lower values are associated with greater estrogen deficiency and the predominance of parabasal cells in a vaginal smear [29]. All of the above tools are useful in the process of diagnosing VVA, but there is still no consensus regarding the definition of vaginal atrophy and, accordingly, a recognized diagnostic method.

Subjective results are more interesting in a clinical context because they are quick and directly useful for further therapeutic decision. In a research setting, objective instruments should be used in combination with symptom assessment [28].

The differential diagnosis of VVA should include all pathological conditions that mimic symptoms and clinical

manifestations, such as lichen sclerosus, lichen planus, and vulvar malignancies as well as other states causing vaginal discharge, chronic vaginal and vulvar itching, pain (e. g., vaginal infections, vulvovaginal dermatoses, local irritation). Vaginal infections can be caused by bacteria, viruses, protozoa, and fungi. The most common vaginal infections are candidal vulvovaginitis, bacterial vaginosis, and trichomoniasis. Bacterial vaginosis can be a consequence of vaginal atrophic changes. Local irritants that can cause vaginal itching include perfumes, any topical lubricant or moisturizer, and soap. Vulvovaginal dermatoses, including lichen sclerosus, lichen planus, and lichen planus chronicus, can cause similar symptoms [30].

Atrophic colpititis (vaginitis) has numerous synonyms reflecting its essence. In the medical literature, such definitions as age-related, postmenopausal, senile, senile colpititis (vaginitis), vulvovaginal atrophy can be found [31,32]. In 2014, a new nomenclature was proposed at a conference involving experts from the International Society for the Study of Women's Sexual Health (ISSWSH) and the North American Menopause Society (NAMS) [2,33]. Since then, the terms atrophic vaginitis and vulvovaginal atrophy have been supplanted by genitourinary menopausal syndrome (GMS or GUMS). It describes a range of unpleasant sexual, genital, and urological symptoms that can either be self-existing or coexisting without association with other diseases [2]. It has been found that 80 % of menopausal women complain of at least one symptom related to GSM [34,35,36].

A climacteric hormonal imbalance with a gradually increasing estrogen deficiency is an underlying the condition, resulting in atrophic changes in the tissues of the female genital organs, thinning of the vaginal epithelium. Such vulvar, vaginal and lower urinary tract changes can seriously affect the quality of life in menopausal women, especially sexually active ones [8,37,38,39,40,41,42]. The hypoestrogenic state and resultant hormonal and anatomical changes lead to the GUMS development with a polymorphic disease pattern and manifest by such symptoms as vaginal dryness, genital burning and irritation, decreased lubrication, dysuria, as well as acute or recurrent urinary tract infections, uncomfortable feelings of pain and dryness during sexual intimacy [6,43]. Degenerative changes are accompanied by inflammatory phenomena and violations of the vaginal microflora. Women have many complaints, and the disease takes a chronic course, gradually progresses and threatens with serious complications. GUMS usually progresses if left untreated [43,44].

Low-dose vaginal estrogen therapy or other local treatments are recommended for the GSM management that is resistant to non-prescription medicinal products, in the absence of indications or in the presence of contraindications to systemic hormone therapy [45]. This NAMS position statement has been approved by the Academy of Women's Health, American Association of Clinical Endocrinologists, American Association of Nurse Practitioners, American Medical Women's Association, American Society for Reproductive Medicine, Asociación Mexicana para el Estudio del Climaterio, Association of Reproductive Health Professionals, Australasian Menopause Society, Chinese Menopause Society, Colegio Mexicano de Especialistas en Ginecología y Obstetricia, Czech Menopause and Andropause Society, Dominican Menopause Society, European Menopause and Andropause Society, German Menopause Society, Groupe

d'études de la ménopause et du vieillissement Hormonal, HealthyWomen, Indian Menopause Society, International Menopause Society, International Osteoporosis Foundation, International Society for the Study of Women's Sexual Health, Israeli Menopause Society, Japan Society of Menopause and Women's Health, Korean Society of Menopause, Menopause Research Society of Singapore, National Association of Nurse Practitioners in Women's Health, SOBRAC and FEBRASGO, SIGMA Canadian Menopause Society, Società Italiana della Menopausa, Society of Obstetricians and Gynaecologists of Canada, South African Menopause Society, Taiwanese Menopause Society, and the Thai Menopause Society.

Treatment of this pathology depends on the severity and type of symptoms, as well as on the preferences and expectations of a woman. The main therapeutic goal is to relieve symptoms, and hormone therapy remains the most effective choice for treating clinical manifestations, despite the side effects of its use. Since there are many treatment options, therapy should be selected individually [6,20,45].

First-line therapy for minor symptoms is non-hormonal vulvar and vaginal lubricants, vaginal moisturizers, which are applied regularly (several times a week). Although not supported by clinical trials, regular, gentle vaginal stretching exercises or sexual activity may be effective [46]. Individual lubricants and moisturizers are effective in relieving discomfort and pain during intercourse for women with mild-to-moderate vaginal dryness, especially with estrogen contraindications or preferences not to use estrogen. Given differences between moisturizers, women should be recommended to choose a treatment that is optimally balanced in both osmolality and pH as well as the most physiologically similar to natural vaginal secretions [47].

Usually, the treatment for atrophic vaginitis begins with intravaginal administration of estrogen. Intravaginal estrogen medications, estrogen creams, estradiol tablets, estradiol transdermal patch and estradiol vaginal rings have shown significant alleviation of local clinical signs [48,49]. To reduce adverse systemic effects, it is recommended to use the lowest effective estrogen dose, gradually titrated downwards after improvements in symptoms and functions [50]. The VMI can be used as a clinical measure to assess an estrogen therapy response. It has been noted that the predominance of *Lactobacillus* was associated with milder genital symptoms compared to pH changes [18].

Low-dose vaginal suppositories containing dehydroepiandrosterone was approved in the US and Canada for daily use to treat moderate-to-severe dyspareunia in postmenopausal women (also known as prasterone): a steroid hormone with the ability to transform into androgens and estrogens [46].

Hormonal therapy with topical estrogens is considered the "gold standard", but it is not always safe or acceptable. The number of women have concerns about its use or choose non-hormonal methods. Thus, they need safe and effective non-hormonal agents to improve their symptoms. Besides, moisturizers and lubricants are a first-line therapy for breast cancer survivors [37,41]. A randomized controlled trial has demonstrated the efficacy and safety of disposable applicators prefilled with hyaluronic acid-based vaginal gel for the treatment of VVA-related symptoms in postmenopausal women [51].

In addition to pregnancy, estrogen-receptor-positive breast cancer, migraines with aura or allergy to estrogen, thromboembolic disorders, heart disease, liver disease, other estrogen-dependent cancers (breast and uterine cancer subtypes), undiagnosed vaginal bleeding, endometrial hyperplasia should be noted among the contraindications to estrogen therapy [52,53].

For women with moderate-to-severe dyspareunia associated with GUMS with accompanying vasomotor symptoms, transdermal and oral hormone therapy is an effective option [46]. Oral estrogen or a combination of estrogen and progesterone used as a hormone replacement therapy in postmenopausal women may also be useful in the treatment of urogenital atrophy with vasomotor symptoms [4].

Complementary or alternative therapies include selective estrogen receptor modulators, tissue-selective estrogen complexes, estriol, platelet-rich plasma, herbal medicine [54]. Selective estrogen receptor modulators are now used to treat menopausal symptoms, breast cancer, bone loss and metabolic neurodegenerative diseases. Depending on the target organ, this group of drugs can act as both estrogen agonists and antagonists [55]. Ospemifene is a selective estrogen receptor modulator [5,46] acting as an estrogen agonist in the vagina with no clinically significant estrogenic effects on the endometrium or the breast. Ospemifene is approved by the U. S. Food and Drug Administration (FDA). It has a lower risk of venous thrombosis than other selective estrogen receptor modulators in postmenopausal women with VVA [5,56].

For symptomatic treatment and with systemic estrogen therapy contraindications, patients may use lubricants. Lubricants may improve symptoms without any histological changes. Other non-hormonal treatments include carbon dioxide laser therapy, fractional microablation and transcutaneous temperature-controlled radiofrequency treatment, which improve vaginal dryness, vulvovaginal laxity, and dyspareunia within 6 to 12 months [54,57,58,59,60].

One of the promising methods in the treatment of precancerous and cancerous lesions is photodynamic therapy – this is a minimally invasive approach to treatment, known for its ability to activate the body's immune response [61,62,63]. 5-Aminolevulinic acid photodynamic therapy (ALA-PDT) is a technology for the treatment of epithelial, superficial, non-melanoma skin cancers, as well as for infectious lesions and inflammatory skin diseases [64,65,66,67,68].

Conclusions

1. The analysis of national and foreign academic publications has shown that vulvovaginal atrophy is a common disease, especially among women in the postmenopausal period, caused by decreased estrogen levels. Given the new nomenclature and terminology, it is appropriate to use the term "genitourinary menopausal syndrome" (GMS or GUMS) in lieu of "vulvovaginal atrophy" as more accurate and complete according to the characteristics of this pathology.

2. The pathogenesis of vulvovaginal atrophy is related to hypoestrogeny resulting in structural and functional abnormalities in the genital organs, such as tissue thinning, loss of elasticity, changes in the microbiota, and increased

pH. Timely diagnosis of vulvovaginal atrophy in view of its specificity and possible complications is of primary importance for the patients' health and quality of life as well as for successful treatment and management proceeding from serious consequences of the disease.

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