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Vulvovaginal atrophy: current methods of diagnosis and treatment

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ABSTRACT

Aim. To review modern methods of diagnosis and treatment of vulvovaginal atrophy (VVA), which is one of the manifestations of genitourinary syndrome of menopause in peri- and postmenopausal women.

Materials and methods. A review of domestic and foreign literature on the prevalence and modern methods of diagnosis and treatment of VVA was carried out.

Results. Unlike vasomotor symptoms, VVA progresses with age, causing a significant impairment in women's quality of life. Symptoms usually begin to bother perimenopausal patients, but their frequency and severity increase significantly in postmenopausal women. Diagnosis of VVA can present some difficulties, as many women perceive their condition as a natural manifestation of aging and do not seek medical care. Currently, drug and non-drug therapies for VVA have been proposed, each of which has its own characteristics, indications, and contraindications. However, the safety and effectiveness of some of them have not been fully proven.

Conclusion. VVA is common in peri- and postmenopausal women. Modern aspects of the diagnosis and treatment of this pathology can significantly improve the quality of life of patients with VVA symptoms. However, further research is needed to confirm safety of the proposed treatment methods, and search for new techniques is required.

Keywords: vulvovaginal atrophy, genitourinary syndrome of menopause, peri- and postmenopause

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Вульвовагинальная атрофия: современные методы диагностики и лечения (обзор литературы)

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РЕЗЮМЕ

Целью публикации является обзор современных методов диагностики и лечения вульво-вагинальной атрофии (ВВА), которая является одним из проявлений генитоуринарного менопаузального синдрома у женщин в пери- и постменопаузе.

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Материалы и методы. Проведен обзор отечественных и зарубежных источников, посвященных распространенности, диагностике и методам лечения ВВА.

Результаты. В отличие от вазомоторных симптомов, ВВА прогрессирует с возрастом, вызывая значительное нарушение качества жизни женщин. Симптомы, как правило, начинают беспокоить пациенток в перименопаузе, но их частота и выраженность значительно возрастают в постменопаузе. Диагностика ВВА может представлять некоторые трудности, так как многие женщины воспринимают свое состояние как естественное проявление старения организма и не обращаются за медицинской помощью. В настоящее время предложены медикаментозные и немедикаментозные методы лечения ВВА, каждый из которых имеет свои особенности, показания и противопоказания. Однако безопасность и эффективность некоторых из них полностью не доказана.

Заключение. Вульво-вагинальная атрофия часто встречается у женщин пери- и постменопаузального возраста. Современные аспекты диагностики и лечения данной патологии позволяют значительно повысить качество жизни пациенток с симптомами ВВА, однако необходимы дальнейшие исследования для подтверждения безопасности предлагаемых методов лечения и поиск новых.

Ключевые слова: вульво-вагинальная атрофия, генитоуринарный менопаузальный синдром, пери- и постменопауза

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

One of the urgent problems in gynecology, which reduces the quality of life of women in menopause, is the genitourinary syndrome of menopause (GSM). The term GSM was proposed in 2014 by the North American Menopause Society (NAMS) and the International Society for the Study of Women's Sexual Health (ISSWSH), and was endorsed by the Russian Society of Gynecological Endocrinology and Menopause (ROSGEM) in 2015. This is a symptom complex associated with a decrease in estrogens and other sex steroids, including changes that occur in the external genitalia, perineum, vagina, urethra, and bladder [1, 2].

Symptoms of GSM typically begin in the perimenopause and progress into the postmenopausal period leading to functional and anatomical changes [3]. The incidence of GSM in perimenopausal women is 15–19%, and in postmenopausal women, it is 40–90% [4–9]. The prevalence of vulvovaginal atrophy (VVA), as one of the GSM manifestations, is 19% in women aged 40–45 years, in peri- and postmenopause, it ranges from 36 to 90% [5, 6, 10]. According to K. Levine et al. in sexually active women aged 40–65 years, symptoms corresponding to VVA occur in 57% [11]. However, despite the wide prevalence of VVA and GSM in general, this disease is often not diagnosed and treated [11–14].

Histologic changes in the vaginal epithelium in peri- and postmenopausal women include its thinning with signs of keratinization and a high nucleus-to-cytoplasmic ratio, the predominance of basal and parabasal cells, and a sharp decrease in the number of intermediate, surface cells and glycogen. This leads to a decrease in the number of lactobacilli and an increase in the pH of the vagina. Hypoestrogenic state of the vagina also includes smooth muscle atrophy, changes in the composition of the connective tissue with an imbalance in type I / III collagen, elastin, and hyaluronic acid, which leads to a decrease in tissue strength and elasticity and possibly fibrosis and obliteration of the vagina.

Thinning of the vaginal epithelium increases susceptibility to injury, which leads to bleeding, petechiae, ulceration, and inflammation [9, 15–19]. A small number of lactobacilli can cause vaginal colonization with anaerobic bacteria, inflammation,

and abnormal discharge and predispose to urinary tract infection. [20, 21]. According to the literature, in women with VVA, a microbiological examination of the vaginal discharge may show a pattern of normocenosis (44%), atrophic vaginitis (42%), bacterial vaginosis (12%), and non-specific vaginitis (1.7%). There is an increase in the number of neutrophils in atrophic vaginitis compared to vaginal atrophy [22–25]. According to some authors, an increase in anaerobic microflora can contribute to the appearance of VVA symptoms in peri- and postmenopausal women, but not all researchers agree with this [26–28].

VVA is manifested by such symptoms as dryness, burning, itching, irritation, discomfort and pain in the vagina, bloody discharge during and after sexual contact, sexual dysfunction, and superficial dyspareunia, unlike deep dyspareunia, which is characteristic of endometriosis [14]. This is a chronic pathology that progresses over the years. According to E. Moral et al., vaginal dryness is the most common and distressing symptom, affecting up to 93% of women. The severity of this symptom can be moderate or severe in 68% of cases [7].

Diagnosis of VVA is based on anamnestic data, assessment of the patient's complaints, gynecological examination with the determination of clinical signs, as well as laboratory tests. The medical history should include questions about the characteristics of sexual function, the presence of reduced libido and superficial dyspareunia [14]. On examination, the vaginal epithelium is thinned, pale, smooth due to impaired blood supply, there may be prolapse of the walls of the vagina. The thinned vaginal epithelium is easily injured during gynecological examination, and there may be subepithelial hemorrhages [29].

In addition, laboratory tests, such as vaginal pH assessment, vaginal maturation index (VMI), and vaginal health index (VHI), are used. With a decrease in estrogen levels, the vaginal environment becomes alkaline (pH > 4.5). With all these changes, the number of lactobacilli decreases and the growth of opportunictic and obligate anaerobes increases. VMI shows the degree of maturation of the vaginal epithelium by the balance between superficial, intermediate, and parabasal cells. With estrogen deficiency, the number of superficial cells sharply decreases or completely disappears, the number of cells in the intermediate layer decreases, and the number of cells in the parabasal and basal layers increases [29, 30].

VHI is one of the most commonly used parameters in the diagnosis of VVA. It allows specialists to evaluate the elasticity of the vagina, the nature and volume of secretions, pH, the presence of petechiae on the epithelium, and moisture. With vaginal atrophy, VHI does not exceed 15. However, clinical signs do not always correlate with laboratory data. [29, 31].

The Vulvovaginal Symptoms Questionnaire [32, 33], the Day-to-Day Impact of Vaginal Aging Questionnaire [34], and the Vaginal and Vulvar Assessment Scale Questionnaire [35] were highly effective for assessing VVA symptoms and GSM in general. However, despite its high prevalence, VVA is underdiagnosed and undertreated mainly due to the trend of many women to perceive it as a normal sign of natural aging [9, 16, 36–38].

Therapy for VVA and other manifestations of GSM should be started as early as possible, before the onset of irreversible atrophic manifestations, and continued for a long time, since symptoms may return [39–41]. The main goal of treatment is to relieve symptoms. Drug and non-drug treatments are used for this purpose. In 2020, the North American Menopause Society published updated guidelines [42]. For mild manifestations, lubricants and moisturizers are used at the first stage of treatment. They are devoid of side effects and can be used for a long time. This treatment option is recommended for women for whom the use of vaginal estrogen preparations is unacceptable [43, 44]. Vaginal lubricants are especially indicated for women who are concerned about vaginal dryness during sexual intercourse. They may be water soluble and at the same time tend to dry out. Silicone-based or oil-based lubricants are stronger but less lubricating.

Vaginal humectants are insoluble hydrophilic polymers with characteristic bioadhesiveness and the ability to retain moisture that is released locally, mimicking physiological vaginal discharge. They can also contain a large amount of excipients that affect the pH and osmolarity of the solution [43]. They can be used not only during sexual intercourse, but also regularly, as they have a fairly long-lasting effect, increasing the moisture content of the vaginal mucosa and lowering the pH. The frequency of use is directly proportional to the severity of vaginal atrophy. Topical use is recommended in the evening, at bedtime for 7–10 days, and then twice a week to maintain the effect.

Moisturizers most commonly contain hyaluronic acid, a glycosaminoglycan produced by fibroblasts, which is a major component of the extracellular

matrix found in connective and nervous tissue and epithelium, including the vagina. Hyaluronic acid is a strong antioxidant, increases the level of moisture in the cells, and reduces the symptoms of atrophy. When tissues are damaged, hyaluronic acid can stimulate fibroblast migration and proliferation, neoangiogenesis, tissue re-epithelialization, and collagen fiber deposition. With regular, daily or every 2–3-day use of a hyaluronic acid-based product, the severity of vaginal dryness is reduced, and this effect is comparable to the effect of topical estrogen therapy [45, 46]. Hyaluronic acid with phytoestrogens is part of the Estrogial preparation, which contains the sodium salt of hyaluronic acid, extracts of clover, calendula, and hops and can be used as monotherapy in patients with symptoms of vaginal atrophy in case of unwillingness or contraindication to the use of estrogens [47, 48].

The non-hormonal drug Multi-Gyn-Liqui-Gel, which is a gel based on the patented 2QR complex, betaine, glycerol, and xanthan gum, is used to eliminate vaginal dryness and stimulate natural hydration, prevent itching and the development of pathological conditions of the vagina and has the ability to neutralize pathogens and maintain vaginal hydration. This natural, safe agent protects the natural microflora and can be used in patients with breast cancer [49, 50].

A.G. Kedrova notes a good relief of VVA symptoms when Flamena is used in women after gynecological operations or in the process of combined treatment of tumors of the female reproductive system. Flamena is a gel containing active ingredients (dihydroquercetin, lecithin, glycine, and sangviritrin), which diffuses well through the walls of the vagina, moisturizing them and improving microcirculation. Treatment is carried out for 14–21 days until the symptoms of dryness, burning, itching, and irritation of the mucous membranes are relieved. Then it is possible to switch to maintenance therapy 2–3 times a week [51]. G. Capobianco et al. showed the effectiveness of the use of Lactobacillus acidophilus, estriol, and correction of the pelvic floor dysfunction to eliminate the symptoms of VVA in postmenopausal women [52].

Other possible components of vaginal moisturizers are ozonides, ozone intermediates that act as a biological reservoir that retains the therapeutic effect of the molecule. In connection with biological tissues, ozonides are rapidly activated, stimulating local microcirculation, inducing neoangiogenesis, promoting tissue repair, and inhibiting proinflammatory prostaglandins [53]. Fibroblasts are known to play an important role in re-epithelialization, synthesis of collagen fibers, regeneration of the extracellular matrix, tissue remodeling, and release of such endogenous growth factors as FGF, PDGF, TGF-β, and VEGF [54, 55]. Ozone stimulates the formation of collagen and fibroblasts in the wound, as well as growth factors PDGF, TGF-β, and VEGF [56]. Ozone promotes wound healing by activating the transcription factor NF-κB and regulating inflammatory responses [57, 58]. Ozone may influence the expression of proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor α (TNFα), as well as adaptive immune responses, including cyclooxygenase-2 (*COX-2*) gene activation via activation of NF-κB [59, 60].

Non-hormonal VVA therapy provides relief of mild symptoms, while estrogen therapy is most effective in treating moderate and severe symptoms of vaginal atrophy [61]. Topical estrogen hormone therapy is used as the second step in case of failure of vaginal lubricants and moisturizers [62, 63].

Topical VVA therapy includes the use of natural estrogens in the form of tablets, creams, suppositories, or rings [64]. Estriol is the most effective and safest treatment for VVA symptoms, since it has the lowest affinity for estrogen receptors, does not convert to estradiol, and its systemic effects are extremely limited. The absence of a systemic effect of estriol is explained by the binding time to the receptor, which does not exceed 4 hours. [39].

The intravaginal administration of estriol has no age restrictions and can be prescribed to women over 60 years of age. At the beginning of treatment, drugs are prescribed daily at a therapeutic dose for 2–4 weeks (saturation therapy): estriol (vaginal suppositories) 0.5 mg, estriol (vaginal cream) – 1 mg / g; as there is improvement, 2 times a week for a year, then the duration of treatment is determined individually (maintenance therapy) [65]. The rationale for this regimen is that estrogen absorption is the highest during the first few days of treatment, when the vaginal epithelium is atrophic and highly vascularized. Once the epithelium matures, uptake of local estrogen decreases and therefore lower doses of estrogen are sufficient to prevent repeated atrophy [64].

Repeated intravaginal administration of estriol results in a small cumulative effect. However, doses of up to 0.5 mg of estriol twice a week are not associated with a significant increase in serum estrogen levels

after short-term (1 week) and long-term (12 months) treatment [42, 65]. The use of low-dose estriol in VVA does not require protection of the endometrium with progesterone. However, the systemic effects of estrogens are limited to low doses but not completely eliminated, especially at early stages of treatment [66]. Local estrogen therapy leads to a decrease in vaginal pH, an increase in the number of lactobacilli, maturation of the vaginal epithelium, and a decrease in the severity of dyspareunia and dryness symptoms [67–69].

One of the options for treating the symptoms of vaginal atrophy is the use of combined vaginal therapy: lyophilized culture of *Lactobacillus casei rhamnosus* (at least 2 x 10^7 CFU of viable lactobacilli), 0.2 mg estriol and 2.0 mg progesterone [70, 71], as well as an ultra-low dose of estriol (0.03 mg) and a lyophilized culture of *Lactobacillus acidophilus* KS400 (100×10^6 CFU of viable lactobacilli) [72]. Probiotic lactobacilli restore homeostasis in the vagina by enhancing the barrier function of the epithelium, affecting the secretion of antimicrobial peptides and mucosal immunity, and blocking the adhesion of pathogens. This allows not only to maintain the proliferation and maturation of the vaginal epithelium, but also to restore the lactobacillus microflora [70–72].

The presence of vasomotor symptoms is an indication for menopausal hormone therapy (MHT). However, up to 25% of women receiving MHT will continue to experience symptoms of urogenital atrophy. It is recommended that such women take vaginal estriol after reducing the severity or cessation of vasomotor disorders [62, 65].

Topical application of low doses of estrogen can cause side effects, such as burning sensation and swelling of the vaginal mucosa, which can reduce adherence to treatment [73]. There is also evidence that local estrogen therapy is not effective in 23–42% of treated women [74].

More than 60% of peri- and postmenopausal women with a history of breast cancer suffer from VVA symptoms. However, even topical estrogens present significant risks, especially in the estrogen-dependent histologic variant. Therefore, in the case of a history of estrogen-sensitive tumors, such as breast, endometrial, ovarian cancer, it is necessary to individually compare the risk and benefit together with an oncologist [36, 75]. Clinical data from large observational studies, such as Women's Health Initiative, Observational Study (WHI-OS), and the Nurses' Health Study, did not find an increased risk of endometrial cancer in women who used vaginal estrogens [76].

In February 2013, the US Food and Drug Administration (FDA) approved a selective estrogen receptor modulator, ospemifene, for the treatment of symptoms of VVA in menopausal women. It acts as an estrogen agonist in the vagina and has no clinically significant estrogenic effect on the endometrium or mammary glands. However, the safety of ospemifene has not been proven in women with a history of breast cancer or an increased risk of breast cancer or thromboembolism. The disadvantages of ospemifene compared to vaginal estrogens include the need for daily use and systemic side effects (flushing, potential risk of thromboembolism) [77].

Vaginal use of dehydroepiandrosterone sulfate (DHEA) for the treatment of GSM symptoms is due to the fact that DHEA is a precursor hormone and is converted into estrogen and androgens (testosterone, androstenedione and dihydrotestosterone) upon intravaginal administration [2]. The use of DHEA compared with placebo is an effective remedy for vaginal dryness, burning, itching, and dyspareunia and increases libido [78]. However, it has not yet been registered in the UK and Russia, and there are no data confirming its safety in patients with a history of breast cancer [79].

H.A. Torky et al. used oxytocin gel to treat symptoms of VVA in postmenopausal women. During treatment with oxytocin, there was an increase in the thickness of the vaginal epithelium and relief of VVA symptoms due to the ability of oxytocin to stimulate proliferation processes, increase the intensity of blood flow in the mucous membrane, and increase the secretion of growth factors [73].

The use of fractional laser and radiofrequency technologies is a new trend that is gaining popularity in the treatment of VVA. The most widely used technologies include fractional microablative CO_2 laser, non-ablative photothermal erbium-yttrium-aluminum garnet (YAG) laser and radio frequency (RF) energy devices. Laser or radiofrequency waves act by heating the connective tissue of the vaginal wall up to 40–42 °C. The effect of thermal energy on the walls of the vagina and vulva stimulates biological processes, such as proliferation, neovascularization, and synthesis of collagen and growth factors, which restores the elasticity and moisture of the vaginal mucosa and levels the symptoms of atrophy [80–82].

The effectiveness of laser therapy in the treatment of VVA has been assessed by VHI and the female

sexual function index (FSFI) in many studies and is comparable to that of topical estrogens [82–87]. Although the authors generally note that the procedure is well tolerated and proceeds quickly and painlessly, there have also been reports of increased pain in the vagina, scarring, fibrosis, impaired urination, and dyspareunia [88]. For the treatment of vaginal atrophy, three cycles are performed at an interval of 30–40 days, then once a year as maintenance therapy. However, the safety and efficacy of using a laser in vaginal atrophy has not been fully proven; it is not clear how long the effect of the treatment lasts [36, 88].

Temperature controlled transcutaneous radiofrequency (TTCRF) and, more recently, low-energy dynamic quadripolar radiofrequency (DQRF) can be used to treat VVA symptoms, sexual dysfunction, and urinary dysfunction [89–91]. No side effects, including burns or injury, have been reported. The treatment is well tolerated by patients. However, the number of patients is usually small, and the effectiveness of the method should be evaluated in larger studies [90].

Intramucosal (into the vaginal wall) injections of platelet-rich plasma is another direction in VVA treatment, which is under study. Injections are made once every 7–14 days, the course of treatment includes 2–6 procedures. Platelet-rich plasma (PRP) is an increased concentration of autologous platelets suspended in a small amount of plasma after centrifugation. The concept of PRP therapy lies in the ability of platelets to secrete numerous growth factors that are contained in platelet granules and are released from them during the process of platelet activation. Growth factors stimulate cell proliferation, differentiation, and migration to the injection site.

PRP therapy has a remodeling effect, supports tissue regeneration at the injection site, activates fibroblasts that create collagen and elastin, and also has antimicrobial and antifungal effects. PRP therapy is a safe and physiological method, since the patient's own blood components are used. PRP therapy is effective for treating dryness of the vaginal mucosa, burning, itching, discomfort, pain during sexual intercourse, discharge from the genital tract, inflammation of the vaginal mucosa when there is atrophy, as well as for restoring the microflora and, in general, occupies a leading position in anti-age medicine [92]. Stopping smoking may be an important factor in alleviating VVA symptoms, as smoking is associated with an increase in estrogen metabolism leading to vaginal atrophy [75].

Thus, VVA still remains a poorly understood and underdiagnosed disease. It affects the quality of life of millions of peri- and postmenopausal women. Over the past decade, various approaches have been developed to correct disorders of the urogenital tract associated with age-related estrogen deficiency, which create ample opportunities for the treatment of GSM symptoms. However, there is still no comprehensive data on the effectiveness and safety of many of the proposed drug and non-drug treatments.

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