Treatment of Vulvovaginal Atrophy

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Vulvovaginal atrophy (VVA) is a chronic progressive disease involving the female genital apparatus and lower urinary tract. This condition is related to hypoestrogenism consequent to menopause onset but is also due to the hormonal decrease after adjuvant therapy for patients affected by breast cancer. Considering the high prevalence of VVA and the expected growth of this condition due to the increase in the average age of the female population, it is easy to understand its significant social impact. VVA causes uncomfortable disorders, such as vaginal dryness, itching, burning, and dyspareunia, and requires constant treatment, on cessation of which symptoms tend to reappear.

Keywords: genitourinary syndrome menopause ; vulvovaginal atrophy ; vaginal atrophy ; menopause ; vaginal laser ; co2 laser ; erbium yag laser

1. Pathogenesis of Vulvovaginal Atrophy and Anatomopathological Changes after Menopause

The typical symptomatology of VVA is caused by the susceptibility of genital tissues to the decrease in estrogen levels. The genital and lower urinary tract share a common embryologic origin in women and widely express estrogen receptors [1]. In particular, vulvovaginal tissue normally presents alpha- and beta-estrogen receptors, but the latter are demonstrated to disappear after menopausal onset [2].

In the female genitals, the action of estrogen includes maintaining the thickness of the vaginal epithelium, the trophism of the smooth muscle layer, and the morphology and density of blood vessels and nerve endings. Within the extracellular matrix, there are fibroblasts responsible for producing collagen, which are also modulated by the action of estrogen. This mechanism is particularly important because collagen and other substances, such as proteoglycan macromolecules, provide elasticity and strength to the tissues [3].

With the advent of hypoestrogenism, the delicate nervous, muscular, and vascular mechanisms that regulate sexual function are disturbed. Estrogens, in fact, are involved in genital lubrication and trophism but also in complex brain networks that regulate sexual desire and satisfaction [4]. The microstructural changes caused by the estrogen withdrawal are accompanied by major anatomical and functional alterations: the epithelium becomes pale and less elastic, the vagina can narrow and shorten, the labia minora regress, and the introitus may constrict, all leading to severe sexual dysfunction [5].

Estrogens are also responsible for the maintenance of a physiological vaginal microbiome and a correct pH value. A healthy vaginal flora is characterized by a predominance of Lactobacillus species, which metabolizes glucose into lactic acid and acetic acid, lowering the vaginal pH to a range of 3.5–4.5 and protecting from vaginal and lower urinary tract infections [6]. With the thinning of the vaginal epithelium due to menopause, fewer squamous cells are discharged into vaginal secretions, and those that are have lower glycogen content. As vaginal glycogen levels fall, the population of Lactobacilli decreases and the vaginal pH increases [7].

2. Vulvovaginal Atrophy in Breast Cancer Survivors

Breast cancer is the most common neoplasia in women, accounting for 30% of all female malignancies, and invasive breast cancer has a lifetime probability of affecting one in eight women [7]. The increase in survival rate, which now exceeds 90% at 5 years [8], and the improvement in screening methods have led to the widespread diffusion of issues related to the quality-of-life impairments of these patients [9]. Menopausal symptoms affect up to 70% of breast cancer survivors [10] and mainly include vasomotor disorders and disturbances referable to atrophic vaginitis.

A major issue of this situation is the frequent young age of these patients, who often deal with premature menopause following adjuvant treatments for breast cancer. These disturbances can be particularly burdensome for such young

women and can adversely affect their health, social, and intimate life [11].

The currently available therapies for breast cancer have increased the survival rates but have also caused a wide range of biological changes that result in medically induced menopause and, consequently, in quality of life impairment [12]. Up to 80% of breast cancers are estrogen-receptor-positive [13]: this characteristic has allowed the development of targeted therapies that have achieved satisfactory treatment results, such as aromatase inhibitors and tamoxifen. The former block the activity of the aromatase enzyme, which is responsible for converting androgens into estrogens, while the latter is a selective estrogen receptor inhibitor [14].

As a result of this pharmacological hormonal decline, both drugs are responsible for inducing menopausal symptoms, including significant vaginal dryness, dyspareunia, and subsequent sexual dysfunction [12]. Tamoxifen acts as an antagonist of estrogen-positive breast cells, although it has a partial agonist effect on estrogen receptor alpha in the vagina, causing a quasi-estrogenic consequence on genital tissue. This mechanism of action possibly explains why tamoxifen causes a lesser incidence rate of vaginal dryness compared to aromatase inhibitors [14].

3. Treatment Options Available for Vulvovaginal Atrophy

VVA is a chronic and progressive condition that does not resolve spontaneously and often worsens without treatment or on its suspension due to its pathogenesis and correlation with age progression and menopause [15]. The principles underlying the treatment of vulvovaginal atrophy are the recovery of physiological urogenital function and the improvement of symptoms.

Lifestyle changes are important as they act on risk factors that may accelerate estrogen deprivation and aggravate symptoms. For this reason, patients are advised to give up smoking, which reduces estrogen bioavailability, and to lose weight in the case of obesity, which is a condition that appears to decrease blood flow in the genitourinary area [16].

First-line therapies to relieve symptoms of GSM include over-the-counter non-estrogenic vaginal lubricants and moisturizers [1]. Lubricants may be water-, silicone-, or oil-based and are applied to external genitalia before sexual intercourse, providing relief from sexual discomfort [17]. Vaginal moisturizers offer greater genital hydration, and, according to a randomized controlled clinical trial, hyaluronic acid vaginal gel effectively improves clinical disturbances and may be considered as a valid alternative to estrogen-based treatments in relieving the symptoms of vaginal dryness [18]. However, although lubricants are able to alleviate symptoms, the improvement is often temporary, and frequent reapplications are necessary [19]. It should be noted that lubricants and moisturizers do not reverse urogenital ageing but compensate for its anatomo-functional consequences by improving sexual comfort and maintaining vaginal secretions [20].

While systemic estrogens are exclusively recommended for women who complain not only of genital symptoms but also of vasomotor disturbances and problems related to osteoporosis [1], low-dose vaginal estrogens are considered the gold standard for patients of vaginal atrophy and sexual dysfunction who are unresponsive to non-prescription therapies [21]. Vaginal dryness and dyspareunia are, in fact, the most common indications of low-dose local estrogen therapy [1]. With both creams and vaginal ovules, the therapeutic indication is one application per day for 2 weeks, followed by a maintenance dose of two to three applications per week. Ideally, women should be treated with the lowest dose and frequency at which symptom control can be achieved [22]. Despite the availability of a wide range of vaginal hormone products, a recent Cochrane review suggested that there is no conclusive evidence of a difference in efficacy between different preparations when compared to one another, but, more importantly, there is poor quality of evidence regarding the clinical efficacy when compared against placebos [23]. Other issues concerning vaginal estrogens are patients' mistrust of hormone treatment and the low compliance with a daily-application therapy, which often leads women to abandon this prescribed medication [24].

An enormous disadvantage of both moisturizers and local estrogen therapy is precisely this poor compliance. A 2013 survey of more than 3000 post-menopausal women reported on patients' experiences and perceptions of the available treatments: regarding all the vaginal administrated therapies, the women reported high dissatisfaction due to annoying application procedures and bothersome vaginal discharge. In addition to this, topical estrogen treatment was found to be burdened by concerns regarding long-term safety due to hormonal exposure and consequent oncological risk [25].

A hormonal alternative to vaginal estrogens is dehydroepiandrosterone (DEHA), whose vaginal insert was recently approved by the FDA for the treatment of GSM [17]. It is an intermediate steroid hormone in the biosynthesis of androgens and estrogens and has been demonstrated to be effective in improving VVA symptoms and vaginal pH without causing dangerous endometrial stimulation [26].

The only orally available product approved for the treatment of vaginal dryness and moderate to severe dyspareunia is Ospemifene, a selective estrogen receptor modulator with an agonist/antagonist effect [27]. A long-term efficacy and safety clinical study with 180 women showed sustained improvements regarding the symptoms and clinical examination of the vagina, with no cases of endometrial hyperplasia or malignancies [28]. There is still no full clarity on the possible side effects of Ospemifene as it has been shown to possibly cause a worsening of hot flashes and an increase in the risk of venous thromboembolism [29].

The main prescription therapies available for VVA with their pharmaceutical forms and active ingredients are summarized in **Table 1**.

Table 1. Main pharmaceutical options for VVA treatment.

Administration Route	Formulation	Active Ingredients	
Systemic estrogens	Oral	Tablets	Estradiol
	Transdermal	Patches	Conjugated estrogens
Vaginal estrogens	Topical	Vaginal ovules	Estradiol
		Vaginal cream	Estriol
		Vaginal ring	Conjugated estrogens
Ospemifene	Oral	Tablets	Ospemifene
DEHA	Topical	Vaginal ovules	Prasterone

For breast cancer survivors, the guidelines from the American Society of Clinical Oncology (ASCO)/American Cancer Society (ACS) [30] and the North American Menopause Society [21] recommend the use of nonhormonal therapies, such as lubricants and vaginal moisturizers, as first-line therapy for these patients. While systemic hormonal therapy in breast cancer survivors is contraindicated by international guidelines due to the lack of safety data [31], the use of vaginal estrogens is usually not recommended due to the possibility of their systemic absorption and consequent increase in hormonal blood levels; this effect could revert the hormonal suppression achieved by therapy and potentially stimulate occult breast cancer cells [32]. The safety of intravaginal DHEA and oral Ospemifene after breast cancer has not been fully established considering the dearth of long-term clinical investigations [11].

Considering the limitations of the current treatments for VVA, it is essential to provide an alternative for all those women who do not respond, have contraindications, or are not compliant with the previously mentioned available therapies.

4. Laser Functioning and Rationale for Treatment of Vulvovaginal Atrophy

The two main types of lasers currently used for the treatment of VVA are the fractional micro-ablative CO_2 laser and the non-ablative photothermal Erbium:YAG laser.

Several other medical specialties started to use these technologies, with regenerative and rejuvenating purposes [33][34][35].

The effectiveness of the Er:YAG laser for vaginal atrophy was first described in 2015 [36]. Vizintin and colleagues reported this non-surgical, non-ablative thermal technique, which produces vaginal collagen hyperthermia following the remodeling and synthesis of new collagen fibers. This results in enhanced vaginal tissue tightness and elasticity and, consequently, improved symptoms of vaginal atrophy [36].

The vaginal micro-ablative CO_2 laser was introduced in 2014 and, immediately, different histological studies [37][38] confirmed its efficacy in changing and rejuvenating vulvovaginal tissue in patients affected by VVA. Subsequent studies correlated this genital remodeling to vaginal atrophy symptoms improvements.

Erbium:YAG technology is based on the concept of the controlled heating of the vaginal tissue, in particular the deeper mucosa, without over-heating the surface. A calibrated temperature stimulates the collagen fibers to contract and, consequently, the surrounding tissue to shrink as well. The thermal effect then continues throughout the processes of collagen remodeling and neocollagenesis, resulting in the generation of new fibers and an overall improvement in the tightness and elasticity of the treated tissue [36].

The micro-ablative fractional CO_2 laser exploits the heat generated by the vaporization of water in the cells in the deeper lamina propria [39]. Energy and, consequently, the micro-ablative impact are precisely delivered in order to limit surrounding tissue damage. The ultimate effect of this hyper-regulated injury includes neocollagenesis and neovascularization, with consequent improvements in vaginal pH, moisture, blood flow, and ground substance turgidity [40].

The mechanism of function of these two laser technologies and the tissue changes produced by the action of both have led to a realization of their potential for treating vulvovaginal symptoms caused by hypoestrogenism.

New collagen formation, the restoration of its architecture, neovascularization, and production of a ground matrix can contribute to reducing vaginal laxity while restoring the hydration to a more physiological vaginal pH and recreating a protective film that constitutes a barrier to genital infection. All these tissue changes represent a real rejuvenating process of the vaginal wall that is also demonstrated at the ultrastructural level [37].

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