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Review article

Genitourinary syndrome of menopause and the use of laser therapy

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ABSTRACT

Genitourinary syndrome of menopause is a common condition that left untreated can progress and negatively affect quality of life and sexual function. Laser therapy has a therapeutic role for several gynecologic conditions and most recently has gained interest as a non-hormonal treatment for genitourinary syndrome of menopause (GSM). The laser is well tolerated and may increase thickness of the squamous epithelium and improve vascularity of the vagina. These morphological changes presumably alleviate symptoms of dryness, dyspareunia, and irritation. However, the duration of therapeutic effects and safety of repeated applications at this point is not clear. Further research is needed in the form of controlled studies of the laser and other non-hormonal GSM therapies. The objective of this paper is to review the existing literature describing laser therapy for GSM.

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1. Introduction

Genitourinary syndrome of menopause encompasses a constellation of symptoms related to the decline of circulating ovarian

hormones. The syndrome may be characterized by complaints vaginal dryness, dyspareunia, pain, urinary incontinence, and recurrent urinary tract infections. Genitourinary syndrome of menopause (GSM) replaces the prior term vulvovaginal atrophy as agreed upon by the joint terminology conference sponsored by the North American Menopause Society (NAMS) and the International Society for the Study of Women's Sexual Health (ISSWSH) [1]. Since the average age of menopause 51 years and the population is aging, with projected life expectancy of 81 years by 2050, more women will be presenting to their clinician with GSM [2]. As well, because of this

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increased life expectancy, many women will live 40% of their lives after menopause with these associated symptoms.

Several therapeutic options are available to alleviate GSM symptoms, including hormonal and non-hormonal products. Most recently, fractionated laser therapy using the principles of regenerative medicine, has been introduced as another management option. This paper reviews the available data with regards to fractionated laser therapy for treatment of symptoms of GSM. Literature search was performed using PubMed, with key words including genitourinary syndrome, vulvo vaginal atrophy, atrophic vaginitis, postmenopausal symptoms, laser therapy and fractional CO₂ laser treatment. All publications reviewed were in English and were published within the last 8 years.

2. Etiology of the symptoms of genitourinary syndrome of menopause

Genitourinary symptoms may cause progressive symptoms in midlife and menopausal women whereas, the vasomotor symptoms usually ameliorate or resolve over time. Several women desire treatment for the bothersome symptoms that are caused by the metabolic and tissue changes associated with the menopausal hormonal changes and aging changes. The most frequent complaints women with GSM present with include vaginal dryness, itching, burning, dysuria and dyspareunia [3]. Consequently, these symptoms, that include diverse clinical symptoms and dermatologic features, account for a decline in the quality of life in 30–50% of aging women [3]. Recurrent infections also are occurring as the result of a decrease in mucosal lactobacilli and an increase in pathogenic bacteria consequent to a decrease in mucosal glycogen delivery triggered by declining ovarian hormonal levels [3].

The symptoms associated with GSM are often underreported by women, under-recognized by health-care providers and, therefore, under-treated [4]. Health-care providers should be proactive in helping their patients discuss this topic in order for the woman to feel comfortable in disclosing her symptoms and to be prescribed adequate education, counseling and treatment [4].

Genitourinary symptoms can be characterized according to the anatomic and physiologic changes that occur. Most of these changes are directly related to the decline in circulating estrogen levels and aging. The vaginal epithelium is a stratified squamous epithelium, which until menopause is moist and thick with rugae [3]. As epithelial cells exfoliate and die, they release glycogen, which is hydrolyzed to glucose that is subsequently transformed to lactic acid by the action of a normal vaginal commensal organism, lactobacillus. At menopause, epithelial thinning with decreased glycogenated superficial cells leads to changes in vaginal flora and a relative loss of lactobacilli, an increased pH, and a change in the microbiome [1]. The changes in vaginal flora that result are an increased growth of pathogenic bacteria such as group B streptococcus, staphylococci, coliforms, and diphtheroids. These organisms in turn, can cause symptomatic vaginal infections and inflammation [3].

High concentration of estrogen receptors in the vagina, vestibule, and trigone of the bladder modulates cellular proliferation and maturation [1]. The decline of circulating estrogen therefore results in reduced collagen content and hyalinization, decreased elastin, thinning of the epithelium, altered appearance and function of smooth muscle cells, increased density of connective tissue, and fewer blood vessels. The anatomic changes include regression and thinning of the labia minora, retraction of the introitus with reduced elasticity, often leading to significant entry dyspareunia. The urethral meatus becomes prominent

relative to the introitus and is vulnerable to physical irritation and trauma. Physiologic changes result in reduced vaginal blood flow, diminished lubrication, decreased flexibility and elasticity of the vaginal vault, and increased vaginal pH [1]. Furthermore, decreases in vaginal tissue strength and increased friability may predispose to epithelial damage with vaginal penetrative sexual activity, leading to vaginal pain, burning, fissuring, irritation, and bleeding after sex [1].

Symptoms related to vaginal atrophy have been reported to affect up to 45% of women. The Vaginal Health: Insight, Views and Attitudes (VIVA) study, surveyed 1578 women with vaginal discomfort. The most prevalent individual symptoms were vaginal dryness (83%) and pain during intercourse (42%). In this same study most women with discomfort (62%) reported the severity as moderate or severe [5]. Despite the high prevalence of such symptoms, only about 25% of affected women seek medical assistance [6]; reasons for not seeking medical help include patient embarrassment and the belief that their symptoms are an inevitable part of aging [5].

GSM also can have significant impact on quality of life. In the Women's Voices in Menopause study, 52% of the respondents reported some degree of negative impact on their quality of life, including negative consequences of their sex life, self-esteem, marriage/relationship and social life [7]. It also has been reported by Levine et al. that sexually active postmenopausal women with sexual dysfunction were four times more likely to have symptoms of vulvovaginal atrophy [8]. Postmenopausal women also report the avoidance of sexual intimacy because they experience pain or the expectation of pain with the onset of symptoms, making the prospect of sex-life with their partner no longer feasible [9].

In regard to postmenopausal breast cancer survivors (BCS), atrophic vaginitis affect nearly 70% of them as compared to 50% of postmenopausal women without breast cancer [10]. GSM symptoms appear to be more common and severe in older breast cancer survivors, especially in those requiring pharmacologic treatment. The majority of women with breast cancer receive systemic pharmacologic treatment consisting of chemotherapy and/or hormonal therapy. These therapies significantly improve clinical outcomes but lead to biological changes that may affect long-term vaginal health and impact quality of life in survivors [10]. Aromatase inhibitors (AIs) are frequently prescribed for postmenopausal breast cancer patients and have become the standard of care because of improved clinical outcomes as compared to Systemic Estrogen Receptor Modulator (SERMS). However, AIs are associated with increased atrophic vaginitis that may compromise compliance with treatment [11].

3. Treatment options for GSM

3.1. Non-hormonal therapy

First-line therapies to alleviate symptoms of GSM include non-hormonal vaginal lubricants and moisturizers as well as regular sexual activity with a partner, a sex device, or masturbation [12]. Vaginal moisturizers are designed to be used on a regular basis to reduce vaginal dryness [13]. Regular use of non-hormonal, long-acting vaginal moisturizing agents can decrease vaginal pH to premenopausal levels, although they do not improve vaginal maturation index (VMI) [12]. Use of lubricants during vaginal intercourse also may reduce friction-related irritation of atrophic tissue. Lubricants, which may be water-based or silicone-based, are intended to be used during sexual activity, and provide temporary relief from vaginal dryness and dyspareunia; however, they have no long-term therapeutic effects.

3.2. Hormonal/pharmacologic therapy

Local, low-dose estrogen preparations are considered first-line pharmacologic treatment for persistent symptoms related to vulvovaginal atrophy and are recommended over systemic estrogen +/- progestin therapy. Exogenous estrogen has several important effects on the vulvovaginal tissue, including increased blood flow, increased secretions, increased thickness of the vaginal epithelium, and reduced pH. The reduced pH is especially important as this acidity change may help restore the healthy vaginal microorganisms again, which will prevent infection. There are numerous local estrogen delivery products to choose from, including vaginal rings, creams, suppositories, and tablets. Although there are patient and clinician preferences with respect to delivery system, side effect profiles are similar. Systemic hormonal replacement therapy (HRT) may be indicated as a broader approach for severe vasomotor symptoms.

Pharmacologic therapies such as ospemifene, provides an alternative to oral and local estrogen therapies for moderate to severe postmenopausal dyspareunia. This estrogen agonist/antagonist appears to be safe and effective in normalizing vaginal maturation index and pH and improving the symptoms of vaginal dryness and dyspareunia associated with GSM [25]. In patients with a history of hormone-dependent cancer, an oncologist should be consulted before any hormonal treatment. The use of vaginal hormone products, safety profiles, and levels of systemic bioavailability and absorption in breast cancer patients remains understudied.

4. Laser use for therapy of GSM

4.1. Laser use in treatment of GSM

Regenerative medicine offers new ways of being able to replace, restore, or regenerate damages or diseased tissue and organs and further, to reestablish normal function in the human body. The idea is to use laser to activate the body's own repair mechanism, in order to repair, grow and heal tissues. Minimally ablative fractional laser therapy has gained acceptance as a preferred method for skin resurfacing and restoration, especially in the field of dermatology. This method has now been applied to the vaginal tissues and thermoablative fractional CO₂ laser is a recent management method for the treatment of symptomatic vulvar and vaginal atrophy.

In September 2014, the SmartXide² CO₂ laser from the Italian company DEKA, along with a CO₂ laser from the American company Cynosure, were cleared by the US Food and Drug Administration (FDA) for "incision, excision, vaporization and coagulation of body soft tissues in medical specialties including esthetic (dermatology and plastic surgery), podiatry, otolaryngology (ENT), gynecology, neurosurgery, orthopedics, general and thoracic surgery (including open and endoscopic), dental and oral surgery and genitourinary surgery. The use with the scanning unit is indicated for ablative skin resurfacing." [14]. There are now several laser systems marketed for use in the treatment of GSM. Since the FDA release, laser technology is being introduced extensively to healthcare practitioners and directly to consumers.

Historically, laser treatment has been safely and effectively used in many areas of the body such as the skin of the face, neck and chest and also in the mouth. This application has been tested by Salvatore and colleagues on ex vivo vaginal specimens from postmenopausal women. These investigators observed tissue remodeling without damage to surrounding tissue, after the application of fractional CO₂ laser technology [15]. A subsequent pilot study demonstrated the efficacy of microablative fractional CO₂ laser in the treatment of GSM, with significant improvement reported at 12-week follow-up [16]. This technique appears a feasible option in

improving vaginal health in postmenopausal women [17]. Salvatore et al. [17] also reported that women treated noted improvement in vulvo-vaginal symptoms (dryness, itching, dysuria, burning, and dyspareunia); there also was an improvement in the Vaginal Health Index Score at 12 weeks after 3 CO₂ laser applications. Furthermore, women's quality of life and sexual function measured by the SF-12 and FSFI questionnaires were significantly improved over baseline at 12 weeks [18]. Perino and colleagues also confirmed the safety, efficacy and feasibility of vaginal laser therapy in the treatment of GSM [19]. Histologic evidence of the restoration of vaginal mucosal structure following fractional carbon dioxide (CO₂) laser treatment has been published by Zerbinati, and results were attributed to the wavelength, profile pulse and pulse width used [20].

4.2. How does it work? Stratified squamous epithelial restoration of structure

Low-level laser therapy (LLLT) has been proven as a beneficial therapeutic modality for many disease conditions. Very specific laser and light-emitting diode irradiation parameters have been shown to induce specific cellular activities, such as, cellular proliferation and viability [21]. The stimulation of mitochondrial activity, results in adenosine triphosphate (ATP) production, synthesis of DNA and RNA, and activation of cell signaling cascades for the production and release of growth factors and cytokines [21]. The molecular effects of LLLT are not well studied but the clinical effects of increased proliferation and viability of tissue have been demonstrated in dentistry and dermatology, with reduction of patient reported pain, anti-inflammatory effects, wound healing and remodeling of collagen [21].

The development of the new CO₂ laser system for micro-ablative fractional resurfacing, has allowed for superficial epithelial resurfacing as compared to that of the usual CO₂ and Er:YAG lasers. Ablative lasers (usual CO₂ and Er:YAG) used for other treatments and not for epithelial resurfacing, cause complete vaporization of the epidermis and variable thermal damage to the dermis. These deeper penetration lasers result in delayed re-epithelization, persistent erythema, permanent hypopigmentation, and in some cases even scars or keloids [22]. It appears that with proper selection of the wavelength and frequency of laser pulse, selective therapy can be safely administered with a modified device and associated software to deliver fractional CO₂ laser exposures, leaving intact skin between foci of ablated tissue [23]. Morphological findings of improved vaginal epithelial thickness and denser lamina propria were observed in postpartum with vaginal atrophy or relaxation has been shown with the use of the Erbium: YAG laser [24]. These effects were observed at 2 months and improvement quantified with perineometer values and sexual satisfaction scores [24].

5. Research needs in the future

Although laser technology appears to be another option for the treatment of GSM, long-term efficacy and safety data are lacking. What is promising is that the laser has broad indications and applications. Thus far, most studies report observed results after 12 weeks, with no further follow up. Therefore, assumptions cannot yet be made regarding the durability of this treatment nor the long term effects, either positive or negative. Continued evaluations regarding number of treatments and interval of treatment are needed to remove the obvious gaps in knowledge. More research to better outline the indications for and specific applications of this technology is desirable before advocating its universal use for the management of GSM.

6. Summary

Genitourinary syndrome of menopause is a common condition that if left untreated can negatively impact a woman's quality of life and vulvovaginal health. Usually women with contraindications or those declining local vaginal estrogen therapies or ospemifene have limited management options other than vaginal lubricants or other non-hormonal treatments. Short-term data regarding the use of laser therapy has reported improvement in vaginal epithelium morphology and symptoms and therefore appears to be a non-hormonal therapeutic modality. Controlled studies with long-term follow-up are needed to provide more data on how this new treatment can be used for long periods of time, since aging women can have GSM for several decades.

Contributors

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