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REVIEW PAPER

Genitourinary syndrome of menopause treatment using lasers and temperature-controlled radiofrequency

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Abstract

Perimenopausal changes caused by oestrogen deficiency are accompanied by a decrease in the content of collagen and elastin in the tissues, leading to thinning of the epithelium and the resultant disappearance of the superficial layer, which leads to smooth muscle dysfunction as well as connective tissue degradation. This aetiopathogenetic chain results in a set of symptoms experienced by approximately 50% of women in the peri- and postmenopausal period. Symptoms of dryness, burning, dyspareunia and urgency contribute to a significant reduction in the quality of sexual function and general comfort of life due to recurrent infections of the vagina, vulva and urinary tract. Different therapeutic methods may benefit genitourinary syndrome of menopause (GSM), while innovative methods such as lasers or radiofrequency deserve further study in this area.

Key words: genitourinary syndrome of menopause, vulvovaginal atrophy, sexual health, lasers, radiofrequency.

Introduction

Genitourinary syndrome of menopause (GSM) is a new term, which is used to describe a variety of menopausal symptoms and signs that are related to physical changes of the vulva, vagina, and lower urinary tract. Until 2014 terms such as *vulvovaginal atrophy* and *atrophic vaginitis* were widely used, but were considered to be insufficient for the constellation of symptoms and signs associated with genitourinary changes after menopause. In early 2014 the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of the North American Menopause Society (NAMS) formally adopted the term "genitourinary syndrome of menopause".

GSM is characterised by a set of symptoms and signs connected with oestrogen insufficiency involving changes in the labia, introitus, clitoris, vagina, urethra and bladder [1]. Approximately 50% of menopausal women manifest signs and symptoms of GSM [2].

As a result of postmenopausal oestrogen deficiency the following, anatomic and histological changes are noted in female genital tissues:

1) symptoms of GSM:
- vaginal dryness, irritation and dryness,
- burning sensation,
- dyspareunia,
- feeling of pressure,
- yellow malodorous discharge,
- pressure, tenderness,
- urinary frequency,
- incontinence,
- urgency,
- urinary tract infections (UTIs),
- difficulty in sexual arousal,
- inadequate lubrication during arousal,
- vaginal bleeding from fragile atrophic skin,
- dryness of labia;

2) physical signs of genitourinary syndrome of menopause:
- pale, smooth or shiny vaginal epithelium,
- loss of elasticity or turgor of skin,
- sparseness of pubic hair,
- fusion of labia minora,
- introital stenosis,
- pelvic organ prolapse,
- vulvar dermatoses,
- pH changes,
- loss of labial and vulvar fullness.

Many women are seriously affected by these symptoms, which cause physical and psychological discomfort, poor quality of sexual life or even avoidance of intimacy.

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Vulvovaginal atrophy (VVA) is a component of GSM [3]. VVA is very common; it affects up to 84% of menopausal women, according to some studies [4]. In a cross-sectional, population-based study of American women in the age range 40 to 65 years, symptoms corresponding to VVA occurred in 57% of sexually active women [5]. In a study of 913 post-menopausal women, who visited a gynaecologist for a routine examination, GSM was diagnosed in 65% of women just one year after menopause and in 85% women six years after menopause [6]. The most common symptoms reported by these women included vaginal dryness (100%), dyspareunia (78%), burning (57%), itching (57%) and dysuria (32%) [7].

Treatment of genitourinary syndrome of menopause

Given that GSM may have a significant impact on a women's lives, gynaecologists need to talk to their patients and help relieve their symptoms. All menopausal women should be screened for GSM. There are various methods listed below by which it is possible to improve the quality of life in menopausal patients:

- non-pharmacologic therapies – sexual counselling, dilatators, stress reduction therapy;
- non-hormonal OTC products – vaginal lubricants or moisturizers, herbal products,
- prescription products – oral oestrogens, transdermal oestrogens, intravaginal oestrogens, vaginal creams, vaginal tablets, vaginal rings, tibolone.

In this article, the authors will focus on CO_2 lasers, YAG lasers, and a transcutaneous temperature-controlled radiofrequency device.

Lasers

Albert Einstein in 1917 discovered that under certain conditions, atoms could absorb light and be stimulated to shed their energy, although it was not until 1959 that the name LASER (light amplification by stimulated emission of radiation) was introduced by Gordon Gould into the literature [8].

The Food and Drug Administration (FDA) has approved laser therapy for several medical indications (e.g. dental procedures, ophthalmology, including refractive eye surgery, tumour and cataract removal, and cosmetic surgery). In 2014, the FDA approved the use of fractional microablative CO_2 laser therapy for genitourinary surgery, but not for the treatment of GSM.

In relation to GSM therapy, the micro-ablative fractional CO_2 laser, or the non-ablative vaginal erbium YAG laser (VEL), can be considered as a therapeutic option that enables women to avoid hormonal interventions. Also other non-ablative electromagnetic energy, radiofrequency (e.g. low-energy dynamic quadripolar radiofrequency – DQRF) could be considered for this particular indication [9].

Laser therapy improves the vascularization of the vaginal mucosa, stimulates the synthesis of new collagen, extracellular matrix ground substances in the vaginal connective tissue, thickens the vaginal epithelium with the formation of new papillae, replenishes glycogen in the vaginal epithelium, and restores the balance in the mucosa, which reduces the symptoms of vulvovaginal atrophy. Available data suggest that inducing morphologic changes in vaginal tissue with laser and DQRF intervention can relieve the symptoms of vaginal dryness and dyspareunia accompanying GSM [10-12].

CO_2 laser, or VEL treatment, usually consists of a series of 3-4 treatments, 4-6 weeks apart, taking about 1-2 min per session, as an in-office procedure.

Various measurements are used for evaluating the effectiveness of laser GSM treatment:

- Visual Analogue Scale – VAS 0-10,
- Female Sexual Function Index (FSFI), which measures sexual function evaluating 6 domains (desire, arousal, lubrication, orgasm, satisfaction and pain), and provides a total score; higher scores define better sexual function. Vaginal Health Index Score (VHIS): elasticity, fluid volume, pH and epithelial integrity. The sum of the 5 components can provide an upper score of 25 and a lower of 5. A score of ≤ 15 defines the presence of vaginal atrophy,
- a cytological evaluation: calculation of the vaginal maturation value (VMV): $\leq$ 40% defined atrophy on the vaginal smears.

According to Athanasioua *et al.*, who examined 55 postmenopausal women with GSM symptoms, CO_2 laser therapy may enable complete regression of dyspareunia, dryness and reestablishment of normal sexual function after 3 laser sessions. The improvement of vaginal health was reflected by the subjective measurements of VAS and FSFI. The VMV increased following each subsequent therapy, resulting in 80-100% of participants surpassing the thresholds of non-atrophic clinical findings. The study identified several limitations in its design [13].

Among recent publications, a short-term Brazilian clinical trial of the CO_2 laser, compared with 1 mg oestriol cream, in a cohort of 45 women, suggests general efficacy of laser alone or in combination with oestriol after 20 weeks. Although patients experienced alleviation in symptoms in every oestriol treatment group, a significant increase in dyspareunia was noted only in the laser group [11]. In one of the pioneering studies, Salvatore *et al.*, using the same laser system and parameters as used in this study, showed significant improvement in pain and other symptoms by the 12th week [10].

Laser application in postmenopausal breast cancer survivors may be a reasonable alternative, given that

hormonal topical therapy is contraindicated. Pagano *et al*. published a retrospective series of case studies of 82 survivors of breast cancer, who failed to have adequate relief of their GSM symptoms with non-estrogenic local treatments. These women were treated with 3 cycles of CO_2 laser and demonstrated significant improvements in genital sensitivity during intercourse, vaginal dryness, decreased itching or stinging, dyspareunia, dysuria, bleeding, and movement-related pain [14].

Laser therapies lack adequate RCTs and long-term safety. Efficacy data may be considered in women who prefer non-hormonal treatments after a discussion of potential risks, benefits, and need for ongoing treatments, and costs. NAMS recommendations for management of GSM in specific patient populations: women at high risk for breast cancer, women with oestrogen-receptor positive breast cancers, women with triple-negative breast cancers, and women with metastatic disease – choose lasers as a first line therapy [15].

It is necessary to acknowledge that laser therapy for GSM is not FDA-approved at this time. The American College of Obstetricians and Gynecologists in its most recent position statement on laser therapy, dated May 2016, emphasizes the importance of accurately informing patients of a treatment's FDA status. The statement emphasizes that procedures which use lasers and other energy-based devices, such as radiofrequency, when applied to destroy or reshape vaginal tissue "may have serious risks and don't have adequate evidence to support their use for these purposes" according to the FDA Commissioner, Scott Gottlieb. It also should be stressed that the FDA has cleared laser and energy-based devices for destroying abnormal or precancerous cervical or vaginal tissue, as well as condylomas (genital warts) and other serious conditions [16].

The reason for the FDA statement is a lack of larger studies demonstrating long-term safety and efficacy, as well as an analysis of cost-effectiveness in laser GSM therapy. Despite the publication of the first RCT, it is evident that RCTs in vaginal laser treatment for GSM with a true placebo arm are urgently needed [17].

Buttini *et al.* focus in their publication on laser GSM therapy side effects. Clinicians should remain aware of the fact that vaginal laser therapy, as administered in this trial, can also worsen pain, and therefore topical vaginal oestrogen therapy remains the gold standard [17].

According to the FDA, vaginal burns, scarring, pain during sexual intercourse, and recurring or chronic pain can affect women undergoing a laser procedure in GSM therapy. In July 2018, the FDA released a press statement in an effort to safeguard women's health from deceptive health claims and significant risks related to devices being marketed for use in medical procedures for "vaginal rejuvenation" [18].

Slight spotting, scarring and discomfort during the procedure may be related to an atrophic, narrow vestibule and vagina, and the discomfort seems to be transitional. The issue of persistent vulvar pain and dyspareunia cannot be ignored. Unfortunately, GSM symptoms are similar to vulvodynia (dryness, dyspareunia, soreness, dysuria) [19].

On the basis of carefully taken history, if GSM-like symptoms appear before menopause, the clinician can suspect a pre-existing condition. Vulvodynia, in most cases, is caused by pelvic floor muscle dysfunction/hypertonic state. The laser intravaginal shockwave may aggravate muscle spasms and increase side effects, so the procedure is contraindicated in such patients. All of these potential risks require further confirmation, to reduce side effects and promote safe use of the procedure.

Vulvodynia could be suspected in every GSM patient when topical oestrogen is not effective. According to NAMS recommendations, non-hormonal treatment is the first choice, especially when oestrogens are contraindicated (e.g. breast cancer survivals). Moisturizers and lubricants, pelvic floor physical therapy (e.g. manual therapy, biofeedback) dedicated also for vulvodynia patients, and dilator therapy are first-line treatments for GSM symptoms [15, 20].

Radiofrequency

There are different types of radiofrequencies; the most popular is transcutaneous temperature-controlled radiofrequency (TTCRF).

In gynaecology monopolar radiofrequency is commonly used – in this configuration there are two electrodes. One of them, a passive (grounding) electrode, is in contact with the patient's body and the second emits radio frequency radiation that reaches through the body to the passive electrode. Depth and the heating area in this method are larger than in others (bipolar, multipolar). In 2010, Millheiser and colleagues demonstrated the efficacy of monopolar radiofrequency on vaginal laxity after childbirth. This study found that radiofrequency safely improved laxity and sexual function up to 6 months after treatment [21]. This is one of the first articles published about radiofrequency; it was published in 2010. Currently there are a number of new reports on the effectiveness of this method.

TTCRF is safe, tolerable and effective for vulvovaginal rejuvenation. Evidence suggests applications in the treatment of atrophic vaginitis, orgasmic dysfunction, and stress incontinence [22]. Recently, a vaginal probe (ThermiVa) was developed for treatment of vulvovaginal tissues using this technology. TTCRF brings numerous benefits for the treatment of vagina laxity and GSM symptoms. The aim of treatment is to heat vaginal/vulvar epithelium to approximately 40-45°C for a defined treatment time, with each zone being treated for 3-5 minutes, for a total time of 25-30 minutes per treatment session [23]. These sessions may be repeated at

4-6 week intervals [24]. Ultrasound gel is needed during the treatment process. The effect of TTCRF on vaginal epithelium is that it restores most vaginal functions such as secretion, absorption, elasticity, lubrication, and vaginal epithelium thickness.

Mechanism of rejuvenation

The heat generated in the skin under the influence of radio waves, depending on the time and power, shortens and densifies collagen or its partial denaturation. With age, there are fewer collagen fibres in the dermis. These fibres stretch and their structure becomes disordered. Heating the skin results in the re-tensioning of collagen fibres and stimulation of fibroblasts to create new collagen and elastin. The generation of heat in the tissues further extends the blood vessels, which improves the nutrition and oxygenation of skin, as well as its metabolism. As a result, the skin and mucosa become firmer.

In a prospective nonrandomized trial by Monigue *et al.*, 10 female patients with mild-to-moderate vulvovaginal laxity (VVL), with or without atrophic vaginitis (AV), orgasmic dysfunction (OD) and/or stress urinary incontinence (SUI), underwent 3 courses of TTCRF at 4-week intervals. Assessment was performed at baseline and days 10, 30, 60 and 120. One patient was discontinued from the study because of noncompliance with the study protocol.

Radiofrequency energy was applied to the vagina and the labia majora and minora using a special probe. The electrode tip was passed back and forth slowly with wide movements over each treated area for 3 to 5 minutes, for a total treatment time of 30 minutes. The temperature setting was 42°C to 45°C depending on patient tolerance. Overall satisfaction at the final visit (day 120) showed that 77.8% of patients (7 of 9) were "satisfied" or "very satisfied", and 77.8% indicated that they would recommend the procedure to friends and family. A total of 42.9% (3 of 7) reported at least 50% improvement in symptoms of OD and 55.6% (5 of 9) had at least 50% improvement in SUI, while 57.1% (4 of 7) reported a 51-75% improvement in AV. By the last visit at day 120, all patients reported significant satisfaction with their overall sexual life [25].

Alinsod performed a very similar study with 23 patients participating in a prospective study (age range 26-58 years, mean 43.6, and median vaginal births was 2) [22]. All patients reported mild to moderate primary or secondary vulvovaginal laxity. All of them also had associated secondary conditions (orgasmic dysfunction, stress incontinence, or atrophic vaginitis). All patients were treated using TTCRF. The clinical endpoint was achievement of the target temperature range of 40°C to 45°C for approximately 3-5 minutes per zone (or longer, depending on heat tolerance). Total treatment time was less than 30 minutes. A complete course of therapy consisted of three treatments with the TTCRF device, at an interval of approximately 4-6 weeks. Patients were offered up to three treatments. Outcome measures for this study included: subject assessment via the Vaginal Laxity Questionnaire (VLQ), rating on a 7-point scale (where 1 = very loose and 7 = very tight), and the Sexual Satisfaction Questionnaire (SSQ) rating on a six-point scale (where 1 = none and 6 = excellent), as well as noting of associated conditions such as incontinence, atrophic vaginitis, and orgasmic dysfunction. The results showed a median improvement of 5 points on the VLQ scale and 2.5 points on the SSQ scale, with a statistically significant improvement ($p < 0.05$) [22].

Conclusions

GSM is a very common problem among post-menopausal women which severely impacts quality of life. Patients may be reluctant to talk about vaginal dryness, and the specialist may need to initiate a discussion to reduce discomfort. Treatment has to be individualised. The presence or absence of systemic symptoms and comorbidities has to be considered when choosing the best therapy for a patient. Local oestrogen therapy and vaginal moisturizers are highly effective, but there is also laser or radiofrequency therapy, which may be successful. Intra-vaginal, non-ablative, energy-based devices seem to be a promising alternative for the treatment of mild to moderate symptoms related to GSM.

Disclosure

The authors report no conflict of interest.

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