SEXUAL MEDICINE REVIEWS

Sexual Function in Women Suffering From Genitourinary Syndrome of Menopause Treated With Fractionated CO_2 Laser

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ABSTRACT

Introduction: Genitourinary syndrome of menopause (GSM) has a significant impact on the trophism of the genital and lower urinary tracts and can considerably impair sexual function. Fractional CO_2 laser has a regenerative effect on vulvovaginal tissue trophism after menopause.

Aim: To review the available literature on the effect of fractional CO_2 laser on the sexual function of postmenopausal women affected by GSM.

Methods: A database search was carried out using the terms *CO_2 laser, vaginal atrophy, sexual function, dyspareunia,* and *genitourinary syndrome of menopause* and excluding studies using other types of laser or including breast cancer survivors with vulvovaginal atrophy. For statistical analysis, the estimated overall laser effect was computed (when at least two studies were involved) and data type of generic inverse variance was computed using inverse variance as the statistical method, a random-effects model, and the difference in means as an effect measurement.

Main Outcome Measures: Different methods of evaluating sexual function were reported and studies were grouped and analyzed accordingly. Subjective assessment for dyspareunia was evaluated with a 10-point visual analog scale. Patient-reported outcome for an overall perception of sexual function was evaluated with a Likert scale. The Female Sexual Function Index was used as a condition-specific questionnaire.

Results: Six articles were considered for this review. A total of 273 women (mean age = 57.8 years) were treated with the same protocol in all studies. Compared with baseline, at the end of the treatment, dyspareunia significantly decreased in severity ($P < .001$), and the patient's perception of overall sexual function showed a statistically significant improvement ($P < .001$). At the last follow-up visit, the Female Sexual Function Index score for each single domain and overall score was significantly better than at entry ($P < .001$).

Conclusion: Fractional CO_2 laser can improve sexual function in postmenopausal women affected by GSM by restoring a better trophism in the lower genitourinary tract. **Salvatore S, Pitsouni E, Del Deo F, et al. Sexual Function in Women Suffering From Genitourinary Syndrome of Menopause Treated With Fractionated CO_2 Laser. Sex Med Rev 2017;X:XXX–XXX.**

Key Words: CO_2 Laser; Genitourinary Syndrome of Menopause; Sexual Function; Quality of Life

INTRODUCTION

In 1916 Albert Einstein[1] introduced the concept of stimulated emission for energy balance, the primary principle of the laser (acronym for light amplification by stimulated emission of radiation). However, although the first functioning laser was described by Maiman[2] in 1960, the first scientific report of laser medical use was in dermatology and described by Goldman et al[3] in 1963.

The interaction between an electromagnetic wave and biological tissue depends on the wavelength and on the optical properties of the tissue; different light sources are commonly used in medicine with specific wavelengths. The CO_2 laser is in the infrared spectrum, with a wavelength of 10,600 nm and high water absorption, giving it superficial action.

The laser mode of delivery can be continuous or fractionated; the latter avoids possible tissue damage secondary to overheating.

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Tissue modifications produced in this way can vary depending on the machine setting and can include vaporization, ablation, coagulation, collage shrinkage, or collagen neo-synthesis and remodeling. Studies on laser skin resurfacing have demonstrated that shrinkage of collagen fibers, after they have been denatured by laser-generated heat, is the primary mechanism of skin tightening, although vaporization of intracellular water and ablation also contribute. The wound-healing phase is initiated by extremely high levels of collagenases (matrix metalloproteinases), which degrade the fragmented collagenous matrix. Rapid reconstitution of the epidermis from adjacent epidermal cells contrasts with healing after traditional resurfacing in which new epidermis is derived from cells that migrate from adnexal structures. A prolonged period of new dermal collagenesis of up to at least 6 months follows.[4–7]

Because of its regenerative tissue properties, the fractional CO_2 laser was used first in dermatology for many conditions including scars and changes caused by acne and aging, among other indications, and then in many other medical fields. Different studies have described the successful effect of fractional CO_2 laser in treating aging-related and atrophic conditions.[8–12] In 2003 Capon and Mordon[13] reported the mechanism of action of CO_2 laser in regenerating atrophic tissue through micro-ablative and thermal effects. The former induces tissue regeneration, whereas the latter induces some changes in cell metabolism. The heating shock induces the production of some proteins called *heat shock proteins.* Heat shock protein 70 stimulates the action of transforming growth factor-β in activating fibrocytes to become fibroblasts that are responsible for the synthesis of the new extracellular matrix, new collagen, and new elastic fibers. This process of tissue remodeling takes 30 days to occur.

Fractional CO_2 laser also has been used in dentistry for severe conditions such as oral leukoplakia.[14] In all these conditions, the regenerative effect of CO_2 laser can be used to remodel the affected tissue to create healthy tissue.

Genitourinary syndrome of menopause (GSM) is a new terminology used to describe symptoms that occur secondary to vulvovaginal atrophy (VVA).[15] The recent change in terminology from "vulvovaginal atrophy" or "atrophic vaginitis" to "genitourinary syndrome of menopause" stems from a consensus panel consisting of the Board of Directors of the International Society for the Study of Women's Sexual Health and the Board of Trustees of the North American Menopause Society (NAMS). Based on a terminology consensus conference in May 2013, they determined that "genitourinary syndrome of menopause" is a more accurate, all-encompassing, and more publicly acceptable term to indicate the collection of genital, urologic, and sexual sequelae caused by hypoestrogenism after menopause. Premenopausal women also can develop an estrogen deficiency with similar sequelae, in particular those treated with hormonal therapies and chemotherapy for breast cancer.

Regardless of its origin, the hypoestrogenic state results in anatomic and physiologic changes in the genitourinary tract.[16] A loss of superficial epithelial cells, decreased collagen content and hyalinization, decreased elastin, altered appearance and function of smooth muscle cells, and fewer blood vessels are common histologic findings. Then, there is a loss of vaginal rugae and elasticity that results in a narrowing and shortening of the vagina. The vaginal epithelium becomes much thinner and more fragile, resulting in tears that can lead to bleeding and fissures, especially during sexual activity. There also is a loss of subcutaneous fat from the labia majora and these changes can result in narrowing of the introitus, fusion of the labia majora, and shrinkage of the clitoral prepuce and urethra. The vaginal pH becomes more alkaline, which can alter the vaginal microbiota and increase the risk of urogenital infections (specifically, urinary tract infections). Vaginal secretions, largely transudate, from the vaginal vasculature also decrease over time. These menopause-related changes in the genitourinary tract can lead to debilitating symptoms whose prevalence, unlike vasomotor symptoms, tends to increase with the number of years since menopause.

Genital complaints include vaginal or vulvar dryness, burning, and irritation. Lack of lubrication, discomfort, or pain considerably impairs sexual function. Because the urethra and the bladder trigone are derived embryologically from the same estrogen receptor–dense primitive urogenital sinus tissue, women also might complain of "irritative" bladder symptoms such as frequency of micturition, urgency, dysuria, and recurrent urinary tract infections.[15]

In a postmenopausal woman complaining of these symptoms, examination of the external genitalia might show a pale and shiny vaginal mucosa with possible patches of erythema. Lacerations or lesions, labial fusion, or introital stenosis might be present. After the initial clinical assessment, several laboratory tests can be considered to confirm the diagnosis. Vaginal cytology shows an increase in basal epithelial cells and a decrease in superficial cells, whereas vaginal pH, Pap test, and vaginal culture are useful to detect the presence of genitourinary infections.[17]

According to the NAMS position statement on the management of symptomatic VVA, use of non-hormonal lubricants during intercourse and, if indicated, regular use of long-acting vaginal moisturizers are first-line therapies, whereas estrogens remain the therapeutic standard for symptomatic women with moderate to severe VVA and for those with milder VVA that does not respond to lubricants and moisturizers. Estrogens can be administered vaginally or systemically but low-dose vaginal estrogens should be preferred when VVA is the only menopausal symptom.[18]

As stated in the American Congress of the Obstetricians and Gynecologists' (ACOG) practice bulletin on the management of menopausal symptoms, non-estrogen water-based or silicone-based vaginal lubricants and moisturizers might be particularly helpful in women who do not wish to use hormonal therapies.[19] Vaginal lubricants are used to relieve friction and dyspareunia related to vaginal dryness during intercourse and are applied to the vaginal introitus before intercourse. Vaginal moisturizers are

intended to trap moisture and provide long-term relief of vaginal dryness. Although there are limited data on the effectiveness of these products, prospective studies have demonstrated that vaginal moisturizers alleviate vaginal dryness, restore pH balance and elasticity, and decrease vaginal itching, irritation, and dyspareunia.[20]

Dezzutti et al[21] found that hyperosmolar lubricants were associated with toxicity toward epithelial cell lines or ectocervical or colorectal explant tissues, whereas nearly iso-osmolar and silicon-based lubricants demonstrated no significant changes in tissue viability or epithelial modifications. One jelly lubricant and one moisturizer also were found to be toxic to lactobacilli. In a study by Brown et al,[22] women reporting intravaginal use of petroleum jelly during the past month were 2.2 times more likely to test positive for bacterial vaginosis compared with non-users (95% confidence interval = 1.3−3.9) and the intravaginal use of oils was associated with *Candida* species colonization (44.4% vs 5%; $P < .01$). Therefore, when selecting a lubricant or a moisturizer, women should be advised to choose a product that is optimally balanced in osmolality and pH and is physiologically most similar to natural vaginal secretions.[23]

Estrogen therapy effectively alleviates atrophic vaginal symptoms related to menopause.[19] As mentioned earlier, systemic hormone replacement therapy is suggested to patients who seek relief from vasomotor symptoms and protection from osteoporosis in addition to GSM sequelae, whereas topical estrogens alone are indicated if the primary menopausal symptoms are related to vaginal atrophy.[17] According to the NAMS, low-dose vaginal estrogens decrease vaginal pH, increase the number of vaginal lactobacilli, improve vaginal and urethral cytologic results, and prevent frequent urinary tract infections.[18] The Society of Gynecologic Surgeons systemic review group recently reviewed the results of estrogen use for GSM.[24] They concluded that all commercially available vaginal estrogens can effectively relieve common VVA-related complaints and have additional utility in patients with urinary urgency, frequency, stress urinary incontinence, urge urinary incontinence, and recurrent urinary tract infections. Although the meta-analysis clearly demonstrated that estrogen therapy relieves the symptoms of GSM, the investigators also acknowledged that a clearer understanding of the exact risk to the endometrium with sustained use of vaginal estrogen and a more precise assessment of the changes in serum estradiol are needed.

Another currently available agent approved by the US Food and Drug Administration (FDA) for treating moderate to severe dyspareunia in postmenopausal women is ospemifene, a selective estrogen receptor modulator. This synthetic compound selectively stimulates or inhibits estrogen receptors of different target tissues. A study of 826 postmenopausal women randomized to receive ospemifene 30 or 60 mg showed that the 60-mg dose was effective for relieving VVA.[25] Common adverse effects of ospemifene reported during clinical trials included hot flushes, vaginal discharge, muscle spasms, genital discharge, and excessive sweating.

Fractional CO_2 laser has been shown to have an important regenerative effect on the vaginal tissue by remodeling the lamina propria and the epithelial layer. In the lamina propria, CO_2 laser produces a remodeling process with an increase in collagen and elastic fibers and neovascularization. In the epithelium layer, larger papillae and larger epithelial cells rich in glycogen with superficial exfoliating properties also have been reported.[26,27]

The regenerative effect of fractional CO_2 laser on the vaginal tissue significantly alleviates symptoms related to the atrophic changes secondary to menopause. This has been shown with subjective and objective tools and with patient-reported outcome evaluation.[28,29]

As a result of this regenerative effect and improvement in atrophic symptoms, sexual function has been evaluated in women who underwent fractional CO_2 laser treatment.

The aim of this review is to analyze the reported effect on sexual function in postmenopausal women treated with fractional CO_2 laser for GSM.

METHODS

The PubMed (Medline), Scopus, and Web of Science databases were searched systematically for records from 2010 to 2016 using the terms *CO_2 laser, vaginal atrophy, sexual function, dyspareunia,* and *genitourinary syndrome of menopause.* We aimed to identify all original English-language reports describing the outpatient treatment of VVA secondary to GSM with fractional CO_2 laser. The procedure must have been performed in an office setting, and no concomitant treatment for GSM was allowed.

After the exclusion of duplicate publications, non−English-language literature, letters, editorials, and reviews not reporting original data, the remaining articles were reviewed.

References of the included articles were manually searched to identify other potential relevant studies.

In each report, we sought to abstract possible differences in performing the procedure or complications that could interfere with sexual function.

Studies using laser types other than fractional CO_2 or including women with VVA secondary to treatment for breast cancer were excluded.[30,31]

Different methods of evaluating sexual function were reported and studies were grouped and analyzed accordingly. Subjective assessment for dyspareunia was evaluated with a 10-point visual analog scale. Patient-reported outcome for an overall perception of sexual function was evaluated with a Likert scale. The Female Sexual Function Index (FSFI) was used as a condition-specific questionnaire. This 19-item self-report measure has demonstrated appropriate discriminatory power between affected and non-affected populations. It assesses desire, arousal, lubrication, orgasm, satisfaction, and pain with intercourse. It is a validated instrument for female sexual arousal disorder, female orgasmic disorder, and hypoactive sexual desire.[32]

Table1. Characteristics of included studies

Study	Institution	Study design	CO_2 laser equipment	Concomitant treatment
Salvatore et al[28]	San Raffaele Hospital, University Vita e Salute, Milan, Italy	Prospective	DEKA Laser	No
Perino et al[29]	University Hospital P. Giaccone, Palermo, Italy	Prospective	DEKA Laser	No
Salvatore et al[33]	San Raffaele Hospital, University Vita e Salute, Milan, Italy	Prospective	DEKA Laser	No
Salvatore et al[34]	San Raffaele Hospital, University Vita e Salute, Milan, Italy	Prospective	DEKA Laser	No
Perino et al[35]	University Hospital P. Giaccone, Palermo, Italy	Prospective	DEKA Laser	No
Pitsouni et al[36]	Alexandra Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece	Prospective	DEKA Laser	No

For statistical analysis, the estimated overall laser effect (pooled mean difference and 95% confidence intervals) was computed (when at least two studies were involved) using Review Manager 5.3 (Cochrane Collaboration, London, UK) and data type of generic inverse variance was computed using inverse variance as the statistical method, a random-effects model, and difference in means as an effect measurement.

RESULTS

After the exclusion of duplicate publications, non–English-language literature, letters, editorials, and reviews not reporting original data, six articles remained for the review process (Table 1).[28,29,33–36] They referred to prospective and observational studies and no randomized trial vs placebo or other treatments was available. The studies included were carried out in three different units using the same laser equipment (SmartXide2; DEKA Laser, Florence, Italy). In all cases no concomitant treatment interfering with GSM was allowed.

In each study the most important inclusion criterion was the presence of symptoms of GSM. Generally speaking, women included were in their first decade since menopause and less than half had previous hormonal replacement treatment (Table 2).

The treatment protocol was consistent across all studies and included one laser session every month for 3 months and a follow-up evaluation session 1 month after the last laser procedure. The procedure was always performed in an office setting without any use of analgesic or anesthetic drug.

The genital symptoms of GSM can be very disturbing and obviously have an impact on sexual function. Vaginal dryness is certainly the pivotal symptom and its improvement at the end of the three laser treatments compared with baseline was reported with a high statistical significance ($P < .001$) in each considered study.

The FSFI was adopted in three studies included in this review.[33,34,36] It was evaluated for each domain and for its overall score at baseline and after the treatment cycle, with an important significant improvement in all cases (Figure 1).

Dyspareunia secondary to GSM was assessed in all six studies included in this review. The comparison using a 10-point visual analog scale at baseline and at the end of the laser treatment showed a consistent significant decrease in the severity of this complaint (Figure 2).

A Likert scale for patient-reported outcome about the patients' perception of the quality of their sexual life was used only in two studies.[28,36] An important improvement was reported in the two studies (Figure 2).

No clinically significant complications of the laser treatment were reported in any study.

CONCLUSION

GSM is a relatively new terminology[15] describing symptoms affecting the genital and lower urinary tracts after menopause. Estrogen deficiency determines vulvovaginal symptoms secondary to atrophic tissue changes. Therefore, VVA should considered part of GSM.

Changes of the vulvovaginal region involve thinning of the tissue with the epithelium becoming more fragile and more likely to bleed during sexual intercourse. The vagina becomes shorter and narrower; the vaginal pH becomes more alkaline with an ensuing greater susceptibility to develop genital and, particularly, urinary tract infections. Moreover, there is a decrease of lubrication whose result is the occurrence of vaginal dryness and itching. It is quite intuitive how all these modifications and symptoms occurring in the genital tract can have an important impact on women's quality of life and sexual function.

Table 2. Patients' baseline characteristics

Study	Patients, n	Mean age (y)	BMI (kg/m^2)	Previous hormone treatment, %
Salvatore et al[28]	50	59.6	23.8	32.0
Perino et al[29]	48	56.0	24.3	39.6
Salvatore et al[33]	15	57.3	23.1	33.3
Salvatore et al[34]	77	60.6	23.5	37.6
Perino et al[35]	30	56.0	23.9	36.7
Pitsouni et al[36]	53	57.2	26.0	—
Pooled data	273	57.8	24.1	35.8

BMI = body mass index.

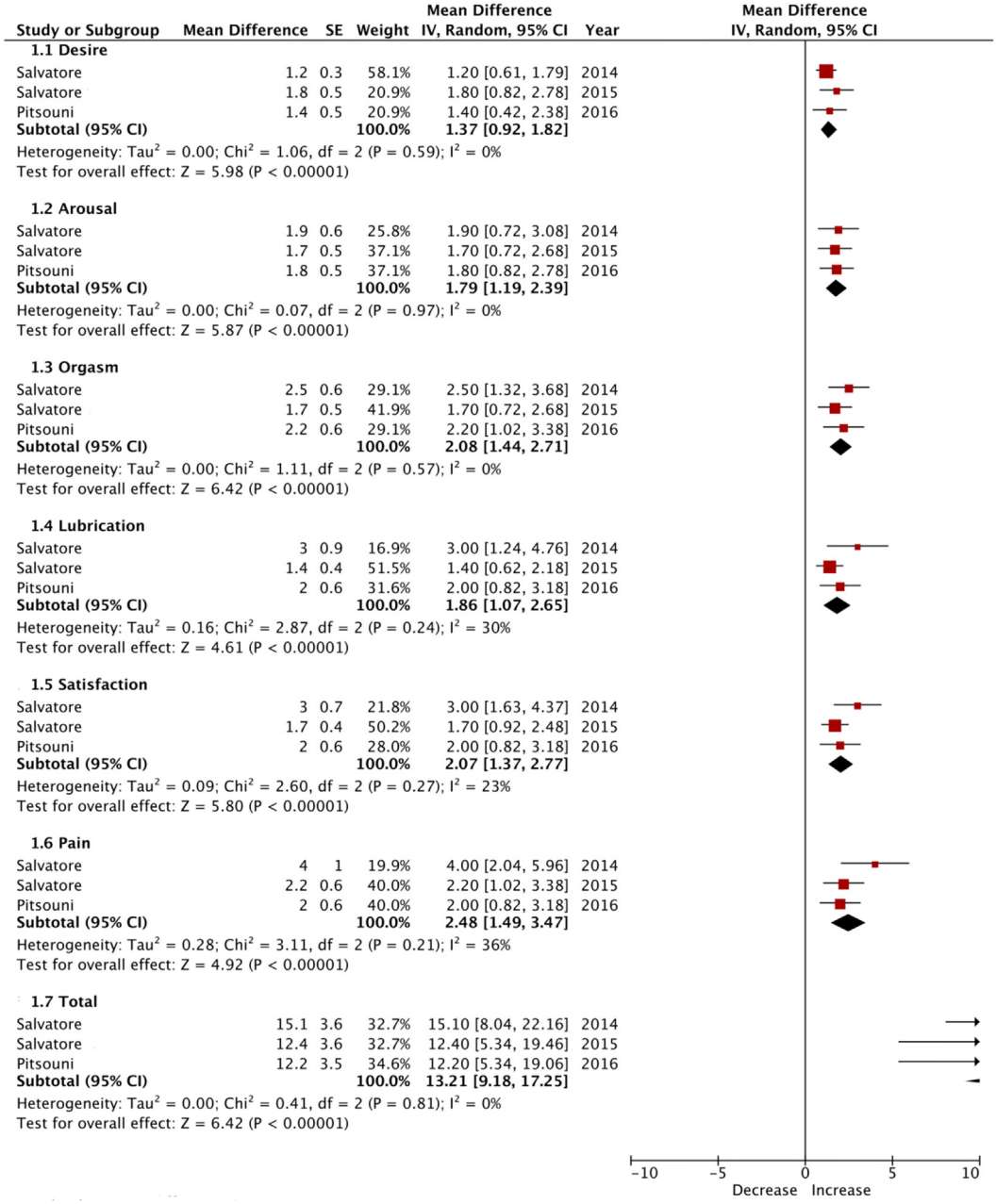

Figure 1. Forest plots of mean differences between mean values before the initiation of laser therapy and 1 month after the last laser session (1-month follow-up) for all components of the Female Sexual Function Index. CI = confidence interval; IV = inverse variance; SE = standard error.

Although the prevalence of GSM is unknown, it is fully appreciated that most women with these significant quality-of-life symptoms do not seek medical attention. Prevalence estimates have noted that approximately half the postmenopausal women in the United States report these atrophy-related symptoms and a significant negative effect on quality of life.[37–39] The Vaginal Health Insights, Views and Attitudes (VIVA) study[40] showed that 80% of women with genital atrophy considered it a negative effect on their lives, 75% reported negative consequences on their sexual life, 68% reported that it made them feel less sexual, 33% reported negative consequences on their marriage and relationship, and 26% reported a negative effect on their self-esteem. Another review on the impact of this condition by Nappi and Palacios[41] noted that by 2025 there will be 1.1 billion women worldwide older than 50 years with specific needs related to the development of GSM. They cited four recent surveys that suggest the need for these women to end their silent suffering and indicated that health care providers should be more proactive to help their patients disclose these symptoms. This is very much in line with other symptoms of the urinary tract such as urinary frequency, urgency, and urinary incontinence, and pelvic floor relaxation. An international survey on vaginal

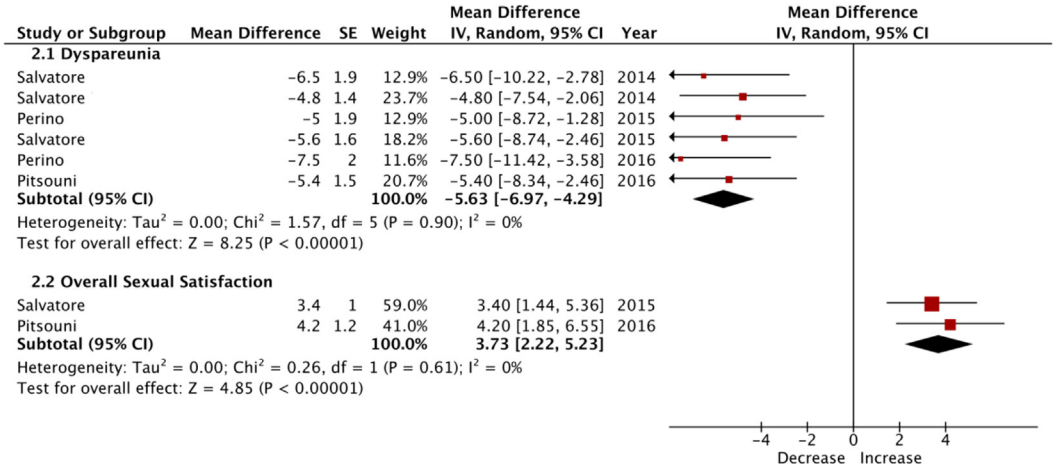

Figure 2. Forest plots of mean differences between mean values before the initiation of laser therapy and 1 month after the last laser session (1-month follow-up) for dyspareunia and overall sexual satisfaction as assessed by the 10-cm visual analog scale. CI = confidence interval; IV = inverse variance; SE = standard error.

atrophy not only noted the extremely high prevalence of the condition but also noted fairly significant differences in attitudes toward symptoms between countries in Europe and North America. Overall, 77% of the respondents of the survey, which included more than 4,000 menopausal women, believed that women were uncomfortable discussing symptoms of vaginal atrophy.[42]

Pastore et al,[37] using data from the Women's Health Initiative, found that the most prevalent urogenital symptoms were vaginal dryness (27%), vaginal irritation or itching (18.6%), vaginal discharge (11.1%), and dysuria (5.2%). Of note, unlike vasomotor symptoms that tend to decrease over time, GSM will not spontaneously remit and commonly recurs when hormone therapy is withdrawn.

In September 2014, a fractional CO_2 laser (SmartXide2) from the Italian company DEKA Laser and a CO_2 laser from the American company Cynosure (Westford, MA, USA) were cleared by the FDA for the indications of "incision, excision, ablation, vaporization, and coagulation of body soft tissues in medical specialties, including aesthetic (dermatology and plastic surgery), podiatry, otolaryngology (ENT), gynaecology, neurosurgery, orthopaedics, general and thoracic surgery (including open and endoscopic), dental and oral surgery and genitourinary surgery."[43] Although without a specific indication for the treatment of VVA, fractional CO_2 laser has been used as a treatment for GSM, with promising results. This is due to its regenerative effect on atrophic vaginal tissue of postmenopausal women.[26,27] The clinical result of this histologic effect is a significant improvement in vulvovaginal symptoms secondary to GSM.[28–31,33–36]

In 2014 for the first time Salvatore et al[28] reported on a 12-week evaluation of the use of pulsed CO_2 laser for the treatment of VVA symptoms in 50 postmenopausal women. The treatment protocol included three outpatient sessions with an interval of 1 month between sessions. At the end of the treatment cycle, statistical significant improvement compared with baseline was observed for objective and subjective outcomes. Patients tolerated the procedure well and reported only mild pain at the insertion of the probe during the first treatment. No complications or side effects were reported. Vaginal samples were taken for histologic evaluation and important vaginal wall changes with remodeling of the lamina propria and the epithelial layer were observed after the first CO_2 laser treatment compared with baseline.

In a study by Perino et al,[29] VVA symptoms and signs were reported to be significantly alleviated ($P < .0001$) after three sessions of vaginal fractional CO_2 laser treatment. More than 90% of patients reported they were satisfied or very satisfied with the procedure and experienced considerable improvement in quality of life. No adverse events from fractional CO_2 laser treatment were reported.

The restoration of a normal trophism can certainly improve women's sexual function. This was first demonstrated by Salvatore et al[34] who investigated the effects of fractional micro-ablative CO_2 laser on sexual function and overall satisfaction with sexual life in postmenopausal women with VVA. Seventy-seven postmenopausal women with VVA symptoms but with the wish to have normal sexual activity with the current partner were included and treated with three sessions of a fractional micro-ablative CO_2 laser system at an interval of 30 days between sessions. Of these patients, 57 were sexually active at baseline despite being symptomatic. A significant improvement in the FSFI total score and in each FSFI domain was observed at 12-week follow-up compared with baseline ($P < .001$). At the end of the treatment cycle, 74 women were sexually active. In a study by Pitsouni et al,[36] all but one of the participants who were not sexually active at baseline from GSM symptoms (16 of the 53 women recruited) had resumed their sexual activity by the 12-week follow up. The frequency of sexual intercourse per month increased significantly from a mean of 1.6 ± 2.1 to 4.1 ± 2.1 ($P < .001$).

In this review we considered all the articles published in peer-reviewed journals in the international literature until December 2016 on the use of fractional CO_2 laser for the treatment of GSM looking at the effect on sexual function.

Sexual function was assessed using different instruments or focusing on a specific symptom, such as dyspareunia. The latter, when secondary to atrophic postmenopausal changes, clearly can be decreased by fractional CO_2 laser treatment.

Overall patient perception of their sexuality also significantly improved and this is certainly a very relevant clinical success.

Although a specific questionnaire for sexual function (FSFI) was used in three studies,[33,34,36] there was a consistency in significant improvement in all domains of the FSFI and in the overall score.

However, there are certainly some limitations in the available literature: no placebo effect was evaluated, studies concerned only a few hospitals, and the length of follow-up was limited.

Nonetheless, despite different evaluation methods, the clinical response in sexual function improvement was extremely important and consistent in the included studies. The procedure seems to be independent of the operator. However, the use of different tools for the assessment of sexual function made a pooled analysis more complicated.

Among symptoms associated with GSM, those related to sexual function are very subjective, so their severity is very much dependent on patient perception. Therefore, the evaluation of changes determined by laser had to be performed with different questionnaires and scales.

A peculiarity of the studies considered is that the same fractional CO_2 laser equipment was used in all included studies. The same clinical results might not be obtained by other fractional CO_2 laser machines. In fact, each model has specific peculiarities in mode of laser emission.

The laser procedure can be performed in an office setting and no clinically significant complications were reported. For the costs of the procedure, it can be offered to women under different circumstances in various countries. In Italy, for example, it can be provided by the national health system with a cost for the patient of €36. In a private setting, the cost can vary from country to country from €200 to €800 per session.

Despite being aware of the ACOG position statement issued in May 2016 to advise obstetrician-gynecologists and patients that laser technology was neither approved nor cleared by the FDA for treating VVA,[44] preliminary observational data have shown undeniable potential benefits of CO_2 laser for patients affected by this condition.

In light of the current lack of data from sham-controlled trials, larger, prospective, randomized studies with long-term follow-up are required to obtain an unbiased evaluation of the efficacy and safety of this procedure. Studies comparing laser technology with the gold standard of low-dose local estrogen treatment also are warranted. Moreover, because laser treatment is a very costly intervention for the patient when not refunded by the national health system, a cost-benefit analysis might be important.

Nevertheless, fractional CO_2 laser could hold promise for the future of GSM treatment and therefore could significantly improve the sexual function of women with this condition.

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