

A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: The VeLVET Trial

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Abstract

Objective: The aim of the study was to compare 6-month efficacy and safety for treatment of vaginal dryness/genitourinary syndrome of menopause in women undergoing fractionated CO₂ vaginal laser therapy to women using estrogen vaginal cream.

Methods: This multicenter, randomized trial compared fractionated CO₂ laser to estrogen cream at 6 institutions. We included menopausal women with significant vaginal atrophy symptoms and we excluded women with prolapse below stage 2, recent pelvic surgery, prior mesh surgery, active genital infection, history of estrogen sensitive malignancy, and other autoimmune conditions. The primary outcome was the visual analog scale vaginal dryness score. Secondary outcomes included evaluation of vaginal atrophy, quality of life symptoms, assessment of sexual function, and urinary symptoms. Adverse events (AEs) and patient global impression of improvement (PGI-I) and satisfaction were also assessed.

Results: Sixty-nine women were enrolled in this trial before enrollment was closed due to the Federal Drug Administration requiring the sponsor to obtain and maintain an Investigational Device Exemption. Of the 69 participants enrolled, 62 completed the 6-month protocol; 30 women were randomized to the laser and 32 to estrogen cream from June 2016 to September 2017. Demographics did not differ between groups except the laser group was less parous (0 [range 0-4] vs 2 [0-6], $P = 0.04$). On patient global impression, 85.8% of laser participants rated their improvement as “better or much better” and 78.5% reported being either “satisfied or very satisfied” compared to 70% and 73.3% in the estrogen group; this was not statistically different between groups. On linear regression, mean difference in female sexual function index scores was no longer statistically significant; and, vaginal maturation index scores remained higher in the estrogen group (adj P value 0.02); although, baseline and 6-month follow-up vaginal maturation index data were only available for 34 participants (16 laser, 18 estrogen).

Conclusions: At 6 months, fractionated CO₂ vaginal laser and vaginal estrogen treatment resulted in similar improvement in genitourinary syndrome of menopause symptoms as well as urinary and sexual function. Overall, 70% to 80% of participants were satisfied or very satisfied with either treatment and there were no serious adverse events.

Key Words: Genitourinary syndrome of menopause – Vaginal atrophy – Vaginal dryness – Vaginal estrogen – Vaginal laser therapy.

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METHODS

Vulvovaginal atrophy, now more commonly incorporated within the term genitourinary syndrome of menopause (GSM), results from involution of the vaginal epithelium and tissues of the vulva and vagina due to declining levels of systemic estrogen during menopause.¹ The vagina may decrease in caliber and the vaginal opening may become more constricted. These changes in the vulvovaginal environment can have a significant negative impact on a woman's sexual health and quality of life.²⁻⁶ Other common changes include progressive loss of vaginal elasticity, vaginal dryness, dyspareunia, vaginal burning, discharge, itching, irritation, and dysuria.⁷⁻¹⁰ Up to 50% of menopausal women report these symptoms.^{2,3,8,11,12}

Choice of therapy for GSM depends on symptom severity, treatment efficacy, and safety. First-line treatment for symptomatic women with GSM, recommended by The North American Menopause Society, includes vaginal moisturizers, vaginal lubricants, and continued sexual activity or vaginal exercise. If these therapies fail, estrogen treatment should be considered in patients without contraindications.¹³ Vaginal estrogen has been shown to be efficacious in the treatment of GSM,^{13,14} but compliance rates vary from 52% to 74%¹⁵ and long-term efficacy data (>1 year) are lacking,¹⁴ especially in high-risk patient groups such as those with known breast or uterine cancer.

Fractional CO₂ lasers have demonstrated safety and efficacy in the remodeling of tissues and production of new collagen, elastic fibers, and angiogenesis in different body regions, including the skin of the face, neck, and chest.¹⁶⁻¹⁹ The mechanism of action involves activation of heat shock proteins and tissue growth factors through lower temperature stimulation than traditional ablative lasers.²⁰ The regenerative effects of intravaginal fractional CO₂ laser therapy in postmenopausal women with GSM has been reported by Salvatore et al.²¹ The fractional CO₂ laser has been shown to be feasible, efficacious, and safe in improving GSM symptoms in postmenopausal women at 12-week follow-up.²² In addition, the technology has been shown to decrease the severity of dyspareunia related to vaginal dryness in patients, and is associated with improvement in sexual function and sexual satisfaction in postmenopausal women with self-reported GSM.^{23,24}

Although several small studies demonstrate safety and efficacy of fractionated CO₂ laser therapy for vulvovaginal conditions, most published outcomes are short-term (≤ 12 weeks) and few prospective randomized controlled trials exist comparing laser to standard therapies. Therefore, the objective of this study is to compare improvement in symptoms of GSM between participants who underwent CO₂ fractional vaginal laser therapy and to those treated with vaginal estrogen alone. Specifically, we sought to compare 6-month quality of life and safety outcomes of fractionated CO₂ vaginal laser therapy to vaginal estrogen for the treatment of GSM. We hypothesize that CO₂ vaginal laser therapy is noninferior to vaginal estrogen therapy in the treatment of GSM.

This is a multicentered, randomized single-blinded clinical trial comparing CO₂ fractionated vaginal laser therapy and vaginal estrogen therapy in the treatment of vulvovaginal atrophy/GSM. IRB approval was obtained for all institutions participating in the study and funding was obtained through the Foundation for Female Health Awareness.

Women were included if they were menopausal with absence of menstruation for at least 12 months and reported bothersome vaginal dryness of 7 cm or more on visual analog scale (VAS). All participants were English speaking and able to give informed consent.

Women were excluded if they had a contraindication to vaginal estrogen therapy, a personal history of vulvovaginal condyloma, vaginal intraepithelial neoplasia, vaginal carcinoma, lichen sclerosus, lichen planus, history of vaginal radiation, history of cervical cancer, other gynecologic cancer or pelvic radiation, acute or recurrent urinary tract infection, or genital infection (eg, bacterial vaginosis, herpes genitalis, candida). Women were also excluded if they had a personal history of thrombophlebitis, heart failure, or myocardial infarction within 12 months, scleroderma, or any chronic condition that could interfere with study compliance. They were also excluded if they had pelvic organ prolapse higher than stage II, if they had undergone pelvic surgery within 6 months, or if they had previously undergone reconstructive pelvic surgery with transvaginal mesh kits. Prior midurethral sling and sacrocolpopexy with synthetic mesh for prolapse were not excluded. Participants were excluded if they had used vaginal estrogen cream, ring or tablet within 1 month before entering the study, or vaginal moisturizers, lubricants, or homeopathic preparations within 2 weeks of therapy.

Patients who met inclusion criteria were asked to voluntarily participate in the trial. Informed consent was obtained for those who agreed to participate. Enrolled participants were then randomized to either fractional CO₂ vaginal laser therapy or vaginal estrogen therapy according to a computer-generated randomization schedule with random block sizes with the use of the SAS statistical software package (SAS Institute, Cary, NC). Participants were not blinded to their allocation.

Vaginal laser protocol

Participants randomized to the laser treatment group underwent a total of three intravaginal treatments at least 6 weeks apart with the fractional microablative CO₂ laser system (SmartXide2 V2LR, MonaLisa Touch, DEKA, Florence, Italy). The following settings were used: dot power 30 W, dwell time 1,000 μ s, dot spacing 1,000 μ m and the smart stack parameter set at 1 at baseline and at 3 at 6 weeks (laser treatment 2) and 3 months (laser treatment 3). The laser beam was applied using a 90° vaginal probe gently inserted up to the top of the vaginal canal and subsequently withdrawn at centimeter intervals while rotated to six positions in an alternating clockwise and counterclockwise fashion to provide complete circumferential treatment of the vagina. At the investigators discretion, a flat probe (vulvar probe) was used

to more efficiently treat the introital area and vestibule. For this portion of the treatment (if performed), the settings were changed and the dot power was decreased to 26 W with the smart stack parameter set to 1. At the clinician's discretion, EMLA cream was applied to the introitus for 10 minutes and wiped clean and dried before vulvar laser therapy. Participants were advised to avoid coital sexual activity for at least 3 days after each laser application and topical lidocaine 5% ointment was prescribed for vulvar pain postprocedure for those patients who desired it.

Vaginal estrogen protocol

Participants randomized to the vaginal estrogen group were prescribed conjugated estrogen cream (Premarin) 0.5 g intravaginally daily (using applicator or fingertip) for 14 days followed by 0.5 g twice weekly for 24 weeks.

All follow-up questionnaires and examinations were administered and performed by study personnel blinded to treatment allocation. At study visits, an examiner performed an assessment of vaginal caliber using a standard vaginal dilator set (Syracuse Medical, Lakeville, MA). Five dilator sizes were used (XS, S, M, L, XL) and the largest dilator that the participant could comfortably place in her vagina was recorded at baseline and at 6 months. Using a five-point Likert scale, the participant was also asked to report how much pain she experienced when the dilator was placed in her vagina.

All participants were asked to complete separate 10 cm VAS for GSM symptoms (vaginal dryness, vaginal burning, vaginal itching, dysuria), the Female Sexual Function Inventory (FSFI) questionnaire,²⁵ the Day-to-day Impact of Vaginal Aging (DIVA) questionnaire,²⁶ and the Urogenital Distress Inventory (UDI-6)²⁷ at baseline (pretreatment), 3 months, and 6 months. Participants also completed the Patient Global Impression of Improvement using a five-point Likert scale at 6 months.

Vaginal pH and vaginal maturation indexes (VMI)²⁸ were planned to be measured at baseline and at 6 months. In order to obtain the specimens for the VMI, the vaginal wall was scraped with a plastic spatula, which was smeared on a slide. The slide was sprayed with cytofixative and allowed to air dry. The pathology lab at the Cleveland Clinic analyzed the slides received. The VMI is a determination of the ratio of superficial:intermediate:parabasal cells of the vaginal epithelium, and calculated using the following formula: $VMI = (\%parabasal\ cells \times 0) + (\%intermediate\ cells \times 0.5) + (\%superficial\ cells \times 1.0)$. After each laser treatment, the clinician performing the laser asked the participant about the degree of discomfort experienced as a result of the treatment using a five-point Likert scale.

Adverse events (AEs) were defined a priori and included prolonged vaginal bleeding beyond 48 hours, heavy vaginal bleeding, bothersome vaginal irritation, bacterial vaginosis, vaginal yeast infection, postprocedural fever, and skin burn. At each visit, study personnel inquired about AEs by specific questioning and by examination.

The primary outcome of this study was to compare subjective improvement of vaginal dryness using the VAS for GSM

symptoms 6 months post-treatment between groups. Secondary outcomes included comparisons between groups of the vaginal health index (VHI) and VMI scores, the effect of GSM symptoms on quality of life, the effect of treatment on sexual function, the effect of treatment on urinary symptoms, and comparison of patient satisfaction.

An a priori power analysis determined that we needed a total of 196 participants in this noninferiority trial comparing vaginal estrogen therapy to laser treatment of vaginal atrophy. Assuming an alpha of 0.025 and a standard deviation of 2.0,²⁴ we determined that 85 participants in each group were needed to provide 90% power to reject the null hypothesis that the true difference in vaginal dryness VAS score (vaginal estrogen – vaginal laser) is less than or equal to 1.0 cm on the VAS (effect size 0.5) in favor of the alternative hypothesis that the true difference is greater than 1.0 cm using a one-sided two-sample *t* test. We accounted for a 15% loss to follow-up and/or drop-rate over the study period.

This study is a noninferiority study design. The predefined noninferiority margin is a difference of 1.0 cm on a 10 cm VAS. To minimize bias toward a finding of noninferiority, data from women who were eligible and received the assigned treatment (per protocol) were used for the analysis of the primary outcome. The primary outcome was presented as the difference in VAS scores between treatments (vaginal estrogen – vaginal laser). The hypothesis of noninferiority between the two treatment groups was tested by comparing the lower limit of the two-sided 95% confidence interval (equivalent of a one-sided significance level of 0.025%) of the absolute difference with the margin set at -1.0 cm. A secondary analysis of the primary outcome according to original treatment assignment (intent-to-treat [ITT]) was also performed as well as standard superiority testing using Student *t* test. For participants who were lost to follow-up, data were imputed for each participant as “last observation carried forward” (eg, 3-month follow-up data) for the purposes of the ITT analysis. For women who had been randomized but withdrew from the trial before undergoing treatment and who did not complete any follow-up, a plausible assumption of “no improvement from treatment” was made to perform the ITT analysis. All outcomes were analyzed using Pearson Chi-square test for categorical data, Student *t* test for parametric continuous data, or Wilcoxon rank sum test for ordinal or nonparametric continuous data. Changes in patient reported outcome questionnaires (FSFI, DIVA, UDI-6) were compared between treatments using repeated measures analysis of covariance. Linear regression analyses were performed for any significant findings, controlling for variables either found to be significant on univariate analysis or thought to be clinically relevant at the time of analysis. *P* values less than 0.05 were considered statistically significant for all analyses.

RESULTS

From June 2016 to September 2017, 69 women from 6 medical centers (Cleveland Clinic *n* = 25, Medstar Washington Hospital Center *n* = 15, Stanford Medical Center *n* = 8,

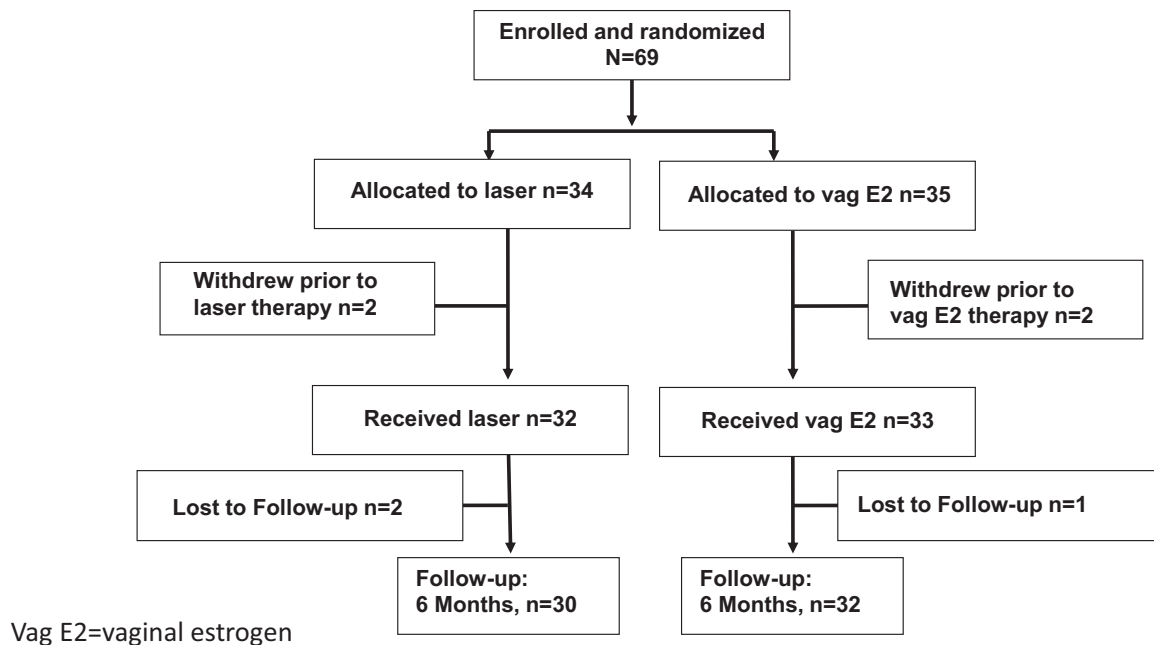


FIG. 1. Patient allocation.

Christ Hospital n = 7, Wake Forest Baptist Medical Center n = 4, and Women and Infants Hospital n = 10) met inclusion criteria and were enrolled in the trial (34 laser, 35 estrogen) with 62 participants completing the 6-month protocol (30 laser, 32 estrogen) (Fig. 1). Enrollment was closed before the completion of the trial due to the Federal Drug Administration (FDA) requiring FFHA to obtain and maintain an Investigational Device Exemption (IDE). Before this requirement, the FDA was aware of the study. Because this IDE would have required a prolonged cessation of enrollment, it was decided to complete treatment of currently enrolled participants and close the study. Analyses were performed on all participants who completed the 6-month protocol.

Table 1 displays patient characteristics for all participants. The mean age of all participants was 61 ± 7 years, body mass index was 25.4 ± 4.6 kg/m², and the majority of women were white (91.4%). Characteristics did not differ between the groups with the exception of the laser group being less parous than the estrogen group (0 [0-4] vs 2 [0-6], P = 0.04).

Data on discomfort were available for 29 of 30 patients who underwent therapy: no women rated the treatment as “very uncomfortable,” 5 women (15%) reported it was “moderately uncomfortable”, 19 (57.6%) women stated that it was only “mildly uncomfortable” and 5 (16.7%) participants reported that they felt no discomfort. Vulvar dystrophy was present in two (6%) women who reported previous biopsies confirming squamous hyperplasia. Both vaginal and vestibular treatment was performed in 16 (48.5%) participants, whereas 17 (51.5%) participants had vaginal therapy only. Of the participants who underwent vaginal estrogen therapy (n = 32), mean percentage compliance with therapy was 81.3% based on a 26-week vaginal estrogen cream calendar.

Table 2 displays a summary of 6-month outcomes. Our primary outcome of VAS scores for vaginal dryness did not differ between groups. VAS scores for the other GSM symptoms (vaginal burning, vaginal itching, and dysuria) did not differ between the two groups. Mean differences in DIVA, FSFI, and UDI scores were also not different between groups. There was also no difference in the VHI scores. Baseline and follow-up VMI data were available for 34 participants (16 laser, 18 estrogen), and changes in VMI were found to be different between the groups as the estrogen group had higher changes in scores after treatment, indicating a higher estrogenic effect (25 ± 22.6 vs 3.9 ± 30.6, P = 0.04). On linear regression, when age, menopausal status, previous estrogen use, and sexual activity were controlled for, VMI scores remained higher in the estrogen group (adj. P value 0.02).

Table 3 shows the mean difference in each FSFI parameter in the laser and estrogen groups. Overall there were no

TABLE 1. Participant characteristics, N = 69

	All participants N = 69	Fractionated CO ₂ laser n = 34	Conjugated estrogen cream n = 35	P
Age	61 ± 7	61 ± 8	60 ± 7	0.69
Race				0.40
White	64 (92.8)	32 (91.4)	32 (94.1)	
Black	2 (2.9)	1 (2.9)	1 (2.9)	
Hispanic	1 (1.4)	0 (0)	1 (2.9)	
Asian	2 (2.9)	2 (5.7)	0 (0)	
Other	0 (0)	0 (0)	0 (0)	
BMI	25.4 ± 4.6	25.1 ± 4.7	25.8 ± 4.4	0.40
Parity	2 (0-6)	2 (0-6)	1 (0-4)	0.58
Menopausal	69 (100)	35 (100)	34 (100)	–
Exogenous hormone use	59 (79.7)	29 (82.9)	26 (74.5)	0.51
Vaginal estrogen use	54 (78.2)	26 (74.3)	27 (79.4)	0.70

BMI, body mass index.

TABLE 2. 6-Month outcome measures, N = 62

Outcome	Fractionated CO ₂ laser n = 30	Conjugated estrogen cream n = 32	P
Mean difference VAS score			
Dryness	-5.48 ± 2.68	-5.76 ± 2.48	0.67
Itching	-1.84 ± 3.01	-1.24 ± 2.96	0.45
Irritation	-3.29 ± 3.73	-3.49 ± 3.19	0.87
Dysuria	-1.4 ± 2.89	-2.11 ± 2.85	0.36
Mean difference VHI	0.9 ± 0.7	1.2 ± 0.9	0.07
Mean difference DIVA	-3.3 ± 3.2	-4.4 ± 3.1	0.18
Mean difference VMI ^a	3.9 ± 30.6	25 ± 22.6	0.04 ^b
Mean difference FSFI	1.7 ± 6.7	4.9 ± 8.3	0.1
Mean difference UDI	-9.4 ± 15.7	-6.2 ± 12	0.37
% Sexually active	45.5 (15)	48.3 (14)	0.82

DIVA, day-to-day impact of vaginal aging; FSFI, Female Sexual Function Index; UDI, Urogenital Distress Inventory; VAS, Visual Analog Scale; VHI, Vaginal Health Index; VMI, Vaginal Maturation Index.

^aRemained statistically significant after controlling for confounding factors.

^bStatistically significant at $P \leq 0.05$; however, baseline and follow-up data were only available for 55% of participants.

differences with the exception of the following: the estrogen group was more likely to have improvement in desire and arousal after treatment. However, on linear regression, when age, menopausal status, previous estrogen use, and sexual activity were controlled for, the mean difference in these FSFI scores was no longer statistically different between the groups.

On patient global impression, 71.9% of laser participants rated their improvement as “better or much better” and 75.8% reported being either “satisfied or very satisfied” compared to 82.8% and 75.9% in the estrogen group; this was not statistically different between groups. Nine (30%) participants in the laser group reported no change in symptoms, whereas no participants reported being worse and three (9%) reported being dissatisfied. Four (13.8%) of participants in the estrogen group reported no changes in symptoms, no women reported being worse, and two (6.9%) reported being dissatisfied. None of these findings were statistically different between the groups.

At 6 months, 16 (48.5%) of participants in the laser group were able to go up at least one size in the vaginal dilator compared to 17 (58.6%) in the estrogen group ($P = 0.5$). A total of 39.4% (13) of participants reported improvement in

TABLE 4. Reported adverse events, N = 62

n (%)	Fractionated CO ₂ laser n = 30	Conjugated estrogen cream n = 32
Vaginal bleeding	2 (6.7)	2 (6.3)
Vaginal pain	1 (3.3)	0 (0)
Vaginal discharge	1 (3.3)	0 (0)
Urinary tract infection	1 (3.3)	0 (0)
Breast tenderness	0 (0)	1 (3.1)
Migraine	0 (0)	1 (3.1)
Abdominal cramping	0 (0)	1 (3.1)

discomfort with dilator placement compared to 55.2% (16) in the estrogen group ($P = 0.26$).

An ITT analysis was performed, comparing all 69 enrolled participants (34 laser, 35 estrogen). For the four women (two laser, two estrogen) who had been randomized but withdrew from the trial before undergoing treatment and who did not complete any follow-up, an assumption of “no improvement from treatment” was made to perform the analysis. For women who were lost to follow-up (two laser, one estrogen), data were imputed for each participant as “last observation carried forward” (3-month follow-up data were available for all participants). The analysis revealed no changes from the per protocol analysis described above (data not shown).

Ten AE were either mild or moderate and included vaginal bleeding, pain, and/or discharge; breast tenderness; urinary tract infection; migraine; and abdominal cramping. AEs did not differ between the two groups (Table 4).

DISCUSSION

This was a multicentered, randomized, prospective, single-blinded clinical trial comparing CO₂ fractionated vaginal laser therapy and vaginal estrogen therapy in the treatment of vulvovaginal atrophy/GSM. We found that at 6 months, fractionated CO₂ laser therapy was similar to vaginal estrogen treatment with regard to GSM symptom improvement, as well as sexual function, urinary symptoms, and overall patient satisfaction with treatment.

Studies looking at the mechanism of action of the CO₂ laser on the vaginal epithelium have been published. In one study, microscopic evaluation was performed 1 hour following laser treatment. The authors describe the activation of regenerative

TABLE 3. 6-Month Female Sexual Function Index outcome, N = 62

	Fractionated CO ₂ laser n = 33	Conjugated estrogen cream n = 29	P
Mean difference FSFI Score 1 Desire ^a	0.32 ± 1.3	1.02 ± 1.4	0.05 ^b
Mean difference FSFI Score 2 Arousal ^a	0.62 ± 1.6	1.63 ± 1.9	0.03 ^b
Mean difference FSFI Score 3 Lubrication	0.11 ± 1.2	0.35 ± 1.4	0.50
Mean difference FSFI Score 4 Orgasm	0.37 ± 1.3	0.9 ± 1.6	0.17
Mean difference FSFI Score 5 Satisfaction	0.88 ± 2.1	1.7 ± 1.7	0.50
Mean difference FSFI Score 6 Pain	-0.59 ± 2.8	-0.04 ± 3.3	0.81

FSFI, Female Sexual Function Index.

^aNo longer statistically significant after controlling for confounding factors.

^bStatistically significant at $P \leq 0.05$.

mechanisms in the connective tissue—with the formation of new vessels, new papillae, and new collagen—and in the epithelium with thickening and desquamation of cells at the epithelial surface.²⁹ These changes lead to remodeling of the vaginal tissues and improved lubrication, which should, in theory, lead to improvement in clinical symptoms of menopause.

Behnia-Willison et al³⁰ were one of the first to publish on outcomes following vaginal CO₂ laser treatment. In a cohort study, they evaluated the safety and efficacy of laser treatment in reducing the severity of symptoms of GSM in 102 menopausal women. The primary outcome of their study was an improvement in symptoms of GSM and their secondary outcomes included bladder function and prolapse symptoms. They reported that 84% of participants experienced significant improvement in their GSM symptoms and scores on measures of sexual function, bladder function, prolapse, and vaginal sensation also improved.

In 2018, Bhide et al³¹ published a review on the use of laser therapy in urogynecology. The authors looked at the published literature on CO₂ and erbium:YAG laser for treatment of pelvic floor disorders. They found that all of the studies were observational and reported effectiveness of these treatments for certain urogynecologic conditions. The authors did acknowledge, however, that the lack of randomized trials examining safety and efficacy of these treatments was concerning given how in vogue the use of these treatments was becoming. Soon after, the FDA put forth an advisory on the use of vaginal laser therapy for the purposes of treating vaginal symptoms. The advisory referenced AEs and outcomes associated with the use of the laser and also raised concerns about the lack of data on its safety and efficacy. In response, the International Urogynecological Association published a committee opinion reviewing laser-based vaginal devices for treatment of GSM, vaginal laxity, and stress urinary incontinence. The committee concluded that the therapeutic advantages of nonsurgical laser-based devices in urogynecology can only be recommended after robust clinical trials have demonstrated their long-term complication profile, safety, and efficacy.³²

The only other randomized trial that exists looking at the efficacy of fractional CO₂ laser therapy in comparison to estrogen therapy for the treatment of vaginal atrophy was published by Cruz et al.³³ The authors performed a trial comparing three arms: laser only (sham estrogen), estrogen only (sham laser), and laser with estrogen therapy. Forty-five participants were randomized in this trial and follow-up was carried out to 20 weeks post-therapy. Outcomes included the VHI, VAS for GSM symptoms, FSFI, and a variation of the VMI. The authors found that the combination (laser and estrogen) group showed the most significant change in VHI, whereas both the laser-only and combination groups had significant improvement in more GSM symptoms (dyspareunia, burning, and dryness) than the estrogen group (dryness only). This study was an equivalence trial and differed from our trial as it was powered to detect differences in VHI and not the other important parameters studied,

including changes in GSM symptoms following treatment. It is our opinion that a subjective patient-reported outcome focusing on improvement may be more important than an objective outcome. Nevertheless, both trials demonstrated efficacy and are supportive of the use of CO₂ laser therapy for the treatment of GSM symptoms.

The greatest strength of this study is its randomized design. Biases inherent to other designs were eliminated by allocating participants to one treatment group in a random fashion and by blinding study personnel to allocation at the time of outcomes assessment. Another significant strength is the multicenter approach we took to conducting this trial. Using different centers allows us to generalize our results in a more robust way. The major limitation of our study was our inability to reach our predetermined statistical power due to early closure of the study because of a request to obtain an IDE to continue. While we cannot state with certainty that CO₂ laser treatment is noninferior to vaginal estrogen therapy due to lack of power, we can conclude from our very preliminary results that fractionated CO₂ vaginal laser and vaginal estrogen treatment both resulted in improvement in GSM symptoms at 6 months. There are few randomized prospective studies looking at these outcomes, and so our findings add to the currently sparse literature on the subject matter. Other significant limitations to this study include (1) the lack of sham or placebo and (2) lack of standardized treatment (optional introital treatment with the vaginal laser). A better study design that would minimize bias is an adequately powered, randomized, double-blinded trial of vaginal laser with placebo cream versus sham laser with estrogen cream and follow-up using validated subjective and objective outcomes at greater than 1 year. Table 1 shows that the majority of participants in both groups had previously taken exogenous hormone therapy and vaginal estrogen therapy. Most likely, the patients had not been happy with previous hormonal therapy so it is possible that they entered the trial with the opinion that vaginal laser therapy would be more effective. Unfortunately, we did not ask our patients what their opinion of anticipated efficacy was at baseline or at 6-month follow-up. The ideal participants in this investigation would have been naïve to hormonal therapy. Finally, laser therapy should have been standardized to either vaginal therapy alone or both vaginal and introital laser therapy in all participants. Introital laser therapy at the investigator's discretion based on the participant's dyspareunia symptoms makes the resultant laser treatment group heterogeneous; hence, the results of laser therapy are difficult to interpret.

CONCLUSIONS

In this underpowered investigation, the CO₂ laser was shown to be safe and effective in treating GSM symptoms, and, preliminarily, CO₂ laser and vaginal estrogen resulted in patient satisfaction and improved clinical outcomes. Laser therapy may be considered for the short-term treatment of GSM. Additional well-designed studies with adequate power and longer-term follow-up are warranted.

REFERENCES

1. Van der Laak JA, De Bie LM, De Leeuw H, De Wilde PC, Hanselaar AG. The effect of Replens on vaginal cytology in the treatment of postmenopausal atrophy: cytomorphology versus computerised cytometry. *J Clin Pathol* 2002;55:446-451.
2. Cumming GP, Herald J, Moncur R, Currie H, Lee AJ. Women's attitudes to hormone replacement therapy, alternative therapy and sexual health: a web-based survey. *Menopause Int* 2007;13:79-83.
3. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause* 2008;15:661-666.
4. Nappi RE, Kingsberg S, Maamari R, Simon J. The CLOSER (Clarifying Vaginal Atrophy's Impact On Sex and Relationships) Survey: implications of vaginal discomfort in postmenopausal women and in male partners. *J Sex Med* 2013;10:2232-2241.
5. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med* 2007;357:762-774.
6. Parish SJ, Nappi RE, Krychman ML, et al. Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. *Int J Womens Health* 2013;5:437-447.
7. Bachmann GA, Cheng RJ, Rovner E. Vulvovaginal complaints. In: Lobo RA, editor. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects*, 3rd ed. Burlington, MA: Academic Press; 2007. pp. 263-270.
8. Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. *J Sex Med* 2009;6:2133-2142.
9. Pastore LM, Carter RA, Hulka BS, Wells E. Self-reported urogenital symptoms in postmenopausal women: Women's Health Initiative. *Maturitas* 2004;49:292-303.
10. Barnabei VM, Cochrane BB, Aragaki AK, et al; Women's Health Initiative Investigators. Menopausal symptoms and treatment-related effects of estrogen and progesterin in the Women's Health Initiative. *Obstet Gynecol* 2005;105:1063-1073.
11. Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views and Attitudes (VIVA)—results from an international survey. *Climacteric* 2012;15:36-44.
12. Cumming GP, Currie HD, Moncur R, Lee AJ. Web-based survey on the effect of menopause on women's libido in a computer-literate population. *Menopause Int* 2009;15:8-12.
13. The North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause* 2013;20:888-902.
14. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2006;4:CD001500.
15. Shulman LP, Portman DJ, Lee WC, et al. A retrospective managed care claims data analysis of medication adherence to vaginal estrogen therapy: implications or clinical practice. *J Womens Health (Larchmt)* 2008;17:569-578.
16. Ong MW, Bashir SJ. Fractional laser resurfacing for acne scars: a review. *Br J Dermatol* 2012;166:1160-1169.
17. Tierney EP, Hanke CW. Fractionated carbon dioxide laser treatment of photoaging: prospective study in 45 patients and review of the literature. *Dermatol Surg* 2011;37:1279-1290.
18. Tierney EP, Hanke CW. Ablative fractionated CO₂ laser resurfacing for the neck: prospective study and review of the literature. *J Drugs Dermatol* 2009;8:723-731.
19. Peterson JD, Goldman MP. Rejuvenation of the aging chest: a review and our experience. *Dermatol Surg* 2011;37:555-571.
20. Tadir Y, Gaspar A, Lev-Sagie A, et al. Light and energy based therapeutics for genitourinary syndrome of menopause: consensus and controversies. *Lasers Surg Med* 2017;49:137-159.
21. Salvatore S, Leone Roberti Maggiore U, Athanasiou S, et al. Histological study on the effects of microablative fractional CO₂ laser on atrophic vaginal tissue: an ex-vivo study. *Menopause* 2015;22:845-849.
22. Salvatore S, Nappi RE, Zerinati N, et al. A 12-week treatment with fractional CO₂ laser for vulvovaginal atrophy: a pilot study. *Climacteric* 2014;17:363-369.
23. Salvatore S, Leone Roberti Maggiore U, Origoni M, et al. Microablative fractional CO₂ laser improves dyspareunia related to vulvovaginal atrophy: a pilot study. *J Endometr* 2014;6:150-156.
24. Salvatore S, Nappi RE, Parma M, et al. Sexual function after fractional microablative CO₂ laser in women with vulvovaginal atrophy. *Climacteric* 2015;18:219-225.
25. Rosen R, Brown C, Heiman J, et al. A multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000;26:191-208.
26. Huang AJ, Gregorich SE, Kuppermann M, et al. Day-to-day impact of vaginal aging questionnaire: a multidimensional measure of the impact of vaginal symptoms on functioning and well-being in postmenopausal women. *Menopause* 2014;22:144-154.
27. Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl AJ. Short forms to assess life quality and symptom distress for urinary incontinence in women: the incontinence impact questionnaire and the urogenital distress inventory. *Neurourol Urodynam* 1995;14:131-139.
28. Meisels A, Schneider V. Hormonal cytology. *Clin Perinatol* 1974;1:53-64.
29. Salvatore S, Franca K, Lotti T, et al. Early regenerative modifications of human postmenopausal atrophic vaginal mucosa following fractional CO₂ laser treatment. *Open Access Maced J Med Sci* 2018;6:6-14.
30. Behnia-Willison F, Sarraf S, Miller J, et al. Safety and long-term efficacy of fractional CO₂ laser treatment in women suffering from genitourinary syndrome of menopause. *Eur J Obstet Gynecol Reprod Biol* 2017;213:39-44.
31. Bhide AA, Khullar V, Swift S, Digesu GA. The use of laser in urogynecology. *Int Urogynecol J* 2019;30:683-692.
32. Shobeiri SA, Kerkhof MH, Minassian VA, Bazi T; IUGA Research and Development Committee. IUGA committee opinion: laser-based vaginal devices for treatment of stress urinary incontinence, genitourinary syndrome of menopause, and vaginal laxity. *Int Urogynecol J* 2019;30:371-376.
33. Cruz VL, Steiner ML, Pompei LM, et al. Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO₂ laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. *Menopause* 2018;25:21-28.