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Original Research

The Efficacy of Fractional CO^2 Laser in the Treatment of Genitourinary Syndrome of Menopause: A Large Prospective Observational Study

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Abstract

Background: Genitourinary syndrome of menopause (GSM) majorly caused by the physiological decline in estrogen, affects up to 90% of menopausal women. Hormonal therapy seems to be an effective treatment, often not executable for contraindication or patient's low compliance to local or systemic medical therapy. Fractional CO^2 laser therapy is an emerging and effective choice for women affected by vulvo-vaginal atrophy (VVA), promoting collagen regeneration and improving blood flow of the vaginal mucosa and elasticity of tissues. **Methods**: Ninety-two menopausal Patients affected by vulvo-vaginal atrophy (VVA) were considered for the present prospective observational study. All women were treated with Fractional CO^2 laser Lumenis AcuPulse in a fractionated sequential mode laser pulse. Patients were requested to complete questionnaires regarding the Female Sexual Functional Index (FSFI), Female Sexual Distress Scale (FSDS) and severity of Most Bothersome Symptoms (MBS) at baseline (T0) and at three-month following three-treatment-sessions (T1). **Results**: Data indicated a significant improvement of MBS (vaginal itching ($p < 0.0001$), post-coital vaginal bleeding ($p < 0.002$), vaginal dryness ($p < 0.0001$), dyspareunia ($p < 0.0001$) and dysuria ($p < 0.0001$), higher Vaginal Health Index Score (VHIS) (4.1 ± 1.21; 95% CI = 3.84–4.35) and reduces pH (-0.53 ± 0.24; 95% CI = 0.48–0.58) after CO^2 laser treatment. A significantly improvement of FSFI Total score ($p < 0.0001$) and FSDS ($p < 0.0001$) have been demonstrated. **Conclusions**: Fractional CO^2 laser improves vaginal health as well as signs and symptoms associated with GSM, while significantly elevating quality of life and sexual functionality among postmenopausal symptomatic women.

Keywords: vulvovaginal atrophy; fractional CO^2 laser; menopause; laser safety; genitourinary syndrome

1. Impact Statement

Fractional CO^2 laser is a valid therapeutic choice for vulvo-vaginal atrophy treatment in menopausal women. Previous studies have a limited number of patients and limited results focused on safety. In this original article the sample is considerable, and the evaluation of efficacy is accurate, including all the main validated questionnaires and scales to evaluate genitourinary syndrome and sexual life: Female Sexual Functional Index (FSFI), Female Sexual Distress Scale (FSDS), severity of Most Bothersome Symptoms (MBS) and Vaginal Health Index Score (VHIS). In this way the results are more precise and structured to assess vaginal and sexual health.

A significant improvement in all domains was recorded. Contrary to other studies, attention was paid to safety and no severe adverse events were reported, with attention also to mild adverse effects such as vaginal infections.

For the future research, this work is an important milestone and these results about laser efficacy and safety can only be taken for granted if studied with precision.

2. Introduction

Genitourinary syndrome of menopause (GSM) majorly caused by the physiological decline in estrogen, affects up to 90% of menopausal women [1]. The syndrome includes vulvovaginal atrophy (VVA), as well as urinary and sexual disorders, compromising quality of life (QoL) in as many as 50% of postmenopausal women [2,3]. Several therapeutic options have been proposed for the relief of GSM symptoms, including both hormonal and non-hormonal products [4–8]. The main therapeutic goal remains the relief of associated symptoms and signs, which could be ideally achieved through the restoration of the urogenital physiology.

Hormonal therapy seems to be an effective treatment, often not executable for contraindication or patient's low compliance to local or systemic medical therapy. Moreover, in the majority of oncologic patients, the use of hormonal therapy is generally not accepted, and women are skeptical.

Fractional CO^2 laser therapy is an emerging and effective choice for women affected by VVA [9,10]. Laser therapy treatment, applied vaginally, promotes tissue regeneration of vaginal wall through the production of collagen and elastic fibers. In particular, the CO^2 laser fractionally ablates the tissue, causing immediate heat-induced collagen contraction and subsequent tissue remodeling, improving elasticity of vaginal canal by increasing the extracellular matrix of the mucosa and increasing the muscle tone. Different studies have successfully evaluated the effectiveness of CO^2 laser for the treatment of VVA symptoms, however now, to our knowledge, there is no prospective study performed who could confirm its effectiveness on a large number of patients [4–13]. Recent studies have a longer follow-up, but on an extremely limited number of patients [14]. The aim of this study, hence, is to evaluate the efficacy of fractional CO^2 Laser and its ability to modifying clinical symptoms that are correlated with GSM, with sexual functioning and sexual distress, among a large number of postmenopausal women suffering from VVA.

3. Materials and Methods

3.1 Clinical Intervention and Procedure

This prospective observational study was conducted at the Maternal and Child Health and Urological Sciences Department, Policlinico Umberto I, Sapienza University of Rome. The research was performed according to Good Practice Guidelines, STROBE (STrengthening the Reporting of Observational studies in Epidemiology) guidelines and IRB approved the study protocol n° CD-1511/2017. Informed consent was obtained from all participants.

Inclusion criteria were as follows: menopausal women, the presence of physiological/iatrogenic menopause that is manifested through one or more of the following VVA's symptoms (itching, burning, reduced lubrication, superficial and/or severe dyspareunia), a desire to preserve sexual activity, negative urine culture, negative pap smear, negative vaginal swabbing, signed informed consent, absence of AUB (abnormal uterine bleeding), in accordance with our institution regulations "Sapienza checklist" [15]. A gynecological exam including cervical, vaginal and vestibular inspection, has been performed prior to each treatment.

Exclusion criteria defined as the following: the use of any hormone therapy (systemic or local) in the six months prior to the enrolment, the use of vaginal moisturizer or lubricants in the thirty days prior to the enrollment, the presence of neurological bladder, urinary tract infection or any current vaginal infection, any serious pathology or chronic condition that could interfere with the study compliance, any psychiatric disorders that might potentially preclude informed consent, any association of Pelvic Organ Prolapse beyond 2nd degree (according to the pelvic organ prolapse quantification (ICS-POP-Q) system), and the use of any anticoagulation medication once a week (or more) prior to and/or during the treatment course. All women were treated by a CO^2 laser (Lumenis AcuPulse DUO, Lumenis, Yokne'am, Israel) in its fractionated mode, with a 28 mm probe (FemTouch™, Lumenis, Yokne'am, Israel) with power setting of 10 microjoules and 10% density, for 3 consecutive times, with 4 weeks apart. The steps of CO^2 laser treatment have been described elsewhere and were performed in an outpatient setting without the requirement of any specific preparation such as analgesia or anesthesia [15]. No local therapy (e.g., lubricants or moisturizers) was recommended, neither for the 48 hours before the treatment, nor after. To avoid vaginal irritation during the healing process, patients were advised to avoid coital activity for at least 1 week following each laser application.

3.2 Patients Reported Outcomes and Evaluation

At baseline (T0) and four weeks after the last CO^2 laser treatment (T1), women were asked to complete the following questionnaires:

The Female Sexual Functional Index (FSFI) questionnaire [16]; a 19-item multidimensional self-reported questionnaire that is often used as an instrument for the assessment of female Sexual Function. The maximum score for each domain is 6.0, obtained by summing item responses and multiplying by a correction factor (desire: 0.6; arousal: 0.3; lubrication: 0.3; orgasm: 0.4; satisfaction: 0.4; pain: 0.4). The total composite sexual function score is a sum of the domain scores, and ranges from 2.0 (not sexually active and no desire) to 36.0.

Female Sexual Distress Scale (FSDS) [17,18]; a 13-item scale that aim to assess and quantify sexually related distress associated with inadequate or impaired sexual function.

Most Bothersome Symptoms (MBS) questionnaire [19]; a 3-point numerical scale running from 0 to 3 (for 'no symptoms' and 'worst possible symptoms', respectively), in which the severity of the most common VVA symptoms is recorded, including vaginal itching, postcoital vaginal bleeding, vaginal dryness, dyspareunia and dysuria.

The questionnaires were filled-out privately, without the presence of healthcare professionals and/or with no time-limit or any other constrain, at two different time points: at the first outpatient-visit and four weeks after the last CO^2 laser treatment session. In the same way, gynecological examination was performed at baseline (T0) and four weeks after the last CO^2 laser treatment (T1), including the evaluation of Vaginal Health Index Score (VHIS) and vaginal wet mount with microscopic evaluation and Whiff test [20]. For vaginal wet 1 drop of 0.9% NaCl was placed on a slide; a spatula is used to take a sample of the discharge

from the vaginal wall; the sample was carefully mixed with the 0.9% NaCl on the glass slide and carefully covered with a cover slide, avoiding "smearing" and air trapping. Optical microscopical evaluation involved count of number of epithelial cells and leucocytes per field and resident flora evaluation in terms of lactobacilli or cocchi presence ($\times$10 magnification). Number and characteristics of squamous cells (typical/atypical) of the vaginal wet mount were evaluated if at least 5 cells per field ($\times$10 magnification) were found. For Whiff test a second discharge sample (prepared in the same way as the wet mount) was incubated with one drop of 10% KOH solution without a cover slip. A sniff test was therefore done immediately to evaluate the fishy amine odor. For the VHIS evaluation five components where evaluated (elasticity, fluid volume, pH, epithelial integrity and moisture). For the pH evaluation, vaginal indicator strips (Auctions Sticks, Arkray Factory, Japan) were applied against the lateral vaginal wall using sterile forceps, followed by a vaginal lavage for wet mount.

3.3 Statistical Analyses

Internal consistency (relatedness of items within a factor) was determined using the Cronbach's alpha statistic, separately for the six domains as well as for all of the individual items; reliability was determined for each of the domains and for the full-scale score. The incidence of events was analyzed for statistical significance by using the Fisher's exact or χ^2 test. The *t*-test and Mann–Whitney U test were used to compare continuous parametric and non-parametric variables, respectively. To assess the impact of different treatments on our endpoints, repeated measures ANOVAs, incorporating baseline scores, were used. Statistical analysis was performed by IBM-Microsoft SPSS version 25.0 (Chicago, IL, USA) for Mac. Repeated measure ANOVA, with Bonferroni corrected post-hoc tests, was used to evaluate the null hypothesis, according to which there is no change in women's pain scores, when measured after each treatment.

4. Results

Ninety-two patients of the hundred and one enrolled in the study (91.1%) completed the treatment with fractional CO^2 laser and returned after 4 weeks for the follow-up visit. Nine patients (8.9%) dropped out and were lost to follow-up. The main characteristics of this study population are described in Table 1.

The mean age of the participants was 58.42 $\pm$ 9.38 years, the average onset of menopause was 47.39 $\pm$ 7.41 years, while the median duration of menopausal status was 12.65 $\pm$ 10.06 years. The mean BMI (Body Mass Index) was 24.07 $\pm$ 4.07. Twenty patients (21.7%) had previously diagnosed cancer (within the six months prior to study's inclusion), 8 patients (15.1%) were previously diagnosed with hypertension, and 3 (5.7%) with dyslipidemia. Further characteristics, including demographic data (i.e., educational background, marital status and past deliveries) are elaborated in Table 1. No severe (G3-G4) complications occurred after a median follow-up of six months (considering from the first visit to the last one) nor did any of the patients complain severe pain. One patient (1.1%) reported dizziness immediately after treatment, which was successfully solved within 15 minutes. A minor bleeding (traces of blood on the probe) probably related to the tip introduction and/or rotation occurred in one patient (1.1%) with severe atrophy. Treatment was successfully completed in this patient. One patient (1.1%) requested to abort the procedure for discomfort upon probe introduction but decided to resume the procedure after two weeks. Two patients (2.2%) reported symptoms of dysuria within 7 days from procedures, which was treated with 3gr Fosfomycin trometamol, repeated after 24 h. One patient (1.1%) reported symptoms of vaginosis 4 weeks after the procedure and was treated with local therapy. No further adverse events have been reported. A significant decrease of vaginal pH between T0 and T1 was observed (–0.53 $\pm$ 0.24; 95% CI = 0.48–0.58; $p < 0.001$). Moreover, a significant increase in VHIS was registered (4.1 $\pm$ 1.21; 95% CI = 3.84–4.35; $p < 0.001$). In vaginal wet mount, lactobacillus as predominant species was identified in 27 patients (29.7%) at baseline and in 74 (81.3%) after treatment ($p < 0.001$). Moreover, a non-

Table 1. Characteristics of patients (n = 92).

Age (mean $\pm$ SD)	58.42 $\pm$ 9.38
Age at menopause	47.39 $\pm$ 7.41
Years since menopause	12.65 $\pm$ 10.06
BMI (mean $\pm$ SD)	24.07 $\pm$ 4.07
Education	
None, n (%)	1 (1.1%)
Primary	4 (3.4%)
Secondary	14 (14.9%)
High school	56 (62.1%)
University	17 (18.4%)
Marital status	
Married	43 (46.7%)
Having a companion	4 (4.4%)
Single	8 (8.9%)
Divorced	30 (32.2%)
Widow	7 (7.8%)
Deliveries	
None	22 (23.5%)
One delivery	29 (31.8%)
Two deliveries	34 (37.6%)
Three deliveries or above	7 (7.8%)
Two deliveries	34 (37.6%)
Three deliveries or above	7 (7.8%)
Comorbidities	
Cancer	20 (21.7%)
Hypertension	8 (15.1%)
Dyslipidemia	3 (5.7%)

SD, Standard Deviation; BMI, Body Mass Index.

significant trend of reduction in pathogenic cocci bacteria was observed. In addition, a significative increase of normal vaginal epithelial cells counts >5 at T1 compared to baseline (T0) was shown: Normal vaginal cell count >5 per field was detectable in 40 patients at T0 (43.9%) and 61 patients at T1 (67.3%), $p = 0.003$. Changes in MBS-score are described in Table 2.

Table 2. Most Bothersome Symptoms (MBS).

MBS	Mean ± SD	95% CI	ST Err.	*p*-value
Dyspareunia	–1.16 ± 1.01	–1.45, –0.87	0.14	<0.0001
RUI	–0.81 ± 1.31	–1.13, –0.50	0.16	<0.0001
Dryness	–1.30 ± 1.15	–1.56, –1.02	0.14	<0.0001
Burning sensation*	–0.60 ± 1.06	–0.86, –0.35	0.13	<0.0001
Postcoital bleeding	–0.42 ± 0.93	–0.70, –0.16	0.13	0.002
Vaginal pruritis	–0.81 ± 1.23	–1.11, –0.52	0.15	<0.0001

MBS, Most Bothersome Symptoms; SD, Standard Deviation; ST Err., Standard Error; RUI, Recurrent urinary infections.
*Upon urinating.

A significantly important improvement has been shown in all six parameters that were evaluated: Dyspareunia (–1.16 ± 1.01, 95% CI = –1.45, –0.87, $p < 0.0001$); RUI (–0.81 ± 1.31, 95% CI = –1.13, –0.50, $p < 0.0001$; Dryness (–1.30 ± 1.15, 95% CI = 1.56, –1.02, $p < 0.0001$); Burning sensation upon urination (–0.60 ± 1.06, 95% CI = –0.86, –0.35, $p < 0.0001$); Post coital bleeding (–0.42 ± 0.93, 95% CI = –0.70, –0.16, $p = 0.002$); Vaginal pruritis (–0.81 ± 1.23, 95% CI = –1.11, –0.52, $p < 0.0001$).

Changes in FSFI are described in Table 3, in Figs. 1,2.

Table 3. Female Sexual Functional Index (FSFI).

FSFI	Mean ± SD	95% CI	ST Err.	*p*-value
Desire	0.63 ± 1.95	0.11–1.14	0.26	0.02
Arousal	1.58 ± 5.01	0.25–1.15	0.66	0.02
Lubrication	2.23 ± 5.45	0.77–3.70	0.73	0.003
Orgasm	1.43 ± 3.99	0.39–2.50	0.53	0.009
Satisfaction	1.70 ± 3.65	0.73–2.67	0.48	0.001
Pain	1.77 ± 3.54	0.83–2.71	0.47	<0.0001
Total	9.54 ± 18.94	4.52–14.57	2.51	<0.0001

FSFI, Female Sexual Functional Index; SD, Standard Deviation; CI, Confidence Interval; ST Err., Standard Error.

A significantly improvement of FSFI Total score (9.54 ± 18.94, 95% CI = 4.52–14.57, $p < 0.0001$) and of all 6 item evaluated were registered: Desire (0.63 ± 1.95, 95% CI = 0.11–1.14, $p = 0.02$); Arousal (1.58 ± 5.01, 95% CI = 0.25–1.15, $p = 0.02$; Lubrication (2.23 ± 5.45, 95% CI = 0.77–3.70, $p = 0.003$); Orgasm (1.43 ± 3.99, 95% CI = 0.39–2.50, $p = 0.009$); Satisfaction (1.70 ± 3.65, 95% CI = 0.73–2.67, $p = 0.001$); Pain (1.77 ± 3.54, 95% CI = 0.83–2.71, $p < 0.0001$). As shown in Table 4, high inter-item correlations were observed for all six domains (Chrombach's alpha 0.925 or 0.810).

Table 4. Domain intercorrelation (Pearson's r: range = –1.00 to +1.00).

	D	A	L	O	S	P
T0						
D	1.000					
A	0.647	1.000				
L	0.476	0.882	1.000			
O	0.532	0.921	0.917	1.000		
S	0.495	0.791	0.709	0.799	1.000	
P	0.353	0.659	0.795	0.710	0.631	1.000
T1						
D	1.000					
A	0.709	1.000				
L	0.608	0.906	1.000			
O	0.562	0.920	0.909	1.000		
S	0.682	0.773	0.762	0.798	1.000	
P	0.502	0.654	0.717	0.686	0.715	1.000

D, desire; A, arousal; L, lubrication; O, orgasm; S, satisfaction; P, pain.

Changes in FSDS are described in Table 5.

A significantly improvement of Total FSDS have been demonstrated (–4.45 ± 8.73, 95% CI = –2.28–6.70, $p < 0.0001$). In particular, 11 parameters out of 13 of FSDS were statically reduced: Distress about sex life (–0.28 ± 1.02, 95% CI = –0.28–0.54, $p = 0.03$); Unhappy about sexual relationship (–0.51 ± 1.07, 95% CI = –0.24–0.78, $p < 0.0001$; Guilty about sexual difficulties (–0.27 ± 0.95, 95% CI = –0.03–0.51, $p = 0.03$); Frustrated about sexual problems (–0.54 ± 0.90, 95% CI = –0.31–0.76, $p < 0.0001$); Stressed about sex (–0.48 ± 0.88, 95% CI = –0.2–0.70, $p < 0.0001$); Unhappy about sexual relationship (–0.16. ± 1.05, 95% CI = 0.10–0.42, $p = 0.235$); Worried about sex (–0.36 ± 0.90, 95% CI = –0.14–0.60, $p = 0.002$); Sexually inadequate (–0.35 ± 1.05, 95% CI = –0.08–0.61, $p = 0.010$); Regrets about sexuality (–0.21 ± 1.03, 95% CI = 0.54–0.46, $p = 0.118$); Embarrassed about sexual problems (–0.41 ± 0.99, 95% CI = –0.16–0.70, $p = 0.002$); Dissatisfied with sex life (–0.41 ± 1.14, 95% CI = –0.12–0.70, $p = 0.006$); Angry about sex life (–0.27 ± 1.06, 95% CI = –0.00–0.54, $p = 0.049$); Bothered by low sexual desire (–0.22 ± 1.01, 95% CI = 0.03–0.47, $p = 0.085$).

5. Discussion

The present large prospective observational study shows that CO^2 fractionated LASER is effective and safe treatment in reducing symptoms related to VVA/GSM, improving sexual function and QoL in postmenopausal women. Many studies in literature have assessed the efficacy of CO^2 Laser treatment of VVA but most of them

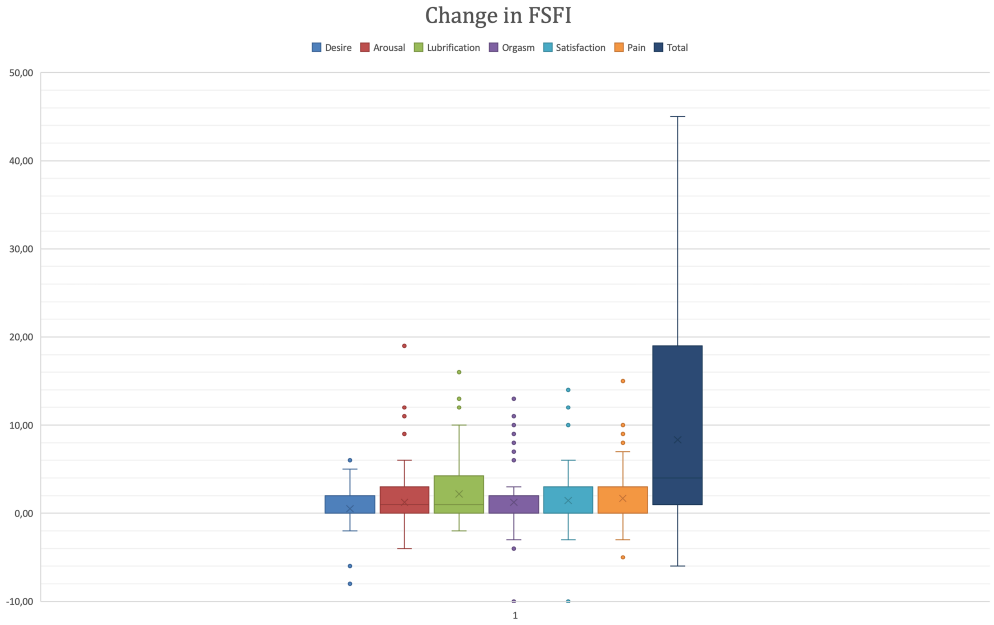

Fig. 1. Changes in FSFI.

Table 5. Female Sexual Distress Scale (FSDS).

FSDS Question	Mean ± SD	95% CI	ST Err.	*p*-value
Q1: Distress about sex life	–0.28 ± 1.02	–0.28–0.54	0.13	0.03
Q2: Unhappy about sexual relationship	–0.51 ± 1.07	–0.24–0.78	1.35	<0.0001
Q3: Guilty about sexual difficulties	–0.27 ± 0.95	–0.03–0.51	0.12	0.03
Q4: Frustrated about sexual problems	–0.54 ± 0.90	–0.31–0.76	0.11	<0.0001
Q5: Stressed about sex	–0.48 ± 0.88	–0.2–0.70	0.11	<0.0001
Q6: Unhappy about sexual relationship	–0.16 ± 1.05	0.10–0.42	0.13	0.235
Q7: Worried about sex	–0.36 ± 0.90	–0.14–0.60	0.11	0.002
Q8: Sexually inadequate	–0.35 ± 1.05	–0.08–0.61	0.13	0.010
Q9: Regrets about sexuality	–0.21 ± 1.03	0.54–0.46	0.13	0.118
Q10: Embarrassed about sexual problems	–0.41 ± 0.99	–0.16–0.70	0.12	0.002
Q11: Dissatisfied with sex life	–0.41 ± 1.14	–0.12–0.70	0.14	0.006
Q12: Angry about sex life	–0.27 ± 1.06	–0.00–0.54	0.13	0.049
Q13: Bothered by low sexual desire	–0.22 ± 1.01	0.03–0.47	0.12	0.085
TOTAL	–4.45 ± 8.73	–2.28–6.70	1.10	<0.0001

FSDS, Female Sexual Distress Scale; SD, Standard Deviation; ST Err., Standard Error.

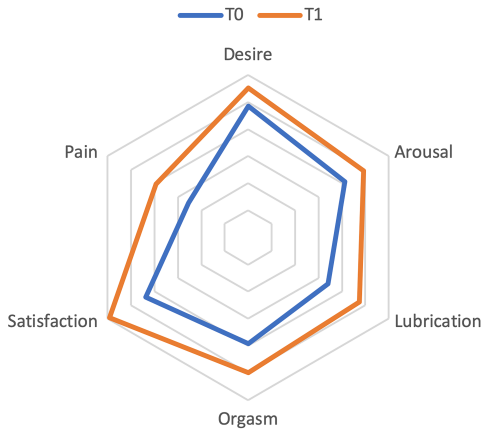

Fig. 2. Changes in FSFI.

included a small number of women [12–22]. Literature on long term effect of laser therapy is lacking; Alexadies *et al.* [14] evaluated a series of three fractional CO^2 laser treatments to the vulva and vagina with a 1-year follow-up in a postmenopausal population but considering 18 postmenopausal females with atrophic vaginitis [15]. The present study demonstrates a significant decrease in incidence of all Most Bothersome Symptoms (MBS) evaluated. This improvement of women's symptomatology is of great importance since GSM, in menopausal population is underreported and underestimated because of limited propensity of patients to discuss with practitioner of this discomforts. Indeed, only 4% of women were able to attribute vulvovaginal symptoms to GSM and only half of women discuss their sexual health with practitioners when asked, while 33% do not discuss it at all [23,24]. The perceived

reduction of all the most bothersome symptoms after laser therapy are translated into a perceived better sexual function and increased self-confidence. This is confirmed through a significant improvement of each item and total score of FSFI. Interestingly, the outcome that showed to be particularly improved was the perception of pain (1.77 ± 3.54; $p < 0.0001$). One of the potential explanations of this finding could be effect of the laser on the vaginal mucosa that seems to increase vaginal thickness and decreasing the exposure of surface area of the nerve endings, reducing the pain threshold [13,25–28]. Another interesting change that occurs because of the laser therapy is the increased vaginal lubrication that could be related to the increase in mucosal growth of capillaries and, consequently, vaginal blood flow [8]. Sexual satisfaction (1.70 ± 3.65; $p = 0.001$) and the possibility of experiencing an orgasm (1.43 ± 3.99; $p = 0.009$) significantly increased as well. In addition, women have demonstrated a lesser fear of experiencing pain and a greater conviction that engaging in sexual intercourse is possible again. Consistently, Desire ($p = 0.02$), Arousal ($p = 0.02$) significantly increased and sexual distress domain's indexes (FSDS) significantly decrease after CO^2 laser treatment. Literature's resources regarding the latter issue are limited and are somehow controversial, probably because they are mostly, conducted among cancer survivors [29,30]. Distress, on the other hand, seems to be increased in cases where therapeutic efficacy does not meet patients' goals and expectations. Our wet microscopy results confirmed the improvement, in terms of vaginal microbial colonization and pH progressive lowering and are consistent with literature evidence [31]. All these benefits (MBS, FSFI, FSDS, VHI) were attributable CO^2 laser treatment since the patients' population was accurately selected by excluding confounding factors such as lubricants-use or ongoing hormonal therapies. Our findings stand in line with recent literature [2,5,7–13,32].

Nevertheless, the major limitation of the present study is the lack of control arm, for the potential risk of placebo effect and follow- up should be longer. For this reason, we have planned confirm our result with a double-blinded randomized controlled trial with a large group of patients who would either go through the full protocol of laser therapy or undergo a sham procedure. One of the future goals should also be to better evaluate how many times could it be possible to safely repeat the treatment. Recently, a randomized study, have compared CO^2 laser treatment versus sham procedure, enrolling a total of 88 patients (44 per each group). In that study sham procedure was able to produce a non-statistically significant improvement in VHI ($p = 0.06$) and ICIQ ($p = 0.07$) scores compared to baseline, while it has demonstrated a significantly higher improvement of both VHI and VAS scores of patients treated by laser compared with sham procedure. It is still unclear whether the association of CO^2 laser and usual medical options could exert a synergistic effect on VVA. A randomized study has evaluated efficacy of fractional CO^2 vaginal laser treatment and compared it to local estrogen therapy and the combination of both treatments (Laser and Estriol), for the treatment of VVA but it found no significant difference in term of FSFI total scores between arms [33]. Therefore, it could be considered as a first option for patients especially those who have previous history of hormone-dependent cancer. A recent retrospective study evaluated fractional CO^2 vestibular laser treatment combination with oral ospemifene in postmenopausal women presenting with dyspareunia and vulvar pain showing a synergistic effect on clinical effectiveness and long-term effect [34].

A recent paper reviewed the short-term effects and safety of vulvovaginal fractional microablative CO^2 laser therapy on atrophy symptoms using validated questionnaires pre- and post-treatment, confirming the efficacy of this treatment [35].

The considerable number of patients makes this article useful for literature, for the low complication rate. We are continuing to collect data to have a longer follow up. Another strength of the following study is to use validated tests to evaluate clinical improvements.

6. Conclusions

Fractional CO^2 laser improves vaginal health as well as signs and symptoms associated with GSM, while significantly elevating QoL and sexual functionality among postmenopausal symptomatic women.

Author Contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by VDD, OD and AG and all authors commented on previous versions of the manuscript. Material preparation—GP and IP. Data collection—MS, CS and MF. Analysis was performed by VDD. Review & editing—MM, LM and PBP. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This prospective observational study was conducted at the Maternal and Child Health and Urological Sciences Department, Policlinico Umberto I, Sapienza University of Rome. IRB approved the study protocol n° CD-1511/2017. Informed consent was obtained from all participants.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. We further confirm that any aspect of the work covered in this

manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. All named authors have contributed significantly to the work, have read the manuscript, attested to the validity and legitimacy of the data and its interpretation, and have agreed to its submission. OD and AG are serving as one of the Guest editors of this journal. LM is serving as one of the Editorial Board members of this journal. We declare that OD, AG and LM had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to PA and SM.

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