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# Microablative fractional $CO_2$ laser for the genitourinary syndrome of menopause: up to 12-month results

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**Abstract**

***Objective:*** The aim of this study is to assess the efficacy of microablative fractional $CO_2$ laser therapy for genitourinary syndrome of menopause (GSM) management, when three, four, or five laser therapies were applied in a follow-up period of 12 months.

***Methods:*** Retrospective study evaluating GSM symptoms at baseline, and 1, 3, 6, and 12 months after last laser therapy. Visual analog scale, International Consultation on Incontinence Questionnaires- Female Urinary Tract Symptoms, International Consultation on Incontinence Questionnaires-Urinary Incontinence Short Form, Urogenital Distress Inventory-6, and Female Sexual Function Index were used for assessment of GSM symptoms' intensity or bothering and parameters of sexual function.

***Results:*** Overall, 94 women were included (35, 35, and 24 received three, four, and five therapies, respectively). All GSM symptoms improved statistically significantly. Intensity of dyspareunia and dryness decreased from 9 (5-10) (median [minimum-maximum]) and 8 (0-10) at baseline to 0 (0-6) and 0 (0-8), 1 month after last laser therapy (all $P < 0.001$), respectively. FSFI and frequency of sexual intercourse increased from 10.8 (2-26.9) and 1 (0-8) at baseline to 27.8 (15.2-35.4) and 4 (2-8) 1 month after last laser therapy (all $P < 0.001$), respectively. The positive laser effect remained unchanged throughout the 12 months of follow-up. The same pattern was followed for symptom-free rates. Four or five laser therapies may be superior in lowering the intensity of GSM symptoms in comparison to three laser therapies, in short and long-term follow-up. Differences between four and five laser therapies were not found.

***Conclusions:*** Laser therapy may provide significant improvement and/or absence of GSM symptoms up to 12 months follow-up, irrespectively to the number of laser therapies applied. Symptoms intensity 1 month after last laser therapy may be indicative of GSM symptoms intensity at 12 months. One month after third laser therapy is the critical time to decide whether treatment extension should be offered.

***Key Words:*** Atrophy – Incontinence – LUTS – Pain – Sexual function – Urgency.

Microablative fractional $CO_2$ laser ($CO_2$ laser) is one of the newly proposed energy-based devices, along with photothermal Er:YAG laser and radiofrequency (RF), for managing genitourinary syndrome of menopause (GSM).[1] Current data suggest that $CO_2$ laser, via the vaginal remodeling pathway, alleviates GSM symptoms,[2-12] as defined by The North American Menopause Society (NAMS) and the International Society for the Study of Women's Sexual Health (ISSWSH).[13] In particular, improvement of dryness, dyspareunia, itching/burning, sexual function, dysuria, urinary frequency/urgency, and incontinence has been reported consistently in studies assessing short-term efficacy of $CO_2$ laser therapy.[14,15]

Furthermore, studies evaluating long-term efficacy (up to 36 months) of three $CO_2$ laser therapies in postmenopausal women concluded that the positive effect on GSM symptoms and stress urinary incontinence (SUI) remained unchanged.[16-19] Additionally, for a period of 24 months, about 20% of women receiving three $CO_2$ laser therapies may not experience painful intercourse.[17] In a study conducted with a short follow-up

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period of 1 month, the addition of a fourth and a fifth laser therapy significantly improved GSM symptoms and symptom-free rates compared with the standard protocol of three laser therapies.[20] However, the long-term efficacy of a fourth or a fifth laser therapy has not been evaluated yet.

The aim of the current study is to evaluate the efficacy of laser therapy in postmenopausal women with moderate-to-severe GSM symptoms, for a period of 12 months. In particular, we aim to investigate the impact of $CO_2$ laser therapy throughout a period of 12 months performing comparisons before the laser application and at 1, 3, 6, and 12 months of follow-up. Furthermore, we intend to assess whether three, four, or five laser sessions may result in different GSM symptoms intensity and symptom-free rates for a period of 12 months.

## METHODS

This is a retrospective study with prospectively collected data conducted in the outpatient Urogynecological Unit of a Tertiary Hospital. Data were obtained from two prospective observational studies evaluating the efficacy of $CO_2$ laser therapy (SmartXide$^2$ V$^2$LR; Monalisa Touch, DEKA, Florence, Italy) in postmenopausal women with moderate-to-severe GSM symptoms. The Institutional Research Ethics Committee approved all studies. Participants had signed informed consent forms.

Eligible for inclusion in this analysis were postmenopausal women with at least one GSM symptom of moderate to severe intensity, as defined by NAMS and ISSWSH.[13] In addition, they should have received three to five laser therapies, had at least 6 months follow-up, normal gynecological examination, and negative screening tests (ie, normal smear Papanicolaou test). The level of applied laser power in the vaginal canal was not considered an exclusion criterion, as it has been shown that there is no difference in safety and effectiveness of $CO_2$ laser therapy when using 30 or 40-watts laser power.[21] Exclusion criteria involved the following: use of any nonhormonal or hormonal therapy (orally or locally administered) within 3 or 6 months, respectively, before the initiation of $CO_2$ laser therapy; presence of active genital lesions; and pelvic organ prolapse $\geq$stage 2 according to Pelvic Organ Prolapse-Quantification.

The $CO_2$ laser therapies were performed every 30 days, following the standard settings and procedures as previously described.[4,5,10] The level of laser power applied at the vaginal canal was 30 or 40 watts, dwell time 1000 $\mu$s, emission mode D-pulse, and spacing 1000 $\mu$m. Smart stack parameter ranged from 1 to 3 for the first to the third laser session, respectively. For more than three laser sessions the smart stack parameter was set to 3. At vaginal introitus the power used was reduced to 24 watts, with smart stack parameter at 1 for all laser sessions. Participants receiving four laser therapies had the choice of a fifth one. On the contrary, participants in the three or five laser therapy group were not allowed to choose additional therapy(ies), according to the study protocols.

Assessment methods included the following psychometrically validated questionnaires:

1. The 10-cm visual analog scale (VAS) for dyspareunia, dryness, and itching/burning: VAS has been used to measure pain intensity due to its simplicity, test-retest reliability, internal consistency, and validity.[22,23] VAS consists of a horizontal line where participants are called to draw a point that reflects their pain intensity between two extremes endpoints—''no pain at all'' and ''worst pain imaginable.''[22-24] In this study, a point drawn at 0 defined absence of symptoms, a point between $>0$ and $<4$ mild, $\geq 4$ and $<8$ moderate, and $\geq 8$ severe symptom intensity.
2. Female Sexual Function Index (FSFI) for sexual function parameters (desire, arousal, lubrication, orgasm, satisfaction, and pain) of women who engage in sexual intercourse (sexually active)[25,26]: is a valid, reliable, and responsive measurement that has been used in other studies evaluating laser therapy.[2,10,14,20,21,25-28] Moreover, the threshold of 26.55 of total FSFI score has been found to discriminate women with normal sexual function from those with sexual dysfunction.[26]
3. International Consultation on Incontinence Questionnaires (ICIQ) modules[29-31] (ICIQ-Female Urinary Tract Symptoms [ICIQ-FLUTS Filling Domain] and ICIQ-Urinary Incontinence Short Form [ICIQ-UI SF]) for lower urinary tract symptoms (LUTS): Urinary frequency-free, nocturia-free, and urgency-free participants were those who answered ''1-6/7-8'', ''0/1'' and ''never'' in the questions ''how often do you pass urine during the day'', ''during the night, how many times do you have to get up to urinate, on average?'' and ''do you have a sudden need to rush to the toilet to urinate?'' of ICIQ-FLUTS (Filling Domain), respectively. Incontinence-free participants were those who had 0 score at ICIQ-UI SF.[31]
4. Urogenital Distress Inventory (UDI-6)[32] for level of LUTS bother.

### Statistical analysis

Statistical analysis was performed before the laser therapy, and 1, 3, 6, and 12 months after the last laser therapy (1, 3, 6, and 12-month follow-up) assessing changes of symptoms intensity and symptoms-free rates. Comparisons between the follow-up periods were also performed. Moreover, comparison of outcomes between three, four, and five therapy groups was also performed in the specified follow-up periods. All assumptions of analysis of variances (ANOVA) were evaluated. Distribution of data was assessed using Shapiro-Wilk test and normality plots. Box plots were used for the detection of outliers. Levene's test was used for the assessment of homogeneity of variances. The violation of assumptions was handled using Kruskal-Wallis H or Friedman's test for independent or related samples, respectively. Whenever statistically significant results were found, post hoc pair-wise comparisons controlled for family wise error by the Bonferroni method were performed. Categorical variables were analyzed using the Chi-square test. Correlation between frequency of sexual intercourse and dyspareunia was assessed using the Pearson's method. Abnormally distributed data are presented as median/range (minimum-maximum). Categorical outcomes are presented as proportions Statistical significance was set at $P < 0.05$,

and analyses were conducted using IBM SPSS statistical software (version 25.0).

## RESULTS

A detailed description of participants included in the current analysis is presented in Fig. 1. Baseline characteristics of participants are presented in Table 1. Statistically significant difference was not detected between any of the baseline characteristics of the three groups (Table 1). Some baseline and 1-month follow-up data of the 80 out of the 94 women included in this analysis have been previously described.[20,21]

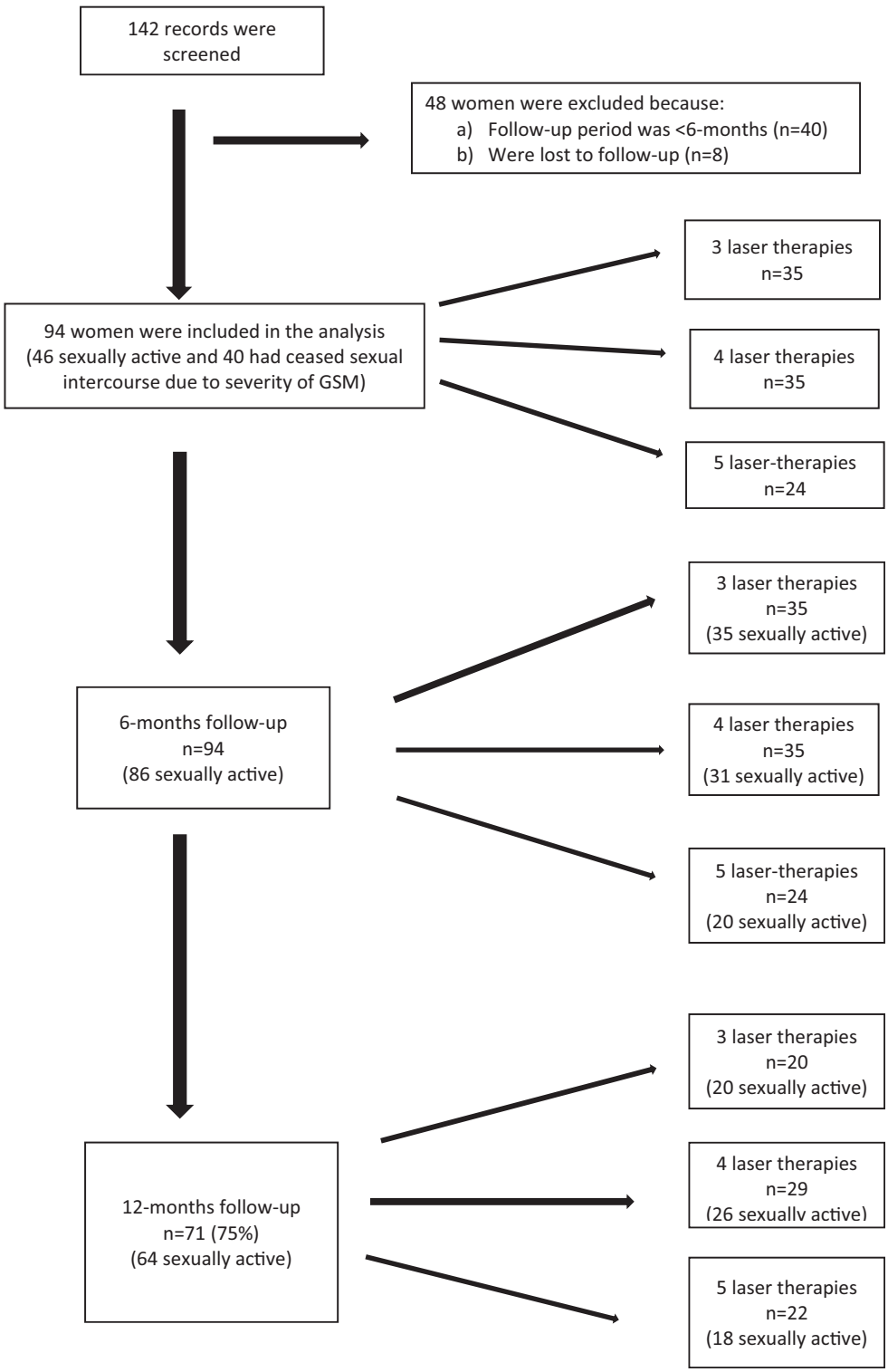


**FIG. 1.** Detailed description of participants included in the current analysis.

 

**TABLE 1.** *Baseline characteristics of participants depending on number of therapies*

| | Three-therapy group (n = 35)[a] | Four-therapy group (n = 35)[a] | Five-therapy group (n = 24)[a] | $P^a$ |
|---|---|---|---|---|
| Age | 57 (45-71) | 57 (44-71) | 57 (52-61) | 0.9 |
| Years since last menstrual period | 8 (2-18) | 7 (2-30) | 7 (2-17) | 0.7 |
| Smokers (%)[b] | 12 (33) | 9 (26) | 13 (52) | 0.1 |
| BMI[b] | 24 (20-32) | 25 (19-41) | 25 (19-33) | 0.5 |
| Dyspareunia[b] | 8 (5-10) | 9 (5-10) | 10 (5-10) | 0.7 |
| Dryness | 8 (5-10) | 7 (0-10) | 8 (0-10) | 0.1 |
| Itching/burning | 5 (0-10) | 0 (0-10) | 0 (0-10) | 0.1 |
| FSFI[b] | | | | |
| Desire | 1.8 (1.2-5.4) | 2.4 (1.2-6) | 2.1 (1.2-3.6) | 0.4 |
| Arousal | 1.2 (0-6) | 2.1 (0-3.9) | 1.7 (0-4.5) | 0.8 |
| Lubrication | 1.6 (0-4.8) | 2 (0-5.6) | 1.8 (0-5.6) | 0.3 |
| Orgasm | 1.2 (0-5.2) | 1.6 (0-5.6) | 1.6 (0-4.8) | 0.5 |
| Satisfaction | 2.4 (0.8-4.8) | 2.4 (0.8-4.8) | 2.3 (0.8-5.6) | 0.8 |
| Pain | 1.2 (0-4) | 1.2 (0-5.6) | 1.2 (0-4.8) | 0.3 |
| Total | 9.2 (2-25.5) | 13.4 (2.3-26.9) | 9.8 (2-26.4) | 0.3 |
| ICIQ-FLUTS (Filling domain) | 4 (0-11) | 3 (0-7) | 3 (0-9) | 0.8 |
| ICIQ-UI SF | 0 (0-18) | 3 (0-18) | 3 (0-21) | 0.2 |
| UDI-6 | 8 (0-7) | 13 (0-67) | 10 (0-79) | 0.8 |

BMI, body mass index; FSFI, Female Sexual Function Index; ICIQ-FLUTS, International Consultation on Incontinence Questionnaires- Female Urinary Tract Symptoms; ICIQ-UI SF, International Consultation on Incontinence Questionnaires-Urinary Incontinence Short Form; UDI-6, Urogenital Distress Inventory-6; VHIS, vaginal health index score; VMV, vaginal maturation value.

[a]Data are presented as median (minimum-maximum), and as numbers (rate) for continuous and categorical variables, respectively. Statistical significance was set at 5% ($P$ value $<0.05$). Comparison of groups was performed using Kruskal-Wallis and chi-square tests for age/years since last menstrual period/ BMI/VMV/VHIS and smokers, respectively.

[b]Smokers: Number of participants (rate). VMV was calculated using the formula %parabasal epithelial vaginal cells x0 + %intermediate epithelial vaginal cells x0.5 + %superficial x1.[28] Values ≤40% defined the atrophic smears.[28] VHIS includes five components: VHIS is calculated by adding the scores of the five components: elasticity, fluid volume, pH, epithelial integrity, and moisture.[28] Each component could receive a score from 1 (poorest) to 5 (best). The sum of the five components could receive an upper bound score of 25 and lower bound score of 5. A score of ≤15 defined the presence of vaginal atrophy.[28] Dyspareunia and FSFI have been calculated in sexually active women (35, 31, and 20 women for three, four, and five-therapy group, respectively).

Continuous outcomes of participants at baseline, and 1, 3, 6, and 12 months follow-up, irrespectively of number of therapies, are presented in Table 2 and Supplementary figures (Fig. 1, http://links.lww.com/MENO/A353; Fig. 2, http://links.lww.com/MENO/A354; and Fig. 3, http://links.lww.com/MENO/A355). There was a statistically significant decrease in all outcomes from baseline to 1-month follow-up (all $P < 0.001$). This positive result was maintained throughout the 12-month follow-up (Table 2). Statistically significant differences between the specified follow-up periods were not found for any of the outcomes. Frequency of sexual intercourse increased statistically significantly from 1 (0-8) (median [range]) to 4 (2-8) at 1-month follow-up ($P < 0.001$), and remained unchanged at 3, 6, and 12-month follow-up (4 [2-8], 4 [2-8], 4 [2-8], respectively). All women who ceased sexual intercourse due to severity of GSM symptoms resumed their sexual activity at 1-month follow-up. The sexual activity was maintained throughout the 12 months of follow-up. At

**TABLE 2.** *Continuous outcomes at baseline and 1, 3, 6, and 12 months follow-up, irrespective of number of laser therapies*

| | Baseline[a] (n = 94) | 1 mos[a] (n = 94) | $P^b$ | 3 mos (n = 94) | $P^b$ | 6 mos[a] (n = 94) | $P^b$ | 12 mos[a] (n = 71) | $P^b$ | $P^c$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Dyspareunia[d] | 9 (5-10) | 0 (0-6) | <0.001 | 0 (0-5) | <0.001 | 0 (0-5) | <0.001 | 0 (0-6) | <0.001 | NS |
| Dryness | 8 (0-10) | 0 (0-8) | <0.001 | 0 (0-6) | <0.001 | 0 (0-6) | <0.001 | 0 (0-6) | <0.001 | NS |
| Itching/burning | 4 (0-10) | 0 (0-5) | <0.001 | 0 (0-4) | <0.001 | 0 (0-4) | <0.001 | 0 (0-3) | <0.001 | NS |
| FSFI[d] | | | | | | | | | | |
| Desire | 2.4 (1.2-6) | 3.6 (2.4-6) | <0.001 | 3.6 (2.4-6) | <0.001 | 3.6 (2.4-6) | <0.001 | 3.6 (2.4-5.4) | <0.001 | NS |
| Arousal | 1.8 (0-6) | 3.8 (2.4-6) | <0.001 | 3.9 (2.4-6) | <0.001 | 3.9 (2.4-6) | <0.001 | 3.9 (2.4-6) | <0.001 | NS |
| Lubrication | 1.6 (0-5.6) | 4.8 (2.4-6) | <0.001 | 4.9 (2.4-6) | <0.001 | 4.9 (2.4-6) | <0.001 | 5.1 (2.4-6) | <0.001 | NS |
| Orgasm | 1.6 (0-5.6) | 4 (2.4-6) | <0.001 | 4 (2.4-6) | <0.001 | 4 (2.4-6) | <0.001 | 4.4 (2.4-6) | <0.001 | NS |
| Satisfaction | 2.4 (0.4-6) | 4.8 (2.4-6) | <0.001 | 4.8 (2.4-6) | <0.001 | 4.8 (2.4-6) | <0.001 | 4.8 (2.4-6) | <0.001 | NS |
| Pain | 1.2 (0-5.6) | 5.2 (2.4-6) | <0.001 | 5.2 (2.4-6) | <0.001 | 5.2 (2.4-6) | <0.001 | 5.4 (2.4-6) | <0.001 | NS |
| Total | 10.8 (2-26.9) | 27 (15.2-35.4) | <0.001 | 27.4 (15.2-35.4) | <0.001 | 27.4 (15.2-35.4) | <0.001 | 27.8 (15.2-35.4) | <0.001 | NS |
| ICIQ-FLUTS (Filling domain) | 3 (0-11) | 1 (0-7) | <0.001 | 1 (0-7) | <0.001 | 1 (0-7) | <0.001 | 1 (0-8.3) | <0.001 | NS |
| ICIQ-UI SF | 0 (0-21) | 0 (0-16) | 0.001 | 0 (0-16) | <0.001 | 0 (0-21) | <0.001 | 0 (0-24) | 0.002 | NS |
| UDI-6 | 12.5 (0-79.2) | 0 (0-54.2) | <0.001 | 0 (0-50) | <0.001 | 0 (0-50) | <0.001 | 0 (0-41.7) | <0.001 | NS |

FSFI, Female Sexual Function Index; ICIQ-FLUTS, ICIQ-Female Urinary Tract Symptoms; ICIQ-UI SF, ICIQ-Urinary Incontinence Short Form; NS, nonstatistically significant; UDI-6, Urogenital Distress Inventory-6.

[a]Data are presented as median (minimum-maximum).

[b]$P$ value was calculated between baseline values, and 1, 3, 6, and 12 months follow-up. Statistical significance was set at a level 5% ($P < 0.05$).

[c]$P$ value was calculated between values at 1, 3, 6, and 12 months follow-up. Statistical significance was set at a level 5% ($P < 0.05$).

[d]Dyspareunia and FSFI domains are calculated in sexually active women (n = 86 and n = 64 at 1-6 months and 12 months follow-up, respectively).

any given time, dyspareunia was moderately or strongly negatively correlated to frequency of sexual intercourse ($-0.7 \geq r \geq -0.5$).

Continuous outcomes of participants at 1, 3, 6, and 12-month follow-up depending on number of therapies (three, four, or five) are presented in Table 3. Frequency of sexual intercourse increased following the same pattern as above in three, four, and five-therapy groups. At 1-month follow-up post hoc pair-wise comparisons indicated significant differences between three and four-therapy groups for dyspareunia, dryness, itching/burning, desire, lubrication, orgasm, pain, total FSFI score, and ICIQ-FLUTS in favor of four therapies. Significant differences between three and five-therapy groups were found for dyspareunia, dryness, desire, total FSFI score, ICIQ-FLUTS, ICIQ-UI SF, and UDI-6 in favor of five therapies. Differences between four and five-therapy groups were not detected for any of the parameters. All the above results were reproduced at 3 and 6-month follow-up.

At 12-month follow-up, post hoc pair-wise comparisons indicated significant differences between three and four-therapy groups for dyspareunia, dryness, desire, pain, total FSFI score, and ICIQ-UI SF in favor of four therapies. Significant differences between three and five-therapy groups were found for dryness, desire, ICIQ-FLUTS, and ICIQ-UI SF in favor of five therapies. No differences were detected between four and five-therapy groups for any of the outcomes.

Rates of VVA symptoms-free participants and normal sexual function from baseline to 12-month follow-up are presented in Fig. 2. The statistically significant increase of symptom-free rates from baseline to 1-month follow-up was maintained through 3, 6, and 12 months of follow-up (all $P < 0.001$). Symptom-free rates and/or normal sexual function rates of each group according to the number of therapies are presented in Table 4. The significant differences between the three groups were maintained throughout the 12-month follow-up, regarding the symptom-free rates of dyspareunia and dryness (Table 4).

The LUTS-free rates are presented in Fig. 3. The statistically significant increase of LUTS-free rates from baseline to 1-month follow-up remained unchanged through 3, 6, and 12 months of follow-up (all $P < 0.001$). LUTS-free rates depending on the number of therapies are presented in Table 4. Significant differences between the three groups, which were maintained throughout the 12 months of follow-up, were found for urgency and incontinence.

Three women (3%) in the three-therapy group at 6-month follow-up had moderate symptoms, and requested and received additional laser therapies. All participants declared not using any alternative complementary vaginal therapy. There were no adverse events reported at the various follow-up periods.

## DISCUSSION

The current study suggests that the use of $CO_2$ laser may have a long-lasting beneficial effect on alleviation and/or complete resolution of GSM symptoms. All assessments at 1,

**TABLE 3.** *Continuous outcomes of participants included in the current study receiving three, four, and five therapies from 1 to 12 months follow-up*

| Number of therapies | 1 mo[a] | | | | 3 mos[a] | | | | 6 mos[a] | | | | 12 mos[a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 | 4 | 5 | $P^{a}$ | 3 | 4 | 5 | $P^{a}$ | 3 | 4 | 5 | $P^{a}$ | 3 | 4 | 5 | $P^{a}$ |
| Dyspareunia[b] | 2 (0-6) | 0 (0-4) | 0 (0-5) | <0.001 | 2 (0-5) | 0 (0-4) | 0 (0-4) | <0.001 | 2 (0-5) | 0 (0-4) | 0 (0-3) | <0.001 | 2 (0-6) | 0 (0-2) | 0 (0-2) | 0.001 |
| Dryness[b] | 2 (0-8) | 0 (0-2) | 0 (0-4) | <0.001 | 2 (0-6) | 0 (0-2) | 0 (0-3) | <0.001 | 2 (0-6) | 0 (0-1) | 0 (0-3) | <0.001 | 0 (0-6) | 0 (0-1) | 0 (0-1) | 0.002 |
| Itching/burning[b] | 0 (0-4) | 0 (0-0) | 0 (0-1) | <0.001 | 0 (0-5) | 0 (0-0) | 0 (0-2) | <0.001 | 0 (0-4) | 0 (0-0) | 0 (0-1) | 0.006 | 0 (0-3) | 0 (0-0) | 0 (0-2) | 0.1 |
| FSFI[b] | | | | | | | | | | | | | | | | |
| Desire | 3.6 (2.4-6) | 4.2 (2.4-6) | 3.9 (2.8-6) | <0.001 | 3.6 (2.4-6) | 4.2 (2.4-6) | 4.2 (2.4-4.8) | <0.001 | 3.6 (2.4-6) | 4.2 (2.4-6) | 4.2 (2.4-4.8) | <0.001 | 3.6 (2.4-5.4) | 4.2 (2.4-4.8) | 4.2 (2.4-4.8) | 0.02 |
| Arousal | 3.6 (2.4-6) | 4.2 (2.4-5.4) | 3.6 (2.4-5.4) | 0.09 | 3.6 (2.4-6) | 4.5 (2.4-5.4) | 3.8 (2.4-5.4) | 0.08 | 3.6 (2.4-6) | 4.5 (2.4-5.4) | 3.8 (2.4-5.4) | 0.2 | 3.9 (2.4-6) | 4.5 (2.4-5.4) | 3.8 (2.4-5.4) | 0.2 |
| Lubrication | 4.8 (2.4-6) | 5.4 (3.6-6) | 5.1 (3.6-6) | 0.007 | 4.8 (2.4-6) | 5.4 (4.5-6) | 5.2 (3.6-6) | 0.006 | 4.8 (2.4-6) | 5.4 (4.5-6) | 5.1 (4.2-6) | 0.006 | 4.8 (2.4-6) | 5.4 (3.6-6) | 5.1 (3.6-6) | 0.08 |
| Orgasm | 3.6 (2.4-6) | 4.8 (2.8-6) | 4.4 (2.4-6) | 0.004 | 3.6 (2.4-6) | 4.8 (2.8-6) | 4.6 (2.4-6) | 0.003 | 3.6 (2.4-6) | 4.8 (2.8-6) | 4.4 (2.4-6) | 0.003 | 3.6 (2.4-6) | 4.8 (2.4-6) | 4.4 (2.4-6) | 0.1 |
| Satisfaction | 4 (2.8-6) | 4.8 (2.4-6) | 4.8 (2.8-6) | 0.1 | 4.4 (2.8-6) | 4.8 (2.4-6) | 4.8 (2.8-6) | 0.09 | 4.4 (3.2-6) | 4.8 (2.4-6) | 4.8 (2.8-6) | 0.09 | 4.8 (3.2-6) | 4.8 (2.4-6) | 4.8 (2.8-6) | 0.5 |
| Pain | 4.8 (2.4-6) | 5.6 (4.8-6) | 5.2 (3.6-6) | <0.001 | 5.2 (2.4-6) | 5.6 (4.8-6) | 5.2 (3.6-6) | 0.001 | 5.2 (2.4-6) | 5.6 (4.8-6) | 5.2 (4-6) | 0.001 | 5.2 (2.4-6) | 5.6 (4.8-6) | 5.2 (3.6-6) | 0.004 |
| Total | 24.6 (15.2-35.4) | 28.8 (23.7-34.1) | 28.8 (17.8-33) | <0.001 | 25.6 (15.2-35.4) | 29.2 (24.5-34.1) | 28.6 (17.8-33) | <0.001 | 25.7 (15.2-35.4) | 29.2 (24.5-34.1) | 28.8 (18.2-33) | <0.001 | 25.8 (15.2-35.4) | 28.8 (19.2-33.6) | 28.8 (17.8-33) | 0.01 |
| ICIQ-FLUTS[b] (Filling domain) | 4 (0-11) | 3 (0-10) | 3 (0-9) | <0.001 | 2 (0-7) | 0 (0-4) | 0 (0-3) | <0.001 | 2 (0-7) | 0 (0-6) | 0 (0-3) | <0.001 | 2 (0-7) | 0 (0-6) | 0 (0-8.3) | 0.01 |
| ICIQ-UI SF[b] | 0 (0-18) | 0 (0-18) | 0 (0-21) | 0.02 | 0 (0-16) | 0 (0-8) | 0 (0-14) | 0.02 | 0 (0-16) | 0 (0-8) | 0 (0-21) | 0.03 | 2 (0-16) | 0 (0-8) | 0 (0-24) | 0.02 |
| UDI-6[b] | 0 (0-54.2) | 0 (0-25) | 0 (0-50) | 0.02 | 0 (0-41.7) | 0 (0-41.7) | 0 (0-50) | 0.03 | 0 (0-41.7) | 0 (0-41.7) | 0 (0-50) | 0.04 | 8.3 (0-54.2) | 0 (0-41.7) | 0 (0-50) | 0.07 |

FSFI, Female Sexual Function Index; ICIQ-FLUTS, ICIQ-Female Urinary Tract Symptoms; ICIQ-UI SF, ICIQ-Urinary Incontinence Short Form; UDI-6, Urogenital Distress Inventory-6.

[a]Comparison between groups was performed using Kruskal-Wallis test. Level of statistical significance was set at 5% ($P < 0.05$).

[b]Dyspareunia, FSFI: At 1, 3, and 6 months, follow-up data were calculated in 35, 31, and 20 participants for three, four, and five-therapy group, respectively. At 1-year follow-up, results were calculated in 20, 26, and 18 participants for three, four, and five-therapy group, respectively; dryness and itching/burning: at 1, 3, and 6-month follow-up data were calculated in 35, 35, and 24 participants for three, four, and five-therapy group, respectively. At 1-year follow-up, results were calculated in 20, 29, and 22 participants for three, four, and five-therapy group, respectively.

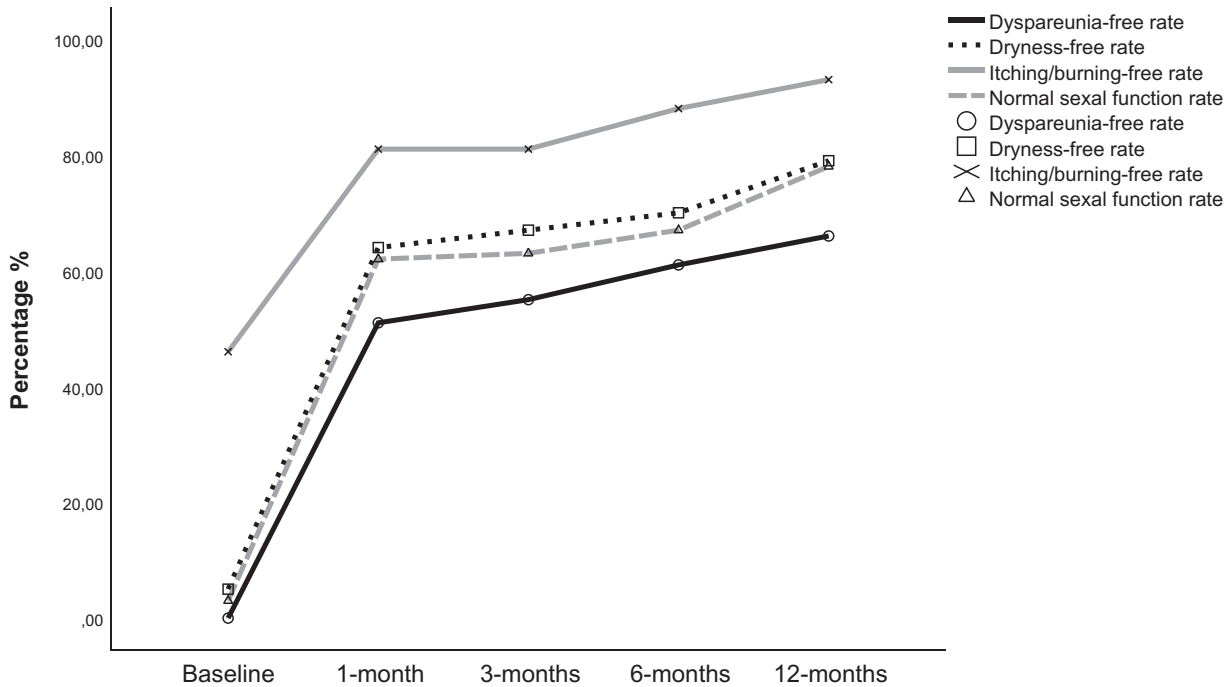


**FIG. 2.** Vulvo-vaginal atrophy symptoms-free rate and normal sexual function rate from baseline to 1, 3, 6, and 12 months of follow-up. At 1, 3, and 6 months follow-up dyspareunia-free rate and normal sexual function were calculated in the participants who had sexual intercourse or had ceased the sexual intercourse due to severity of genitourinary syndrome of menopause symptoms (n = 86), while at 12 months follow-up in 64 (74%) of them. At 1, 3, and 6 months follow-up dryness and itching/burning-free rates were calculated in all the included participants (n = 94), while at 12 months follow-up in 71 (75%) of them.

3, 6, and 12-month follow-up showed a statistically significant improvement compared with baseline values. Moreover, symptom-free rates at 12-month follow-up ranged from 40% to 100%, depending on GSM symptoms and number of therapies. In addition, the long-lasting beneficial effect was detected irrespectively to the number of $CO_2$ laser therapies. However, four or five laser therapies seemed superior to the three laser therapies, on improving most of the GSM symptoms, up to a follow-up period of 12 months.

Up to date, the vast majority of available data regarding the use of $CO_2$ laser therapy for GSM management have short follow-up period of 1 month. Synthesis of these studies revealed a consistent beneficial effect of $CO_2$ laser therapy in all GSM symptoms.[14,15] The latter result was reproduced in the three studies that presented long-term data (12-36 months).[16,17,19] These studies concluded that $CO_2$ laser therapy has the ability to maintain its positive results for 12 to 36 months. Our study confirmed these data. In particular, we found that the intensity of GSM symptoms 1 month after the last laser therapy may be indicative of GSM symptoms' intensity at 12-month follow-up, irrespective of the number of therapies. Thus, the assessment 1 month after the third laser application may provide all the necessary evidence to decide whether additional therapies should be provided.

Frequency of sexual intercourse was increased following the same pattern, in all three groups throughout the 12-month follow-up. We hypothesize therefore that the better results in the four to five-therapy group compared with the

**TABLE 4.** *Number of participants who were symptom-free and/or had normal sexual function from baseline to 12 months follow-up*

| | Baseline[a] | | | | 1 mo[a] | | | | 3 mos[a] | | | | 6 mos[a] | | | | 12 mos[a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of sessions | 3 | 4 | 5 | $P^b$ | 3 | 4 | 5 | $P^b$ | 3 | 4 | 5 | $P^b$ | 3 | 4 | 5 | $P^b$ | 3 | 4 | 5 | $P^b$ |
| Dyspareunia free (%) | 0% | 0% | 0% | 1.0 | 23% | 81% | 55% | <0.001 | 29% | 84% | 55% | <0.001 | 37% | 77% | 60% | 0.003 | 40% | 88% | 61% | 0.006 |
| Dryness free (%) | 0% | 9% | 8% | 1.3 | 34% | 89% | 71% | <0.001 | 40% | 89% | 75% | <0.001 | 43% | 91% | 79% | <0.001 | 45% | 93% | 82% | <0.001 |
| Itching/Burning free (%) | 39% | 54% | 58% | 0.6 | 57% | 100% | 79% | <0.001 | 60% | 100% | 75% | <0.001 | 74% | 100% | 83% | 0.03 | 85% | 100% | 91% | 0.2 |
| Normal sexual function (%) | 0% | 6% | 0% | 0.4 | 57% | 81% | 65% | <0.001 | 60% | 87% | 65% | 0.1 | 51% | 90% | 65% | 0.03 | 50% | 82% | 67% | 0.4 |
| Frequency free (%) | 37% | 74% | 71% | 0.003 | 69% | 94% | 92% | <0.001 | 69% | 91% | 96% | 0.006 | 74% | 86% | 96% | 0.06 | 85% | 90% | 96% | 0.3 |
| Nocturia free (%) | 66% | 63% | 71% | 0.2 | 95% | 95% | 96% | 0.9 | 95% | 95% | 96% | 0.9 | 95% | 95% | 96% | 0.9 | 95% | 87% | 96% | 0.9 |
| Urgency free (%) | 57% | 37% | 96% | <0.001 | 69% | 86% | 100% | 0.02 | 69% | 86% | 100% | 0.02 | 69% | 88% | 100% | 0.01 | 65% | 81% | 96% | 0.03 |
| Incontinence free (%) | 51% | 77% | 67% | 0.08 | 57% | 77% | 83% | 0.06 | 57% | 74% | 83% | 0.08 | 57% | 74% | 83% | 0.08 | 50% | 76% | 82% | 0.04 |

[a]Rates of participants free of symptoms at 1, 3, and 6 months follow-up were calculated in 35, 35, and 24 participants for three, four, and five laser therapies, respectively. Rates of participants free of symptoms at 12 months follow-up were calculated in 20, 29, and 22 participants for three, four, and five laser therapies, respectively. Dyspareunia-free rate and normal sexual function at 1, 3, and 6 months follow-up were calculated in 35, 31, 20 participants for three, four, and five laser therapies. Dyspareunia-free rate and normal sexual function rate at 12 months follow-up were calculated in 20, 26, and 18 participants for three, four, and five laser therapies, respectively.
[b]Comparison between groups was performed using chi-square test for three groups. Level of statistical significance was set at 5% ($P < 0.05$).

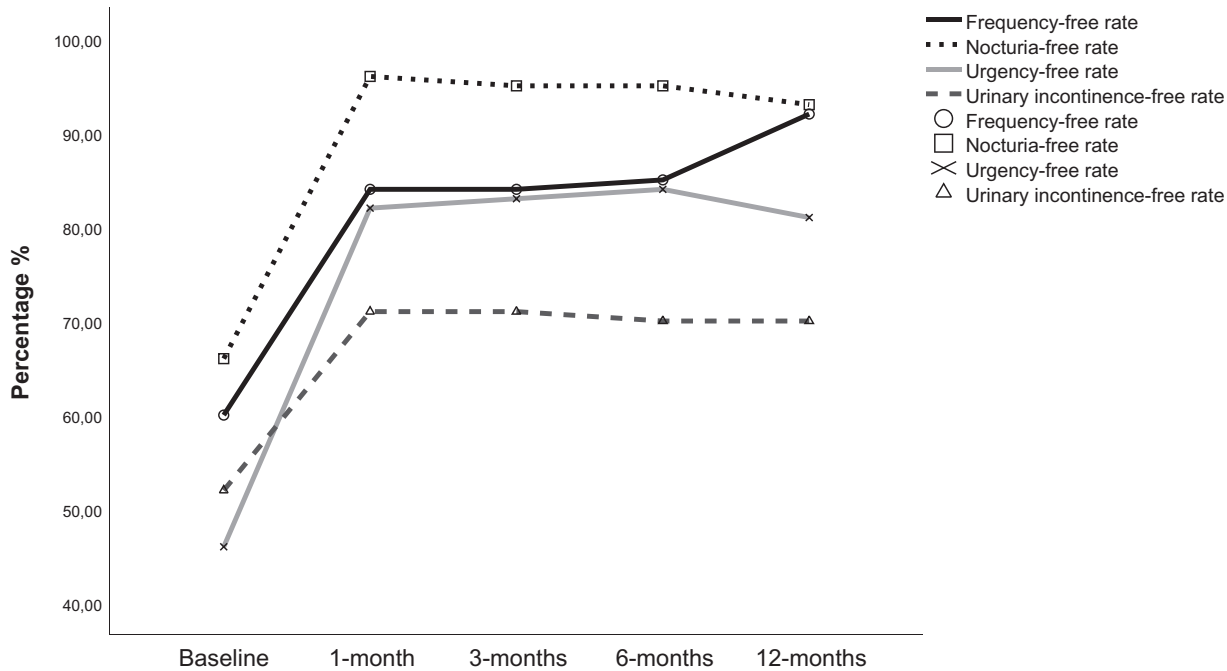


**FIG. 3.** Lower urinary tract symptoms-free rate from baseline to 1, 3, 6, and 12 months of follow-up. At 1, 3, and 6 months follow-up dryness and itching/burning-free rates were calculated in all the included participants (n = 94), while at 12 months follow-up in 71 (75%) of them.

three-therapy group may be attributed to the laser's efficacy and not to the frequency of sexual intercourse. Moreover, at 12-month follow-up after three laser therapies, dyspareunia-free rate, dryness-free rate, and normal sexual function rate were ≤50%. Accordingly, in the four or five laser therapies, these rates were all ≥61%, with the highest ones presenting in the four-laser therapy group. Participants who received four laser therapies were the only of the three groups that had the choice of an additional therapy. However, they decided not to continue with a fifth one, due to absence of symptoms or symptoms not severe enough to justify further treatment. The latter suggests that laser therapies should cease when symptoms are absent or not severe enough to justify extension of treatment, to obtain the optimum laser effect.

In post hoc pair-wise comparison for LUTS, four or five laser therapies were superior to three laser therapies. Five laser therapies seemed to have the lowest symptoms intensity and bothersomeness up to 12-month follow-up. In particular, incontinence-free rate seemed to increase only after five laser therapies, whereas frequency and nocturia-free rates increased and remained unchanged to 12-month follow-up, even after three laser therapies. Perhaps, the necessary structural changes related to urinary incontinence may require longer time and/or higher energy applied. Interestingly, although urgency was significantly reduced after treatment, urgency-free rate did not change from baseline in all groups. The latter, in our view, indicates that other functional problems may be implicated in the pathogenesis of urgency, requiring additional treatment. Hence, in our opinion, if urgency is the most bothersome symptom of GSM and absence of urgency is the treatment goal, clinicians should consider combining laser therapy with other therapeutic options (ie, physiotherapy or pharmacotherapy) or not including laser therapy as a therapeutic option.

The current study has several limitations. One possible limitation is the fact that this is not a randomized placebo-controlled study, but a retrospective one that compares three to four and five laser therapies. Furthermore, the improvement was at 1-month follow-up and remained unchanged throughout the 12-month follow-up. Thus, a possible placebo effect cannot be over-ruled. However, the consistency of positive results throughout the 12-month follow-up period indicates that placebo is not the mode of action of laser therapy. In addition, all women received laser therapies due to VVA symptoms. Hence, our population is not representative for LUTS, because tools for assessing LUTS (ie, bladder diary, cough stress test, urodynamics) were not available. Nevertheless, validated questionnaires for LUTS were provided. Furthermore, our results cannot be confirmed by other studies as this is the first study evaluating the 12-month efficacy of three, four, or five laser therapies.

## CONCLUSIONS

Microablative fractional $CO_2$ laser may be a highly efficacious therapy for management of all GSM symptoms up to 12-month follow-up, irrespective of the number of laser therapies. Response to therapy 1-month after the last laser therapy may be indicative of the 12-month efficacy. However, four or five $CO_2$ laser therapies seem to result in lower symptoms' intensity and higher symptom-free rates for dyspareunia, dryness, sexual function, and incontinence in comparison to standard protocol of three $CO_2$ laser therapies. Hence,

 

1 month after the third laser therapy could be the critical time at which a thorough discussion should be performed, based on type and severity of symptoms, before deciding to cease or extend the laser therapy.

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