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ORIGINAL ARTICLE

A randomized controlled study of vaginal fractional CO_2 laser therapy for female sexual dysfunction

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Abstract

The purpose of this study is to evaluate the efficacy and safety of vaginal fractional CO_2 laser therapy for female sexual dysfunction (FSD). A total of 84 women at high risk of sexual dysfunction were randomly divided into two groups. Women in the laser group received vaginal fractional CO_2 laser therapy. Others in the Kegel group were advised to participate in Kegel exercise training. Sexual distress and sexual function were evaluated by using the Female Sexual Distress Scale-Revised (FSDS-R) and the Chinese version Female Sexual Function Index (CVFSFI), respectively. Adverse events were recorded during the 12-month follow-up. At the end of the 6th and 12th months, the lubrication scores of the CVFSFI in the laser group (4.55±0.05, 4.58 ±0.09) were significantly higher than those in the Kegel group (4.19±0.15, 4.20±0.14) (P<0.05). The satisfaction scores in the laser group (4.43±0.08) were higher than those in the Kegel group (4.20±0.16) at the end of the 6th month (P<0.05). The self-contrast test in the laser group showed significant improvement in lubrication, pain, satisfaction and total scores after CO_2 laser therapy (p<0.05). These improvements were maintained for 1 year. The improvement of FSDS-R in the laser group (10.0±0.2) was more evident than in the Kegel group (11.1±0.4) at the end of the 12th month. There were no major adverse events reported during laser therapy. Vaginal fractional CO_2 laser therapy can effectively improve sexual function without any serious adverse events. It might be an effective and relatively safe treatment option for improving vaginal mucosa status in sexually active women with sexual dysfunction.

Keywords Female sexual dysfunction · Female Sexual Function Index · Fractional CO_2 laser therapy · Kegel exercises · Sexually active women

Introduction and purpose

Female sexual dysfunction (FSD) has been recognized as a global health problem affecting women of all ages and social groups, with a prevalence ranging from 20 to 70% in different areas [1, 2]. In studies performed by Shifren JL et al. [3] of 31,581 US adult women, nearly 44% reported having a sexual problem. In Mainland China, the prevalence of FSD has been estimated at 29.7% based on a large-scale survey using the Female Sexual Function Index (FSFI) [4]. FSD is defined as distressing sexual conditions and sexual health problems experienced by women. It results in significant personal distress and may impact quality of life and interpersonal relationships [5–7]. The aetiology of FSD is complicated and includes gynaecological, obstetrical, endocrinological, neurological, psychological and sociological factors [8, 9]. Consequently, a wide variety of treatments are available that address specific symptoms and involve psychotherapy, lifestyle modifications, pharmacotherapy, physical exercises and topical therapies [10]. Approved drugs, such as ospemifene, are available for the treatment of dyspareunia associated with vulvovaginal atrophy [11]. Tibolone has been proven effective in ameliorating sexual desire [12]. Behavioural training, such as Kegel exercises, can improve sexual satisfaction by tightening relaxed musculature of the pelvic floor [13, 14]. Hormonal creams are also available for postmenopausal women with genitourinary syndrome of menopause (GSM) and sexual

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problems [15]. However, the effectiveness of each treatment method is somewhat limited and must be balanced against the risks.

Vaginal mucous contains a very high water percentage. It is a good target for fractional CO_2 laser. The CO_2 laser energy is well absorbed, and the incident photon energy causes controlled damage, which stimulates blood circulation and tissue regeneration. Recently, several clinical trials have examined the role of vaginal fractional laser therapy, a nonsurgical procedure, for the treatment of GSM/vulvovaginal atrophy (VVA), stress urinary incontinence and vaginal relaxation syndrome [16, 17]. Salvatore S [18] reported that fractional CO_2 laser therapy contributed to the complete regression of dyspareunia and dryness and re-established normal sexual function in 273 postmenopausal women. Then he published a study that revealed the early regenerative modifications of mucosa in postmenopausal women following fractional CO_2 laser treatment [19]. Perino A et al. [20] also reported a 30-day study in which the VVA symptoms improved significantly in 48 patients who had undergone 3 sessions of vaginal fractional CO_2 laser treatment. 91.7% of patients were satisfied or very satisfied with the procedure and experienced considerable improvement in quality of life. In a recent systematic review, there were 14 prospective, uncontrolled studies with 542 participants comparing the women's sexual dysfunction and vaginal symptoms before and after vaginal laser therapy [21]. These studies opened a new window for non-hormone therapy of GSM. Furthermore, it is therefore reasonable to presume that laser therapy may improve female sexual function as it provides functional restoration of the vaginal mucosa. However, a few data currently exist regarding the long-term effects of vaginal laser therapy for FSD, and the physiological mechanism of this therapy is as yet unclear. It is also important to assess the safety and tolerability of this new therapy before it can be widely implemented.

In this study, the efficacy of vaginal fractional CO_2 laser therapy for FSD was compared with that of Kegel exercises in sexually active women. Adverse events were also recorded during the 12-month follow-up.

Materials and methods

Study design and participants

The present study was a randomized controlled trial that included a baseline period followed by a 3-month treatment period and a 12-month post-treatment follow-up period. From September 2017 to February 2018, adult women who consulted the gynaecological clinic at the Peking Union Medical College Hospital seeking services for sexual dysfunction were selected if they met the following criteria: (1) regular menstrual cycle, (2) good physical condition, (3) normal cognitive ability, (4) heterosexuality, (5) married or with a long-term partner and (6) defined as 'at high risk of sexual dysfunction' by the Chinese version of the Women's Sexual Function Index (CVFSFI) with a total score ≤26.55.

Women were excluded if they (1) were widowed, divorced or separated; (2) had a history of genital tract malformation; (3) had urinary incontinence and/or symptomatic pelvic organ prolapse (uterine descent POP-Q stage 2 or higher); (4) had major levator ani muscle defects; (5) had a history of undergoing mesh implantation surgery in the pelvic floor; (6) had acute pelvic inflammatory disease; (7) currently had malignant gynaecological tumours; (8) had abnormal liquid-based cervical cytology test results; (9) had a previous history of receiving medication for FSD or mental disease; or (10) were currently pregnant or in puerperium.

The participants enrolled in this study were divided into two groups according to a random number table prepared by the Department of Epidemiology and Statistics. All investigators were blinded to group location and the participants' answers. The women in the laser group received monthly vaginal fractional CO_2 laser therapy for a total of 3 treatments. The participants in the Kegel group were advised to participate in Kegel exercise training. The consultations and treatments offered in this study were provided at no cost to the participants, and all participants signed the informed consent form. This study obtained approval from the ethics committee, which follows international safety standards, and it was registered with the Chinese Clinical Trial Registry (ChiCTR) (www.chictr.org.cn) with the following identifier: ChiCTR1900021657.

The technology of vaginal fractional CO_2 laser therapy

Vaginal fractional CO_2 laser treatments (Alma Lasers Ltd, Femilift Pixel CO_2, Israel) were performed in the outpatient department without anaesthesia or sedation. The head of the probe pixelated the beam into 81 microscopic pixels in an 11×11 mm pattern. The laser was set to a power of 60 W, with a dwelling time of 1000 μs, no dot spacing. The maximum energy setting was 120 mJ/pixel. The energy intensity was decreased if women expressed any signs of discomfort. The women in the laser group were placed in the lithotomy position with a gauze pad. Routine local antiseptic cleaning was performed. A single-use hygienic probe was lubricated with baby oil to facilitate entry. It is rotated by 45° at a time after each laser pulse, delivering energy to the deep submucosal vaginal tissue. The average length of each therapy session was 15 min. Since a minimum interval of 30 days was required between sessions, the women in the laser group received monthly vaginal fractional CO_2 laser treatments for a total of 3 sessions, avoiding the period of menstruation. In this study, a clinician who was experienced and trained in this therapy performed each procedure.

Kegel exercises

Kegel exercises, named for Dr. Arnold Kegel, start by lifting and holding the pelvic floor muscles for 3 s and then relaxing for 3 s. Ten repetitions of this muscle contraction count as one set [22]. In this study, the women in the Kegel group attended an exercise class led by well-trained physical therapists. They were then advised to repeat this set of exercises twice a day at home at least 3 days per week during the entire follow-up period, and they were encouraged to keep an exercise diary. Every 2 weeks, a pelvic floor specialist monitored the participants' performance of the exercises during appointments at the outpatient clinic.

Assessments

The vaginal resting pressure was measured by a pressure sensor placed in the vagina. Pelvic muscle strength was evaluated using the Modified Oxford Grading System, a measurement scale widely used in clinical evaluations that was developed by Laycock [23] (Grade 0, no discernible contraction; Grade 1, very weak contraction, a 'flicker'; Grade 2, weak contraction; Grade 3, moderate contraction with some squeeze and lift ability; Grade 4, good contraction, squeeze and lift against resistance; Grade 5, strong contraction, squeeze and lift against strong resistance). The Modified Oxford Grading System was used with vaginal palpation by the clinicians in this study.

In 2000, Rosen [24] developed the Female Sexual Function Index (FSFI), which is a brief questionnaire that measures the sexual function of women over the past 4 weeks. It has been globally accepted for assessing 6 domains of sexual function: desire, arousal, lubrication, orgasm, satisfaction and pain. The domain scores are weighted so that every domain contributes a maximum of six points to the total score. Possible FSFI total score ranges from 2.0 to 36.0. Higher scores indicate better sexual function. Wiegel M et al. [25] developed the optimal diagnostic cut-off score for the FSFI (≤26.55), which differentiated between women with and without sexual dysfunction. This cut-off threshold has been widely used in many other countries. The reliability and validity of the Chinese version of the FSFI (CVFSFI) have been evaluated by Sun X [26] at the Peking Union Medical College Hospital. In this study, an individual was defined as having 'female sexual dysfunction' if the total CVFSFI score was ≤26.55. The FSFI scores before and after treatments were compared to assess any improvements in sexual function.

The concept of sexually related personal distress is currently central to the diagnosis of all FSD. In 2002, Derogatis L et al. [27, 28] developed the Female Sexual Distress Scale (FSDS) and its revised version (FSDS-R) to measure sexually related personal distress in women. The Female Sexual Distress Scale-Revised used in this study is a self-administered questionnaire consisting of 13 items measuring sexual distress. Items are rated as never (0), rarely (1), occasionally (2), frequently (3) or always (4). The total FSDS-R score ranges from 0 to 52. The cut-off score is ≥ 11.

The baseline characteristics and questionnaire scores were compared between the two groups at each time point. Data collection was repeated at the end of the 3rd, 6th and 12th months post-treatment. The participants were required to complete the questionnaires independently. The questionnaires were delivered with uniform instructions and collected immediately after completion each time. Specially trained nurses were employed for quality control and data entry.

Statistical analysis

Statistical analyses were performed with SPSS for Windows (version 22.0) and JASP (V0.12). The results are expressed as the mean ± SEM. For continuous data, Student's t test was used, and within-group analysis was also performed. The distribution of pelvic muscle strength was highly skewed; therefore, nonparametric methods were used. The chi-square test was used for the comparison of epidemiological characteristics. A P value<0.05 was considered statistically significant. The Cohen's d and effect size (r) were also evaluated if necessary.

Results

A total of 84 women were randomly divided into two groups. After follow-up, the overall compliance rate was 96.4% (81/84). Two (2/42, 4.8%) women in the laser group dropped out because of the long distance between the clinic and their homes, and one (1/42, 2.4%) woman in the Kegel group was lost to follow-up because of a phone number change. The remaining 81 women were followed for 12 months. The participant flowchart is illustrated in Fig. 1.

All of the participants were women of childbearing age with an average age of 36.5±6.9 years. Before treatment, there was no significant difference in baseline characteristics (Table 1), vaginal resting pressure/muscle strength or questionnaire scores (Tables 2 and 3) between these two groups. All the participants had regular menstrual cycles, lasting from 21 to 35 days. Each group was divided into three levels based on the fertility/ovarian function in relation to cycle length according to most previous researches. There was no significant difference in menstrual cycle characteristics between these two groups (Table 1). The investigation and treatment were not required performing in a specific menstrual cycle phase. Each participant had her own follow-up point in a menstrual cycle except menses. The distribution was random, and there was no significant difference between the two groups. The medical histories of each of the participants

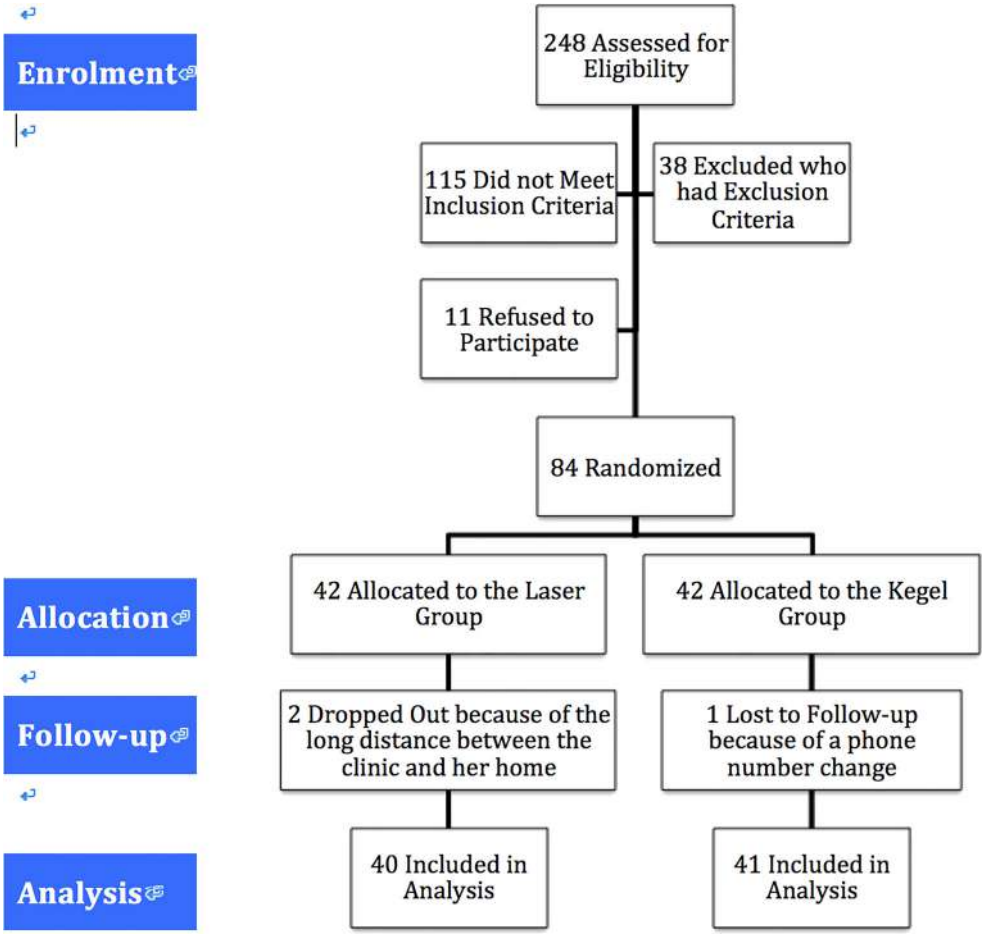

Fig. 1 The participant flowchart

enrolled in this study were carefully investigated and reviewed. None of the participants had a previous history of receiving medication for FSD or mental disease. None of them took any medicine that could affect the functions of vessels, nerves, incretion or psychosis during the treatment or follow-up periods.

At the end of the 6th and 12th months, the CVFSFI lubrication scores in the laser group (4.55±0.05, 4.58±0.09) were higher than those in the Kegel group [4.19±0.15, Cohen's *d*: 0.481, effect size (*r*): 0.234; 4.20±0.14, Cohen's *d*: 0.483, effect size (*r*): 0.234], a medium effect size with statistically significant differences ($P<0.05$). In addition, the satisfaction scores in the laser group were higher than those in the Kegel group at the end of the 6th month [$P<0.05$, Cohen's *d*: 0.280, effect size (*r*): 0.139]. Regarding within-group changes, the laser group showed significant improvements in lubrication, pain, satisfaction and total CVFSFI scores at the end of the 3rd month after fractional CO_2 laser therapy ($P<0.05$). These improvements were maintained for the next 9 months. However, significant improvement in orgasm appeared later in the laser group, beginning at the 6th month and continuing to the end of the follow-up period. Similarly, the Kegel group had a significant improvement in orgasm at the end of the 6th and 12th months. However, improvements in satisfaction and total scores were not found in the Kegel group until 12 months after initiating the exercises, which was later than in the laser group. Neither of the two groups reported significant improvements in sexual desire or arousal (Table 2).

Before the treatment, all participants were considered 'female sexual dysfunction', with a total CVFSFI score equal to or less than the cut-off value (26.55). One year after the vaginal fractional CO_2 laser treatments, 11 of the women in the laser group had CVFSFI scores over 26.55 (27.5%, 11/40), and only 4 women in the Kegel group had total CVFSFI scores over the cut-off value (9.8%, 4/41) after at least 12 months of Kegel exercises. The percentage of women with scores over the cut-off value in the laser group was significantly higher than that in the Kegel group (Pearson chi-square test, X: 4.02, $P<0.05$).

The within-group comparisons showed a statistically significant reduction in distress in both groups. However, at the end of the 12th month, the total FSDS-R score of the laser group (10.0±0.2) was lower than that of the Kegel group (11.1±0.4), a difference that was statistically significant with a medium effect size [$P<0.05$, Cohen's *d*: 0.490, effect size (*r*): 0.238]. This difference

Table 1 The baseline characteristics of the participants

Baseline characteristics	Laser group (n=40) N (%)	Kegel group (n=41) N (%)
BMI		
BMI<18.5	6 (15.0)	4 (9.76)
18.5≤BMI<24	26 (65.0)	31 (75.6)
24≤BMI<28	8 (20.0)	6 (14.6)
BMI≥28	0	0
Economic situation (Monthly income/Yuan)		
≤4000	5 (12.5)	4 (9.8)
4000—10000	22 (55.0)	21 (51.2)
>10000	13 (32.5)	16 (39.0)
Education level		
Senior high school	2 (5.0)	5 (12.2)
University graduate	25 (62.5)	24 (58.5)
Master's degree or above	13 (32.5)	12 (29.3)
Mode of delivery		
Nonparous	7 (17.5)	6 (14.6)
Vaginal delivery	18 (45.0)	17 (41.5)
Caesarean section	15 (37.5)	18 (43.9)
Delivery times		
0	7 (17.5)	6 (14.6)
1	29 (72.5)	28 (68.3)
≥2	4 (10.0)	7 (17.1)
History of dystocia/assisted deliveries/macrosomia		
No	23 (57.5)	21 (51.2)
Yes	17 (42.5)	20 (48.8)
Asymptomatic POP		
POP-Q stage 1	21 (52.5)	18 (43.9)
Without POP	19 (47.5)	23 (56.1)
Menstrual cycle length (days)		
Short cycles (21≤length≤24)	4 (10.0)	6 (14.6)
Moderate cycles(24<length<32)	27 (67.5)	25 (60.9)
Long cycles (32≤ length ≤35)	9 (22.5)	10 (24.4)

BMI body mass index, *POP* pelvic organ prolapse

suggested that women's sexually related emotions improved more evidently in the laser group (Table 3).

Conversely, the pelvic muscle strength of the laser group was lower than that of the Kegel group at the end of the 12th month (Mann-Whitney test, two independent samples tests, $P < 0.05$). Furthermore, the pelvic muscle strength of the Kegel group showed significant improvements at the end of the 6th and 12th months (Wilcoxon signed-rank test, two related samples tests, $P < 0.05$) (Table 4). However, there was no significant change in the vaginal resting pressure for either group.

Adverse events

Pain during vaginal fractional CO_2 laser therapy was assessed using a visual analogue scale (VAS, range from 0 to 10). Twenty-nine women (72.5%) in the laser group felt mild pain according to their self-assessed VAS score of 1, while the remaining 11 women felt warmth but no pain.

Nine of the women (22.5%, 9/40) reported a small amount of bloody vaginal discharge after vaginal fractional CO_2 laser therapy, and this symptom resolved within 1–5 days. One woman's vaginal secretions decreased after fractional CO_2 laser therapy (2.5%, 1/40) and recovered 3 weeks later. No potential adverse effects of this therapy, including infection, pain, active bleeding or burns, were observed during this study.

Discussion

In this study, the lubrication scores of the laser group were significantly higher than those of the Kegel group beginning in the 6th month. The reason for the small absolute difference may be attributed to the CVFSFI score calculation rules. For instance, the lubrication domain contributes such a small absolute score to the total score of a maximum of only 6 points after being weighted. The Cohen's d and effect size also support the difference that the vaginal CO_2 laser therapy does have a more positive effect than Kegel exercises for vaginal lubrication and sex-related distress reduction with a medium effect size (the Cohen's d values were 0.481, 0.483 and 0.490, respectively). The within-group test of the laser group also showed significant improvements in lubrication, pain, satisfaction and total scores in the 3rd month. All these changes were preserved until the end of follow-up. Fractional CO_2 laser and other laser types (e.g. Er:YAG laser) induce morphological changes in the vaginal mucosa. Zerbinati et al. [29] published elegant studies related to the histological evidence of the increase in vaginal epithelial thickness after fractional CO_2 laser therapy, as well as the formation of new papilla. Accordingly, the long-term follow-up data in our study suggest that epithelial regeneration and collagen production after laser therapy are relatively durable.

At the end of follow-up, 27.5% of the women in the laser group passed the FSFI cut-off score. This percentage was significantly higher than that in the Kegel group (9.8%). In addition, the satisfaction scores in the laser group were higher than those in the Kegel group. The comparison of FSDS-R scores between the two groups also showed that the women in the laser group reported feeling much less depressed during the follow-up period. The above data suggest that vaginal fractional CO_2 laser therapy is more effective than Kegel exercises. Consequently, vaginal fractional CO_2 laser therapy

Table 2 Statistical analysis of the FSFI scores pre- and post-treatment and the differences between the Laser and Kegel groups

Domain	Baseline		3 months after treatment		6 months after treatment		12 months after treatment	
	Laser group (n=40)	Kegel group (n=41)	Laser group (n=40)	Kegel group (n=41)	Laser group (n=40)	Kegel group (n=41)	Laser group (n=40)	Kegel group (n=41)
Desire	2.61±0.10	2.60±0.10	2.61±0.10	2.66±0.12	2.64±0.10	2.64±0.12	2.65±0.10	2.63±0.12
Arousal	3.71±0.16	3.68±0.17	3.71±0.16	3.68±0.17	3.64±0.16	3.85±0.18	3.68±0.15	3.71±0.16
Lubrication	4.06±0.15	4.17±0.16	4.49±0.06[a]	4.19±0.16	4.55±0.05[a,b]	4.19±0.15[b]	4.58±0.09[a,b]	4.20±0.14[b]
Orgasm	3.84±0.17	3.75±0.17	3.90±0.15	4.14±0.09	4.00±0.15[a]	4.21±0.95[a]	4.06±0.17[a]	4.17±0.08[a]
Satisfaction	4.05±0.17	4.07±0.16	4.38±0.08[a]	4.21±0.16[a]	4.43±0.08[a,b]	4.20±0.16[b]	4.51±0.11[a]	4.26±0.16[a]
Pain	4.83±0.07	4.96±0.07	4.91±0.05[a]	4.79±0.72	4.93±0.04[a]	4.78±0.70	4.95±0.06[a]	4.91±0.08
Total score	23.34±0.33	23.22±0.54	23.99±0.23[a]	23.66±0.46	24.13±0.23[a]	23.82±0.52	24.42±0.35[a]	23.87±0.49[a]

The difference between pre- and post-treatment in the same group (paired t test, [a] P<0.05)

The difference between two groups at the same point in time (two-sample t test, [b] P<0.05)

may be appropriate for women who want to improve sexual function but reject the practice of long-term Kegel exercises.

The most common adverse events reported for the medical treatment of FSD (e.g. with flibanserin) are somnolence, dizziness and headaches [30, 31]. In the laser group, however, the most common complaint (72.5%) was slight pain, with a VAS score of 1, and no anaesthetic was necessary. Additionally, 22.5% of the women in this study had a small amount of bloody vaginal discharge after laser therapy, a symptom that spontaneously resolved within days. No major adverse events were reported. Vaginal fractional CO_2 laser therapy, therefore, may be a relatively safe option for women who cannot tolerate the possible serious side effects of medication therapy.

The use of laser therapy has been widely adopted in various medical conditions, such as dermatology, dentistry, ophthalmology and cosmetic medicine. Over the last few years, fractional CO_2 laser technology has been available as a new method in dermatological areas, such as the treatment for acne scars, thermal burns scars, striae distensae, xanthelasma palpebrarum, onychomycosis, vitiligo and eyelid tightening [32–35]. It is a therapeutic option for the dermatologist with shorter downtime and higher satisfaction compared with traditional pulsed CO_2 laser treatment. The CO_2 laser has been used safely and effectively in gynaecology for more than 30 years for the treatment of condylomata and intraepithelial neoplasia of the lower genital tract. More recently, several innovative studies on the application of fractional CO_2 laser in gynaecology have also been published. In 2011, Gaspar et al. [36] first demonstrated that vaginal fractional CO_2 laser therapy plays a role in stimulating tissue repair and restoring normal vaginal function. Salvatore et al. [37] reported a 12-week study in which vaginal dryness improved in 43 women (86.0%) after 3 sessions of fractional CO_2 laser therapy. Athanasiou S et al. [38] reported a 3-month study in which fractional CO_2 laser therapy decreased the vaginal pH in 53 women. The prevalence of *Lactobacillus* changed from 30 to 79%. Samuels J B et al. [39] presented similar data on the positive effects of CO_2 laser therapy on the Vaginal Health Index as well as histological findings from 40 postmenopausal women after 12 months of follow-up. In the last year or two, there have been two relevant controlled clinical studies published. In 2018, Cruz, Vera L. et al. [40] first reported a randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO_2 laser compared with topical estriol in the treatment of VVA in 45 postmenopausal women. After 20-week follow-up, the laser and combination

Table 3 Statistical analysis of the FSDS-R scores pre- and post-treatment and the differences between the Laser and Kegel groups

	Baseline	3 months after treatment		6 months after treatment		12 months after treatment	
	Score	Score	[a]P value	Score	[a]P value	Score	[a]P value
Laser group (n=40)	12.6±0.4	11.6±0.3	[a]P<0.01	10.8±0.3	[a]P<0.01	10.0±0.2	[a]P<0.01
Kegel group (n=41)	12.5±0.5	11.8±0.4	[a]P<0.01	11.2±0.4	[a]P<0.01	11.1±0.4	[a]P<0.01
[b]P value	[b]P=0.893	[b]P=0.722		[b]P=0.073		[b]P=0.03	

The difference between pre- and post-treatment in the same group (paired t test, [a] P<0.05)

The difference between two groups at the same point of time (two-sample t test, [b] P<0.05)

Table 4 The change in pelvic muscle strength before and after treatment (by the Modified Oxford Grading System)

Muscle strength	Before treatment		3 months after treatment		6 months after treatment		12 months after treatment	
	Laser group *n* (%)	Kegel group *n* (%)	Laser group *n* (%)	Kegel group *n* (%)	Laser group *n* (%)	Kegel group *n* (%)	Laser group *n* (%)	Kegel group *n* (%)
Grade 0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 1	5 (12.5)	6 (14.6)	3 (7.5)	5 (12.2)	6 (15.0)	4 (9.8)	4 (10.0)	1 (2.4)
Grade 2	7 (17.5)	7 (17.1)	10 (25.0)	8 (19.5)	5 (12.5)	8 (19.5)	5 (12.5)	5 (12.2)
Grade 3	13 (32.5)	11 (26.8)	14 (35.0)	10 (24.4)	14 (35.0)	11 (26.8)	17 (42.5)	9 (22.0)
Grade 4	11 (27.5)	13 (31.7)	8 (20.0)	14 (34.1)	11 (27.5)	13 (31.7)	9 (22.5)	18 (43.9)
Grade 5	4 (10.0)	4 (9.8)	5 (12.5)	4 (9.8)	4 (10.0)	5 (12.5)	5 (12.5)	8 (19.5)
[c]*P*	-	-	>0.05	>0.05	>0.05	0.046[c]	>0.05	0.01[c]
[d]*P*	>0.05		>0.05		>0.05		0.035[d]	

The difference between pre- and post-treatment in the same group (Wilcoxon signed-rank test, two related sample tests, [c] $P<0.05$)

The difference between two groups at the same point in time (Mann-Whitney test, two independent sample tests, [d] $P<0.05$)

(laser + estriol) groups showed a significant improvement of dyspareunia, burning and dryness and the estriol arm only of dryness. The combination group also presented significant improvement of total Female Sex Function Index (FSFI) score and individual domains of pain, desire and lubrication. Politano et al. [41] compared the effects of fractional CO_2 laser therapy, promestriene and vaginal lubricants on genitourinary syndrome treatment and sexual function in 72 postmenopausal women after 14 weeks of therapy. The effect of fractional CO_2 laser therapy was demonstrated to be better in short term than those of promestriene or lubricant with respect to improving the vaginal health in postmenopausal women. Although the sample size is small, these two studies clearly show that the effect of laser treatment appears to be comparable to local hormone treatment for GSM in a relatively short period of time. Therefore, it can be presumed that the same physiological mechanism may underlie the ability of CO_2 laser therapy to improve vaginal health and mucosal condition. Consequently, the effects of CO_2 laser therapy might exploit a new field of non-hormonal treatment of the vaginal mucosa for FSD women at different ages.

According to past research, the increase in the lubrication score may be either a cause or an effect for the improvement of sexual function in this study. The improved vaginal mucosal condition resulting from laser therapy is considered to induce an increase in vaginal microcirculatory blood flow. Furthermore, vaginal lubrication may relieve pain caused by friction. In addition, it is possible that vaginal CO_2 laser therapy could improve mucosal sensitivity due to the formation of new papilla. FSD is a combination of sexual problems and distress related to those problems, which include microcirculation disturbance, sensory deficits, lubrication disorder and sexual pain. In this study, all of the improvements combined may contribute to the significant improvements in satisfaction and total FSFI scores of the laser group. Eventually, the decreasing FSDS-R scores reflected the improvements in personal distress after laser therapy.

Citak et al. [42] conducted a single blind RCT with 118 primiparous women that showed a significant increase in sexual arousal, lubrication and orgasm after performing Kegel exercises. In contrast, vaginal CO_2 laser therapy only impacts the first few micrometres of tissue; it cannot improve pelvic floor muscle strength. In the present study, the pelvic floor muscle strength of the Kegel group was significantly higher than that of the laser group; this observation is consistent with the physiological mechanisms of the two treatments.

Basing on the above analysis, fractional CO_2 laser technology may be appropriate for FSD women who cannot or do not want to be treated with pharmacological therapy for medical reasons as well as for women who reject the practice of long-term Kegel exercises at different ages. The data from observational studies appear to suggest that fractional CO_2 laser is safe and well accepted, with no major side effects or adverse events reported. Future investigations should focus on large randomized trials and cost reduction.

The strengths of this study are that it was well controlled and that the follow-up time was 12 months, longer than most of previous studies related. Additionally, partially because of the fact that the treatments and consultations were offered at no cost, very few participants dropped out, which ensured the integrity of the data. However, this study is limited by a small sample size and a lack of histological evidence. Psychological and relationship factors are also not adequately addressed. Future investigations need to be designed to include histological assessments, psychosocial factors and perennial follow-up evaluations.

Summary

According to this study, vaginal CO_2 laser therapy can effectively improve sexual functioning in sexually active women, especially in the areas of lubrication and satisfaction. Vaginal CO_2 laser therapy was well tolerated during this study and had no serious adverse events. It might therefore be an effective and relatively safe treatment option for improving vaginal mucosa status in sexually active women with sexual dysfunction. However, further clinical trials with longer follow-up periods and rigorous impact evaluations are still needed.

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Declarations

Competing interests The authors declare no competing interests.

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