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Evaluation of the Safety and Efficacy of Fractional Micro-ablative Carbon Dioxide Laser in Genito-urinary Syndrome of Menopause; A Review of Literature

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1. Abstract

1.1. Background: The scientific impact paper by RCOG (Royal College of obstetricians and gynaecologists) has seconded FDA on the adverse effects of energy-based devices (Philip et al, 2022). RCOG still recommend vaginal oestrogens as the gold standard for treating GSM (Philip et al, 2022). This review aims to evaluate the safety and efficacy of fractional microablative carbon dioxide lasers in treatment of vulvovaginal atrophy or genito-urinary syndrome of menopause.

1.2. Methods: The search criteria involved using "CO2 laser AND Genitourinary Syndrome of Menopause", "C02 laser AND Vulvovaginal atrophy" in PUBMED, MEDLINE,and Clinical trials.gov. The search was done between May 2023 to September 2023.

1.3. Results: A total of nine randomized control trials were analyzed for the review. This summed up to five hundred and thirty-two (n=532) participants being randomised, with two hundred and forty five women (n=245) in treatment group and two hundred and eighty seven (n=287) in control group/groups.

1.4. Discussion: The strengths of this review are many. All the papers included were randomised control studies comparing use of Carbon monoxide laser with with sham trials or with topical vaginal estrogen and all the studies included had validated questionnaires thereby improving internal validity. The limitations of the study are only three papers included in the study were able to show statistically significant results. Many trials included had no power calculation done and hence very small sample size.

1.5. Conclusion: To conclude, there is no statistically significant evidence that the fractional microablative CO_2 lasers are better in comparison to sham procedure or laser for treatment of genito-urinary syndrome of menopause.

1.6. Funding: This study is part of MCh dissertation and have received no funding from any external resource.

2. Introduction

Genitourinary syndrome of menopause (GSM)/Vulvovaginal atrophy (VVA) affects approximately 27-84% of post-menopausal women mainly due to reduced levels of oestrogen during old age (Sarmento et al, 2021). Over time, vaginal, labial and vulvar tissues tend to lax due to a plethora of reasons like trauma, repeated childbirth, weight fluctuations, genetics etc (Gold et al,2018) (Paul's et al,2012). This leads to vaginal/vulvar scarring, atrophy, dryness, damage to mucosa which affects the tone of pelvic floor culminating in more severe issues like cystocele, rectocele, urinary incontinence and uterine prolapse (Gold et al, 2018) (Pauls et al, 2012). The following physiological and psychological distress affects not just the women's quality of life and her self-confidence/esteem but also the overall sexuality (Karcher and Sadick,2016).

The conventional modalities include topical moisturisers, hyaluronidase acid preparations, lubricants and low-dose estrogen therapy (Photiou et al, 2020). The surgical options are labioplasty, monsplasty and vaginoplasty (Photiou et al,2020). Nevertheless, over the recent years, many aesthetic clinics, salons and doctors have promoted energy-based devices (EBD) as effective non-invasive method for "vaginal rejuvenation" to mitigate problems of peri and post-menopausal women and for "cosmetic procedures" with

great zeal (Philip et al, 2022). Some even have gone to the extent of claiming that lasers can restore vaginal pH and combat infections (RejuvaMed Skin Clinic, n.d).

The devices used in gynaecology are carbon dioxide (CO2) and Erbium YAG (Er:YAG) lasers and thermal-controlled radio frequency devices (Philip et al,2022). The micro-ablative CO2 laser was introduced in 2014 and use specific pulse modes (D-Pulse) on lamina propria and vaginal epithelium (to vaporise) by an initial high-peak portion and a low-peak tail to diffuse the energy (Philip et al, 2022). These pulses in repetition stimulate vaginal tissue regeneration by neogenesis and stimulation of elastin and collagen fibres devoid of fibrosis in post-menopausal women with vulvovaginal atrophy or genitourinary syndrome of menopause (Zerbinati et al, 2014). The Er:YAG laser with a wavelength of 2940nm has more affinity for water absorption and thereby exert a gradual thermal effect causing water-rich controlled heating of sub-epithelial connective tissue (Philip et al, 2020)(Philip et al,2022). This causes disruption of collagen cross linkages and shortening of collagen fibrils, and this interaction with deeper layers cause tissue retraction, shrinkage and new collagen fibre formation (Tadir et al, 2017) and ultimately connective tissue remodelling (Salvatore et al, 2015) (Lapii et al, 2017).

The radiofrequency devices use "focused electromagnetic waves" (Phillip et al, 2020) to generate heat upon tissue impedance repeatedly along with intermittent cooling in a controlled environment to avoid blisters and burns (Photiou et al, 2020). The connective tissue remodelling by neocollagenesis and fibroblast activation remedies vaginal laxity and improves sexual function (Ahluwalia et al, 2019). In July 2018 United States Food and Drug Administration (FDA) clearly warned against the egregious use of energy devices for "Vaginal Rejuvenation" (Commissioner,2020). They explicitly stated that energy devices are approved only for treatment of pre-cancerous or cancerous cervical or vaginal conditions (Commissioner,2020). This statement came in-light of reviewing various literature for the adverse reactions of these devices like vaginal scarring, burns, chronic bladder pain and dyspareunia (Commissioner,2020). The organisation also urged practitioners to report any future adverse effects on its MAUDE (Manufacturer and User Facility Device Experience) database (Commissioner,2020).

An intriguing article on STAT NEWS by a board-certified breast cancer surgeon and gynaecologist states that these procedures are nothing but sham and there are about forty-one adverse effects reported in MAUDE (Manufacturer and User Facility Device Experience) database till 2022 (Skerrett, 2022). And since about 70% of cancer survivors experience sexual health problems, many ended up using energy devices resulting in chronic bladder pain or vaginal scarring post treatment (Skerrett, 2022). The scientific impact paper by RCOG (Royal College of obstetricians and gynaecologists) has seconded FDA on the adverse effects of energy-based device. However, RCOG encourage a "potential" of restricted use in women with failed oestrogen treatments, or have contraindications like breast cancer treatment, or have declined other treatments (Philip et al, 2022). RCOG still recommend vaginal oestrogens as the gold standard for treating GSM (Philip et al, 2022).

The review by (Photiou et al, 2020) clearly pointed that the duration and number of treatments varied drastically among devices. The fractional micro-ablative CO2 lasers with same wavelength and treatment duration was being used in two sessions over one month (Cruz et al, 2018) to five sessions over five months (Athanasiou et al, 2017). Some radio-frequency devices are used just once (Carothers,2018) while others with same parameters tend to be used for about four to six times over three months (Vicariotto et al, 2017). Hence, a huge disparity exists among the duration and number of treatments required to show positive outcomes even if the devices used share the same mechanical parameters and treatment time. There are no standard guidelines on the duration, number and time intervals between treatment sessions, even if the same device with same parameters is used and it becomes more challenging with several types of devices available in the market (Philip et al, 2022). NICE (2021) guidelines on lasers for stress urinary incontinence and urogenital atrophy clearly show the gap in evidence on the long-term safety and efficacy of these energy devices.

3. Mechanism of Action of Various Co2 Lasers in the Market

MonaLisa Touch, SmartXide2, V2LR is manufactured by DEKA, Florence,Italy: Uses fractional laser beam by creating DOTs(Dermal Optical Thermolysis) which are microscopic channels or small spots in mucosa created laser and are separated from the healthy mucosa thereby helping the pulse distribution over entire vagina in a spaced manner called DOT spacing. The stack mode prevents excessive pulses at the same point by limiting the number of pulses between one to five thereby reducing side-effects and facilitating deeper focused tissue penetration effect. DEKA (D-pulse) mode has two components: a high peak power to help ablate the atrophic mucosa followed by a lower peak mode with longer emission time facilitating further penetration of the laser into the mucosa (MonaLisa Touch-DEKA,2023).

FemTouch AcuPulsd and DUO system are manufactured by lumenis, Israel. It works with a laser beam of 10600nm and three-time exposure and power modes namely Pulser, Super-pulse and Continuous Wave (CW). Super-pulse contains high peak power short duration pulses for low thermal effect on the tissue, Pulser contain variable pulse length and constant frequency pulses for moderate thermal effects and CW contain continuous energy beam and provide higher thermal effects on the tissue. The DUO system is a combination of free beam and CO2- laser fibre energy with all the same features of AcuPulse system. 40 watts is the maximum peak power (Lumenis, 2023). Aphrodite is manufactured by BH

Laser,France and uses Ultra Pulse and continuous wave to deliver laser beam to target tissue. Its maximum peak power is 75 watts (Aphrodite | BHlaser,2021). SmaXel multi-functional fractional CO2- laser is manufactured by IDS LASER, South Korea and uses a double part pulse (Smart Pulse). The first step is an ablative high-power pulse with short duration targeting laser energy at optimal depth into tissue followed by a longer duration lower power pulse sending thermal energy for deeper tissue penetration (IDS, 2023).

4. Methodology

The search criteria involved using "CO2 laser AND Genitourinary Syndrome of Menopause", "CO2 laser AND Vulvovaginal atrophy" in PUBMED and Clinical trials.gov. The search was carried out between May 2023 to September 2023.

Inclusion criteria were randomised control trials written in english and published between 2014 to 2023 since fractional micro-ablative carbon dioxide (Mona Lisa Touch) laser was (MonaLisa Touch) was first cleared by FDA (Food and Drug Administration) in 2014 (Skerrett, 2020). Participants were post-menopausal women above 50 years of age with symptoms of vulvovaginal atrophy or genitourinary syndrome of menopause using CO_2 in the treatment group. Exclusion criteria included all studied other than randomised control trials like cohort, case-control studies, case reports, conference abstracts and grey literature. Patients with a history of breast or/and gynaecological cancers were excluded. Patients who developed pelvic organ prolapse, vulvovaginitis, vulvodynia, dyspareunia or other problems due to chronic illness like Sjögren's syndrome, pelvic brachytherapy or any cause other than GSM were excluded. Patients with active or previous history of lichen sclerosis and had used CO2 laser were also excluded. Selection process involved including papers that met the above-mentioned criteria's and with full-text publication easily accessible using student ID were only included.

5. Data Collection

The following data were collected from each trial:

•The author and year of publication

•The duration of the study

•The number of participants

•The baseline characteristics like age, age of menopause, mode of menopause, ethnicity etc where it was possible for both intervention and control groups.

•The design of study, duration between repeat procedures length of follow-up.

•The exact type and settings of laser used treatment procedures and outcomes and adverse events and p-values in the intervention group.

•The exact settings, treatment procedures and outcomes and adverse events if any in the control group.

The outcomes were mainly measured using the following standardised scales/scores:

•Visual Analogue Scale (VAS is a numerical scale used to evaluate intensity of vaginal atrophy symptoms. It ranges from 0 to 10 with a 4-7 score and 8-10 score indicating moderate and severe symptoms respectively. Sometimes a 0-3 score with one, two and three for mild, moderate and severe symptoms respectively are also used.

•Vaginal Health Index Score (VHIS) estimates five elements of vaginal epithelium namely elasticity, pH , fluid volume , vaginal moisture and integrity. A range of 1 to 5 with 1 being the poorest and 5 being the best score is used. The total VHI score is represented by the sum of five components and a score below or equal to fifteen is definitive of vaginal atrophy.

•Vaginal Maturation Value (VMV) use the percentage of superficial, intermediate and parabasal epithelial cells on the smear to cytologically evaluate the level of vaginal atrophy which is defined at a threshold of 40.

•Incontinence Modular Questionnaire-Vaginal symptoms Questionnaire (ICIQ-VS) is a assessment tool to evaluate the severity of vaginal dryness and atrophy. It comprises of three blocks namely vaginal symptoms, sexual matter and QoL (Quality of Life) and a total of fourteen items.

•Female Sexual Function Index (FSFI) evaluate sexual function by investigating six domains namely desire, arousal, orgasm, lubrication, pain and satisfaction using a 19-item questionnaire. Presence or absence of sexual dysfunction is defined by a threshold of 26.55 (Rosen et al, 2000).

6. Results

Flowchart Depicting the Identification of Studies (Figure 1)

A total of nine randomised control trials were included in the review.

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**All the records were excluded by the author.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

The search produced three forty citations and after removing the duplicates and documents where full text was not available about two ninety citations were screened. Two hundred records were removed as they contained only the search words but were not related to the proposed protocol. All the articles were screened by the author. Then ninety records were screened for eligibility and sixty-five articles were excluded as they were not randomised control

trials. Eight studies did not have the results published in journals. Three studies involved participants with gynaecological cancers or breast cancer. Two studies had participants with lichen sclerosis and three studies involved intervention group using a non-carbon dioxide-based laser. After the screening process a total of nine randomised control trials were deemed fit for the review (Table 1 and 2).

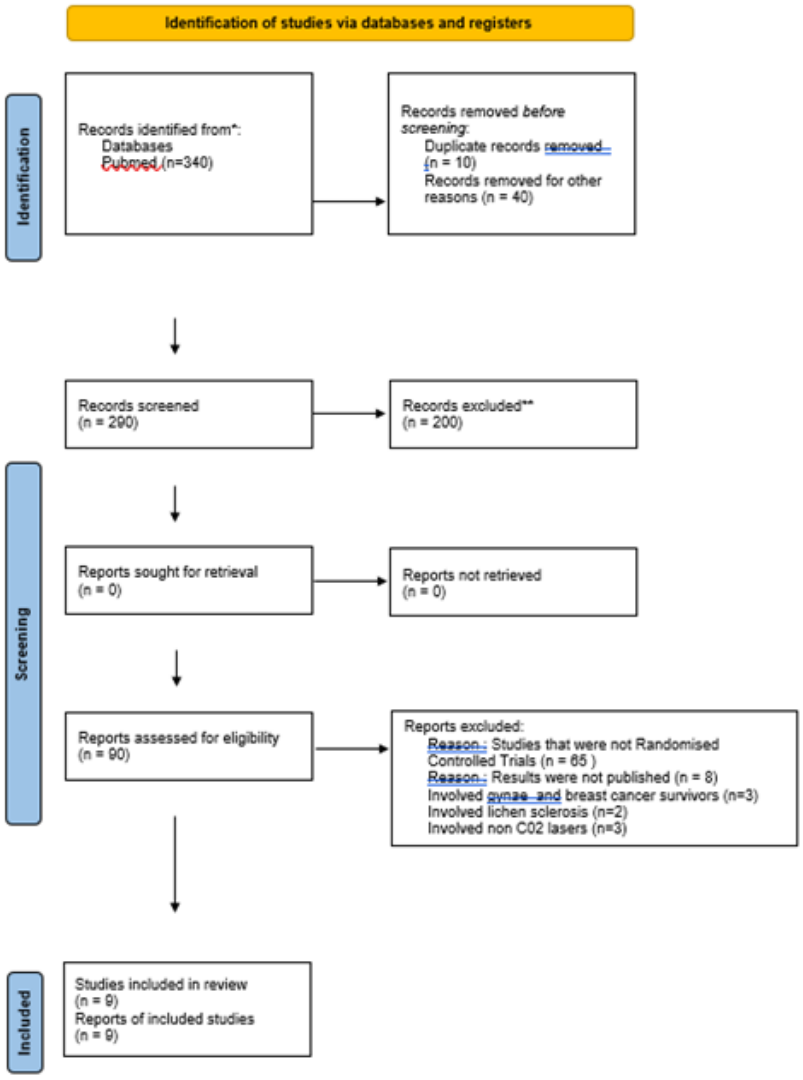

Figure 1: Flowchart Depicting the Identification of Studies

Table 1: The baseline characteristics of the included studies are: 138

Study	Parameter	Baseline	Control	Treatment	P Value
Cruff and Khandwala, 2021	Age (years)	59 (56–65)	61 (54–66)		0.94
	BMI (kg/m²)	29.8 (27.2–36.2)	27.3 (25.8–30.0)		0.14
	Parity	2 (2–3)	2 (2–3)		0.984
	Years postmenopause	10 (4–15)	14 (5–24)		0.197
	Dyspareunia present	16 (100)	14 (100)		1
	Dyspareunia severity	Moderate: 6 (40)	Moderate: 6 (46)	Severe: 9 (60)	Severe: 7 (54)
	Prior estrogen use	5 (36)	5 (36)		1
	VHI score	11.5 (8.0–13.0)	10.5 (9.0–13.5)		0.865
	VAS (mm)	80	81		0.92
	UDI-6	33.3 (11.5–52.1)	54.2 (41.7–62.5)		0.046

	VAS treatment 1 (mm)	26.0 (10.0−41.0)	45.0 (10.0−62.0)		0.49
	VAS treatment 2 (mm)	17.5 (4.3−48.3)	33.0 (16.3−64.5)		0.271
	VAS treatment 3 (mm)	18.0 (6.0−35.8)	23.0 (9.5−44.8)		0.826
Li et al., 2021	Age (years)	58	55		
	Race and ethnicity: White	40	42		
	Other	2	1		
	Tertiary education	32	35		
	Age at menarche (years)	13	13		
	Age at menopause (years)	49	48		
	Time after menopause (years)	6 (3−9)	8 (4−14)		
	Iatrogenic menopause (years)	21	20		
	Parity				
	0	6	4		
	-1	7	10		
	-2	16	17		
	- ≥3	8	9		
	Sexually active	21	23		
	Regular alcohol consumption	26	33		
	Current nonsmoker	42	41		
	Regular exercise	34	33		
	Other medical comorbidities	19	17		
	Previous hysterectomy	4	2		
Paraiso et al., 2019	Age (years)	60 ± 7	61.8		
	Race: White	32	32		
	Race: Black	1	1		
	Race: Hispanic	1	0		
	Race: Asian	2	0		
	BMI	25.8 ± 4.4	25.1 ± 4.7		
	Parity	1 (0−4)	2 (0−6)		
	Exogenous hormone use	26	29		
	Vaginal estrogen use	27	26		
Politano et al., 2019	Age (years)	52−62	52−62	51−62	0.784
	Post-menopause years	5−13	2−16	2−14	0.446
	Menopause age (years)	44−52	41−53	43−53	
	Race: White	23	16	17	0.032
	Race: Non-white	1	8	7	
	Smoking: Smoker/ex-smoker	5	8	9	0.792
	Smoking: Non-smoker	19	16	15	
	Parity				
	0	1	3	2	
	-1	4	4	3	
	- >2	19	17	19	
Ruanphoo and Bunyavejchevin, 2020	Age (mean, years)	61.73	59.84		
	Age at menopause (mean, years)	48.95	49.47		
	Number of children (mean)	2.11	2.2		
	Normal labor (% within group)	33 (75%)	26 (59.1%)		
	Cesarean section (% within group)	10 (22.75%)	18 (40.91%)		
	History of vaginal surgery (% within group)	5 (11.36%)	1 (2.27%)		

	History of hormone use (% within group)	10 (22.73%)	8 (18.18%)		
	Active sexual life (% within group)	10 (22.73%)	24 (54.55%)		
Page et al., 2022	Age (mean, years)	57.40 ± 7.07	56.20 ± 6.30		
	Years since menopause (mean)	7.30 ± 5.22	6.40 ± 5.64		
	Spontaneous menopause (n)	21	21		
	Iatrogenic menopause (n)	9	9		
	Smoking (n)	2	4		

Table 2: The comparative table shows details of duration of study, the exact procedure used in intervention (laser) and control (sham or estriol) groups along with their outcomes are given below.

Study	Intervention	Control	Outcomes	Intervention	Control	Inference
Cuff and Khandwala, 2021	Fractional microablative CO2 laser therapy	Laser in standby mode, non-activated, same procedure performed using vaginal probe, foot pedal pressed systematically	Primary Outcome:	7	8	P=1.00 (non-significant)
From September 2017 to November 2018	Settings: dot power 30 W, dwell time 1000 ms, dot spacing 1000 mm, SmartStack 1-3, 3 treatments every 6 weeks		Dyspareunia improved after 6 months	3	5	P=0.298 (non-significant)
Participants: n=30 (Intervention: n=14, Sham: n=16)			Secondary Outcomes (after 6 months):	-19	-31	P=0.246 (non-significant)
			Median difference VHI	-18.8	-8.3	P=0.342 (non-significant)
			Median difference VAS			
			Median difference UDI-6			
Li et al., 2021	Fractional microablative CO2 laser at standard settings	Laser at minimal energy settings, no tissue effect	Primary Outcomes (mean difference):	-17.2	-26.6	P=0.66 (non-significant)
From September 2016 to June 2019	Power: 40 W, dwell time 1000 µs, DOT spacing 1000 µm, SmartStack 2 on DP emission mode, fluence: 5.37 J/cm², 3 treatments 4 weeks apart	Power: 0.5 W, dwell time: 100 µs, DOT spacing: 2000 µm, SmartStack 1 on SmartPulse emission mode, fluence: 0 J/cm²	VAS for overall symptoms: -17.2	-28.8	-4	P=0.75 (non-significant)
Participants: n=85 (Intervention: n=43, Control: n=42)			VAS for dyspareunia: -28.8	-3.1	-1.6	P=0.91 (non-significant)
			VSQ: -3.1	6.3	1.4	P=0.58 (non-significant)
			Secondary Outcomes:	0.9	1.3	P=0.38 (non-significant)
			AQoL-6D (Quality of Life): 6.3			
			VHI: 0.9			
Salvatore et al., 2020	Fractional microablative CO2 laser	Laser with Power: 0.5 W; dwell time: 1000 µs; spacing: 1000 µm; depth: SmartStack 1; SmartPulse mode; pulse energy: 0 mJ for all sessions.	Primary Outcomes (4 months):	Dryness: 2.4 (2.9)	Dryness: 5.6 (2.9)	P<0.001 (Significant for Dryness and Dyspareunia)

Participants: n=58 (Intervention: n=28, Control: n=30)	Power: 30 W; dwell time: 1000 µs; spacing: 1000 µm; depth: SmartStack 1–3 depending on session; D-pulse mode; pulse energy: 43.2 mJ, 86.4 mJ, and 129.6 mJ for the 1st, 2nd, and 3rd sessions, respectively.	Three sessions 4 weeks apart	Dryness	Dyspareunia: 8.6 (1.5)	Dyspareunia: 8.7 (1.4)	P=0.181 (Non-significant for Dysuria)
	Three sessions 4 weeks apart		Dyspareunia	Dysuria: 0.6 (1.5)	Dysuria: 0.6 (1.2)	P=0.363 (Non-significant for UDI-6)
			Secondary Outcomes (4 months):	UDI-6: 15.9 (17.4)	UDI-6: 14.7 (21.3)	P=0.001 (Significant for FSFI)
			Dysuria	FSFI: 23.8 (6.6)	FSFI: 12.1 (8.3)	
			UDI-6			
			FSFI			
Paraiso et al., 2019, From June 2016 to September 2017, Participants: n=69 (Intervention: n=34, Control: n=35)	Fractional microablative CO2 laser, Dot power: 30 W; dwell time: 1000 µs; dot spacing: 1000 µm, SmartStack: 1 (baseline), 3 (at 6 weeks, 3 months)	Conjugated estrogen cream (Premarin), 0.5 g intravaginally daily for 14 days, then 0.5 g twice weekly for 24 weeks	Mean Differences: VAS scores for Dryness, Itching, Irritation, Dysuria,VHI, DIVA, VMI, FSFI, UDI, % Sexually Active	Dryness: -5.48	Dryness: -5.76	P=0.67 (Non-significant for Dryness)
				Itching: -1.84	Itching: -1.24	P=0.45 (Non-significant for Itching)
				Irritation: -3.29	Irritation: 3.49	P=0.87 (Non-significant for Irritation)
				Dysuria: -1.4	Dysuria: -2.11	P=0.36 (Non-significant for Dysuria)
				VHI: 0.9	VHI: 1.2	P=0.07 (Non-significant for VHI)
				DIVA: -3.3	DIVA: -4.4	P=0.18 (Non-significant for DIVA)
				VMI: 3.9	VMI: 25	P=0.04 (Significant for VMI)
				FSFI: 1.7	FSFI: 4.9	P=0.1 (Non-significant for FSFI)
				UDI: -9.4	UDI: -6.2	P=0.37 (Non-significant for UDI)
				Sexually active: 45.5% (15)	Sexually active: 48.3% (14)	P=0.82 (Non-significant for % Sexually Active)
Politano et al., 2019, From March 2017 to November 2018, Participants: n=72 (Intervention: Laser, n=24; Promestriene, n=24; Lubricant, n=24)	Fractional microablative CO2 laser, Power: 40 W; dwelling time: 1000 µs; dot spacing: 1000 µm; SmartStack: 2.0, Introduced using cylindrical vaginal probe thrice at 4-week intervals.	1st Group: Vaginal cream with promestriene (1 g cream with 10 mg promestriene, applied 3×/week for 12 weeks) 2nd Group: Water-based lubricant gel applied during sexual activity.	VHI Elasticity, fluid volume, pH, moisture, epithelial integrity	18.68 (3.20)	Promestriene: 15.11 (3.98) Lubricant: 10.44 (2.78)	P<0.001: Significant, Laser showed short-term benefits over promestriene and lubricant.

Dutra et al., 2021, From February 2017 to February 2018, Participants: n=25 (Intervention: n=13, Control: n=12)	Fractional microablative CO2 laser Power: 30 W; dwell time: 1000 µs; dot spacing: 1000 µm; SmartStack: 2.0 Introduced by manual 360° rotation of the vaginal probe. Three sessions performed, cytology repeated 30 days after last treatment.	Vaginal estriol cream Daily application for 30 days, then twice weekly for 2 months. Cytology repeated 30 days after last treatment.	Epithelial Thickness (mm) Initial, Final, Increase	Initial: 0.14 (0.06) Final: 0.28 (0.15) Increase: 0.14 (0.13)	Initial: 0.19 (0.09) Final: 0.33 (0.07) Increase: 0.14 (0.11)	Inference: Epithelial thickness increased in 10 participants (both groups). No change in 3 treatment participants, 1 control participant. Thickness decreased in 1 control participant.
Ruanphoo and Bunyavejchevin, 2020	Microablative fractional CO2 laser	Sham procedure: Vaginal probe introduced, same steps but without laser activation.	VHI	12 weeks VHI: 17.45 (2.61)	12 weeks VHI: 16.08 (3.27)	Significant (Laser: p<0.001, Control: p=0.48)
June 2016–May 2017	Power: 40 W; dwell time: 1000 ms; dot spacing: 1000 µm; SmartStack: 1–3.	3 sessions, 4 weeks apart.	Baseline: 14.18 (3.39)			Significant improvement in vaginal dryness (Laser: p=0.02, Control: p=0.07)
Participants: n=88 (Intervention: n=44, Control: n=44)	Procedure repeated every 4 weeks for 3 sessions.		12 weeks post-treatment: 17.45 (2.61)			
			VAS			
			Baseline: 2.27 (0.42)			
			12 weeks post-treatment: 1.83 (0.51)			
			Vaginal Dryness (Median): Baseline: 5.00			
			12 weeks: 3.24			
Page et al., 2022	Fractional microablative CO2 laser	Laser at minimal energy (0.5 W) with the same settings as treatment group.	MBS Severity Score	Dyspareunia: -0.61 (0.84)	Dyspareunia: -0.36 (0.73)	Significant improvement for laser treatment.
August 2019–February 2020	360° exposure		Dyspareunia: -0.61 (0.84)			Notable difference in FSFI and MBS scores between intervention and control groups.
Participants: n=60 (Intervention: n=30, Control: n=30)	Power: 30 W; dwell time: 1000 ms; dot spacing: 1000 µm; SmartStack: 2.0.		Vaginal dryness: -1.50 (2.12)			
			Vaginal itching: -0.50 (0.71)			
			VAS: -0.69			
			FSFI: 3.51 (6.22)			
Cruz et al., 2018	Fractional SmartXide2 microablative CO2 laser	C1: Estriol (1 mg estriol substitute applied 3×/week for 20 weeks)	VAS (p-values):	VAS Dyspareunia: p=0.01	C1: 0.058	Significant improvements in laser group for dryness and FSFI scores.
Participants: n=45 (Intervention: Laser: n=15; C1: Estriol: n=15; C2: Sham+Estriol: n=15)	Power: 30 W; dot spacing: 1000 µm; dwell time: 1000 ms; SmartStack: 2.0.	C2: Sham laser+estriol (0 W power, same procedure).	Dyspareunia: 0.01		C2: 0.009	Laser also reduced parabasal cells and improved maturation index compared to control groups.
			Dryness: <0.0001			
			Burning: 0.02			
			Total FSFI Score (p-values): 0.26			
			Parabasal Cells (%/HPF): 0.01			
			Meisels Index: 0.02			

7. Discussion

A total of nine randomised control trials were analysed for the review. This summed up to five hundred and thirty-two (n=532) participants being randomised, with two hundred and forty-five women (n=245) in treatment group and two hundred and eighty seven (n=287) in control group/groups. All the nine RCTs involved in the study used fractional micro-ablative laser and had the probe inserted and rotated in the vagina at 360-degree angle under a dot power setting of 30 or 40W, dot spacing of 1000 micrometer and dwell time of 1000 milliseconds which is same as the therapeutic range available in NICE guidelines (IP 1817,2022). Pitsouni et Al,(2017) in their retrospective case-control study compared if there were any statistically significance between the use of 30 vs 40 W power settings and the study yielded no significant results. Hence, both the dot powers (30W and 40 W) are safe to use. And the lasers were repeated at four-to-six-week intervals up till three sessions which is the standard protocol.

Cruff and Khandwala,(2021) used parallel double-blinding and validate tools alongside priority sample size calculation. These resulted in increased internal validity and reduced selection bias. The study used inactive sham treatment for the control group and this design takes placebo account into effect and controls confounding factors. Even though the study provided inconclusive results it did open eyes to the requirement of higher quality research in various related fields like the therapeutic benefit of these lasers in urinary incontinence and sexual dysfunction.

Li et al, (2021) used a broad inclusion criterion to enhance the external validity of the double blinded full sham-based trial. This reduced the selection bias and helped them quantity the placebo effect. They used validated objective assessment tools to increase internal validity and a laboratory-based evaluation of vaginal cytology. This is one of the few studies in the review that analysed histological improvement of the atrophy. Li et al,(2021) looked in adverse effects of the lasers and reported complications like vaginal wall postcoital lacerations, increased scarring, rigidity of vaginal tissues and deteriorating dyspareunia. However, these were not statistically significant.

Salvatore et al, (2020) evaluated the use of lasers against the RCOG standard of vaginal estrogens. The study used double-blinding and allocation concealment thereby decreasing selection bias. The multi-centered approach enhanced the transferability and reproducibility of the study. The accurate sample size calculation were few strengths of the study thereby improving its internal validity and credibility. Paraiso et al,(2019) conducted a multi-centeric study which increased the reproducibility. The study explored the effectiveness of lasers against the RCOG gold-standard treatment of vaginal estrogen at six months interval. This study is one of the few that explored the effectiveness and safety of the lasers in a multi-ethnic diaspora. The study was extensively transparent in reporting all the adverse effects encountered like vaginal bleeding, pain, discharge, breast tenderness, urinary tract infection. However, none of the adverse reactions were statistically significant. The results were not statistically significant.

Politano et al,(2019) used a robust inclusion and exclusion criteria with adequatedetails of the baseline demographics thereby increasing validity and reproducibility of the study. Primary and secondary outcomes were well tabulated using p-values.If Intention to treat or per protocol analysis were done to statistically analyse the participants is not clearly evident. The use of ANOVA was accurate since there were more than two independent variables. Small sample size and shorter duration of follow up along with lack of sham lasers as control can be considered as limitations of the study. The use of objective assessment tools along with a appropriate analytics and blinding were the strengths of the study. The study concluded that the use of fractional carbon dioxide lasers to treat genitourinary syndrome had statistically significant results in the laser group in comparison to lubricant or promestriene groups at fourteen weeks. There were no adverse effects reported during the study thereby reiterating that the lasers are safe to use.

Dutra et al,(2021) provided clear information on inclusion and exclusion criteria thereby enhancing the reproducibility of the study. Tabulated baseline information regarding the treatment and control groups were lacking so the scope of epidemiological comparison between the groups and reproducibility were reduced.Provision of demographic details like ethnicity of the study participants would have helped to estimate if the study is safe and generalisable in a wider and versatile ethnic diaspora.The exact sequence of events involved in both treatment and control procedures were mentioned making it reproducible.The computer website used for randomisation is clearly mentioned, however there is no information on what type of randomisation was done and if allocation concealment was used or not and if yes what type of concealment was used. Unblinding and partial information about randomisation makes it difficult to completely exclude selection bias.The CONSORT flow diagram was well documented with all the information regarding follow-up and allocation numbers, it would have been more insightful to know whether intentional to treat or per protocol analysis was performed. The use of objective histomorphic assessment tools to measure outcomes improved its internal validity and is one of the strengths of the study. Secondary outcome of female sexual function was evaluated using a validated questionnaire with the point system hence increasing its internal validity and generalisability. The results were well tabulated along with a scatter plot comparison diagram. There was statistically significant increase in epithelial thickness at the end of treatment/ after four months in both the control (n=0.001) and laser (n<0.001) groups. There is no statistically significant precedence of outcomes in the laser over the estriol group. There were no significant adverse effects reported which reiterates that lasers are safe to use.Hence, lasers can't be deemed more efficacious than the gold standard treatment

of estradiol.

Ruanphoo and Bunyavejchevin, (2020) used simple randomisation and had adequate information on how it was generated were provided alongside the accurate details of the allocation concealment (envelopes) used is well documented, thereby securing randomisation and eliminating bias. Also, a clear inclusion and exclusion criteria with exact steps involved throughout the procedure were given to increase its reproducibility. Baseline demographic characteristics like age, years since menopause and others were provided thereby making the study easily reproducible. It is one of the few studies being done in asia however the ethnicity of the studied participants was not included in the demographic data. The sample size was accurately derived by using a previous pilot study as reference. The study also used double blinding thereby eliminating selection bias. All the analytics were done using a computer statistical software and intention to treat was followed. Details of the follow-up were tabulated using a CONSORT flowchart. This study did use a questionnaire with a point-scale. The use of validated and objective assessment tools like vagina health index score, dryness score increased its internal validity and generalisability. It also looked into the participant satisfaction along with acknowledging the complications encountered by both the treatment and control group making the study increasingly transparent. The study reported complications and adverse effects like vaginal bleeding, vaginal discharge, vaginitis, pain after the procedure and de-novo dyspareunia in both the laser and sham groups. The complications were statistically non-significant. Hence lasers can be considered as a safe option in treatment of vulvovaginal atrophy. All the statistical analyses were accurate, and the p-vales were statistically significant in the treatment group at 12 weeks in comparison to the control group. Hence it concluded that lasers could be considered as an effective treatment option for vaginal atrophy or Genitourinary syndrome of menopause.

Page et al,(2022) had informed consent taken from the participants along with the study being registered after ethical committee approval hence increasing its validity and transparency. The inclusion and the exclusion criteria along with all the steps involved in the laser procedure as well as the sham were documented making the study reproducible. It was a single centre study and no data about the ethnicity of the participants were given hence the generalisability of the study is questionable.The baseline demographic characteristics were limited to age and the cause of menopause along with two risk factors but exploring other demographic characteristics like parity, ethnicity etc would have made the study more reproducible and generalisable. The study used a block randomisation by a third party thereby blinding the participant and the assessor and reducing selection bias.The randomisation was generated using a computer software thereby reducing the possibility of error and imbalances amongst the sample size in regard to confounders. There is no evidence regarding the use of allocation concealment. Whether power or prior analysis to derive the sample size was carried out or not isn't clear. The use of P values to determine whether the results were significant or not would have been ideal rather than using confidence intervals and it would have helped to carry out a post ad-hoc analysis to explore the cause of non-significant results. The study says that complications and adverse effects were documented however it was not made available in the journal article published. The objective measurement of outcomes using a point scoring systems similar to linkert scale along with the difficulties faced by the surgeon being documented on a 5-point linkert scale improved the validity and credibility of the study and is indeed one of its strengths.The CONSORT flow diagram used to trace the allotted participants and data regarding their follow up made the study transparent and reproducible. To summarise, use of double- blind, broader inclusion criteria which which increase the external validity and use of validated assessment tools were indeed strengths of the study amongst others. Lack of transparent documentation about power analysis and small sample size were the limitations. There were no statically significant improvement /difference between laser and sham groups at 12 week follow up. There were no reported adverse effects in both intervention and control groups thereby reiterating that use of lasers are safe.

Cruz et al, (2018) had their study registered after taking ethical committee approval and informed consent from the participants thereby increasing its validity and transparency. The exact inclusion and exclusion criteria were documented along with the exact steps involved in both the laser and sham group, thereby making the study more transparent and reproducible. The participant and the doctor were blinded by a third party (nurse), thereby reducing selection bias. Block randomisation using a computer software was used to prevent severe imbalances amongst the sample size and groups with respect to unknown and known confounders.However, if any allocation concealment was used or not isn't evident.There is no clear evidence on how the sample size was derived, whether a power or priory analysis were carried out or not. A CONSORT flow chart showing all the details of the allocated participants and their follow up was available making this study more transparent and reproducible. P values of the difference-at twenty weeks from the baseline for the estriol and sham plus estradiol groups were provided with most of the values being significant in all the groups. The study did not explicitly document the complications or adverse effects that happened amongst all the three groups.The use of objective assessment tools like vaginal health index scores and validated questionnaires like FSFI scales increased the external validity of the study and made it more robust. Also, statistical analysis using ANOVA since there were more than two categorical variables for comparison along with were appropriate. There were no reported adverse effects in both intervention and control groups thereby reiterating that use of lasers are safe .Another strength of this study is the use of sham laser along with estradiol in one of

the control arms making the treatment group more reliable and decreasing the result bias.Small sample size study conducted in a single centre and lack of data on the ethnicity of the studied group reduces its generalisability and questions the safety aspect in a more diverse ethnic population. Cruz et Al, (2018) concluded that there were no significant differences between the carbon dioxide laser and estriol groups at 20 week follow up. However, one year or longer follow up is required evaluate long term effects of the treatments.

Five RCTs namely (Cruff and Khandwala,2021), (Li et al,2021),(Salvatore et al.,2020), (Ruanphoo and Bunyavejchevin, 2020) and (Page et Al,2022) included in this review compared the treatment (laser group) with sham procedures (an intervention carried out by omitting the therapeutically essential step by mimicking all the others in the exact same way). This did allow for a more precise and accurate evaluation of the treatment effect and increase the scientific validity of this review. Three RCTs of laser vs sham procedure namely (Cruff and Khandwala,2021), (Li et al, 2021) and (Page et al, 2021) showed that laser treatment had no statistically significant results (p-value<0.05) in comparison to sham procedure group at the end of six months, twelve months and twelve weeks follow up respectively. Two RCTs namely (Salvatore et al,2020) and (Ruanphoo and Bunvavejchevin, 2020) showed that the lasers group did have statistically significant results in comparison to sham group at four months and twelve weeks follow up respectively. Paraiso et Al, (2019) and (Dutra et Al,2021) compared lasers with the gold standard treatment option of topical estrogen and both the options were not statistically significant.

Politano et Al,(2019) did show that lasers had statistically significant benefits over promestriene (a topical estrogen) and a water based lubricant at the end of fourteen weeks. Cruz et Al, (2018) did compare laser treatment with estriol as one control group and a sham plus estriol as another control group and found that all the three groups yielded statistically significant results at twenty-week follow-up. However, there were no significant difference/advantage of one group over other.

Ruanphoo and Bunyavejchevin, (2020) documented adverse effects like vaginal bleeding, discharge, vaginitis, pain post procedure and de-novo dyspareunia and none of them were statistically significant. It was also the only study to document participants satisfaction and dissatisfaction and derive a comparison between them. Paraiso et Al, (2019) reported adverse effects like vaginal bleeding, pain discharge, urinary tract infection, breast tenderness, migraine and abdominal cramping and these were similar in laser and control groups and all of them were not statistically significant. Two out of nine Randomised control trials were multi-centric namely (Salvatore et Al, 2020) and (Paraiso et Al, 2019). They both had better generalisability. Six out of the nine randomised control trials did provide a baseline demographic characteristic of the participants. Only three trials namely (Li et Al, 2021), (Paraiso et Al, 2019) and (Politano et Al,2019) compared ethnicity of the participants and major proportion of the participants were caucasians. More studies exploring multi-ethnic groups like afro-caribbeans, hispanics, middle eastern, south and east asians is required to comment on the safety in a diverse diaspora and generalise it.

All the remaining six randomised clinical trials reported no serious effects. Hence lasers can be considered safe to use if used within the advised therapeutic range.

8. Strengths and Limitations

The strengths of this review are many. All the papers included were randomised control studies which are the highest form of evidence in the hierarchy of evidence. The primary objective of all the papers included were to compare the same parameter, which is improvement in vaginal atrophy thereby enhancing the credibility of the review. Six out of the nine trials that is sixty six percent provide information about the baseline demographic characters and reiterated that both the treatment, and the control groups had similar characters at the start of the study. All the trials compared the use of a single (fractional micro-ablative carbon dioxide laser) in postmenopausal women with genitourinary syndrome of menopause thereby making the analysis straightforward. All the nine trials use validated and objective assessment tools like visual analogue scale, vaginal health index, female sexual function index to compare their outcomes. Validated and objective assessment tools enhance the internal validity of these studies included thereby enhancing the future potential of carrying out a systematic review and meta-analysis. All the studies had their randomisation done using a computer software and majority of them were double or at least single blinded thereby tremendously reducing the chance of selection bias.

The limitations of the study are only three papers included in the study were able to show statistically significant results. Many trials included had no power calculation done. Hence it is exceeding difficult to appraise whether the sample size of those individual studies was adequate. Caucasians or white was the predominantly represented race in the studies that revealed ethnic distribution of their participants (Li et al.,2021),(Paraiso et al.,2019),(Politano et al.,2019). Hence, the safety and effectiveness of these laser techniques in non-white ethnic population remain under-explored.

9. Conclusion

Amongst nine randomised control trials that were selected and analysed for this review only three (two studies that were compared with sham procedures, and one compared with promestriene) showed statistically significant result that lasers were more efficacious form of treatment. Even when multiple studies showed improvement in comparison to the baseline at the end of treatment, most of them were not significant statistically. Hence there is no scientific evidence to prove that lasers are better than other modalities of treatments for vulvovaginal atrophy in post-menopausal

women. However, some of the studies analysed in the review did conclude that lasers showed statistically significant improvement in the vaginal atrophy in comparison to baseline, this is in line with the RCOG recommendation of the "potential" of restricted use of these lasers in women with failed oestrogen treatments (Philip et Al, 2022).

Vaginal oestrogen should be continued as the gold standard for treating genitourinary syndrome of menopause. This review did not explore the safety of lasers in patients who have contraindications for the use of vaginal oestrogen like breast cancer or declined treatment groups. Hence, propaganda promoting the use of lasers for genito-urinary syndrome of menopause over gold standard treatment of estrogen is baseless and is not backed by scientific evidence and should not be encouraged. More stringent regulations have to be placed in aesthetic practices and practitioners promoting the same.

References

1. Ahluwalia J, Avram MM, Ortiz AE. Lasers and energy-based devices marketed for vaginal rejuvenation: A cross-sectional analysis of the MAUDE database. Lasers in Surgery and Medicine. 2019; 51(8):671–677.
2. Aphrodite | BHlaser. Available at: http://bhlaser.fr/?portfolio=aphrodite. Accessed January 25, 2022.
3. Athanasiou S, Pitsouni E, Falagas ME, Salvatore S, Grigoriadis T. CO2 laser for the genitourinary syndrome of menopause. How many laser sessions? Maturitas. 2017; 104:24–28.
4. Alvisi S, Lami A, Baldassarre M, et al. Short-Term Efficacy and Safety of Non-Ablative Laser Treatment Alone or with Estriol or Moisturizers in Postmenopausal Women with Vulvovaginal Atrophy. The Journal of Sexual Medicine. 2022; 19(5):761–770.
5. Commissioner, O. of the. Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to safeguard women's health from deceptive health claims and significant risks related to devices marketed for use in medical procedures for 'vaginal rejuvenation'.
6. Cheng C, Cao Y, Ma S-X, et al. The strategy for vaginal rejuvenation: CO2 laser or vaginoplasty? Annals of Translational Medicine. 2021; 9(7):604.
7. Cruff J, Khandwala S. A Double-Blind Randomized Sham-Controlled Trial to Evaluate the Efficacy of Fractional Carbon Dioxide Laser Therapy on Genitourinary Syndrome of Menopause. The Journal of Sexual Medicine. 2021; 18(4):761–769.
8. Cruz V, Wajsfeld T, Steiner M, et al. Vaginal CO2 Laser Versus Topical Estriol Treatment for Vaginal Atrophy in Postmenopausal Women: 1-Year Follow-up. Obstetrics & Gynecology. 2019; 133(1):175–176.
9. Dutra PFSP, Heinke T, Pinho SC, et al. Comparison of topical fractional CO2 laser and vaginal estrogen for the treatment of genitourinary syndrome in postmenopausal women. Menopause. Published Ahead of Print, 2021.
10. Gold M, Andriessen A, Bader A, et al. Review and clinical experience exploring evidence, clinical efficacy, and safety regarding nonsurgical treatment of feminine rejuvenation. Journal of Cosmetic Dermatology. 2018; 17(3):289–297.
11. IDS. Available at: http://ids.co.kr. Accessed September 10, 2023.
12. IP 1817. Interventional procedure overview of transvaginal laser therapy for urogenital atrophy. National Institute for Health and Care Excellence. No date provided.
13. Karcher C, Sadick N. Vaginal rejuvenation using energy-based devices. International Journal of Women's Dermatology. 2016; 2(3):85–88.
14. MonaLisa Touch®. DEKA. Available. Accessed November 25, 2023.
15. Lapii GA, Yakovleva AY, Neimark AI. Structural Reorganization of the Vaginal Mucosa in Stress Urinary Incontinence under Conditions of Er:YAG Laser Treatment. Bulletin of Experimental Biology and Medicine. 2017; 162(4):510–514.
16. Li FG, Maheux-Lacroix S, Deans R, et al. Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Symptom Severity in Women With Postmenopausal Vaginal Symptoms. JAMA. 2021; 326(14):1381.
17. Lumenis. Leading Medical Equipment & Innovative Laser Technologies. Accessed November 25, 2023.
18. NICE. Transvaginal laser therapy for stress urinary incontinence: Committee considerations. Accessed November 27, 2022.
19. NICE. Transvaginal laser therapy for urogenital atrophy: Recommendations. Available at: https://www.nice.org.uk/guidance/ipg697/chapter/1-Recommendations. Accessed November 27, 2022.
20. Page A, Verbakel JY, Verhaeghe J, et al. Laser versus sham for genitourinary syndrome of menopause: A randomised controlled trial. BJOG: An International Journal of Obstetrics & Gynaecology. 2022; 130(3):312–319.
21. Paraiso MFR, Ferrando CA, Sokol ER, et al. A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause. Menopause. 2019; 1.
22. Pauls RN, Fellner AN, Davila GW. Vaginal laxity: a poorly understood quality of life problem; a survey of physician members of the International Urogynecological Association (IUGA). International Urogynecology Journal. 2012; 23(10):1435–1448.
23. Phillips C, Hillard T, Salvatore S, et al. Lasers in gynaecology. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020; 251:146–155.
24. Phillips C, Hillard T, Salvatore S, et al. Laser treatment for genitourinary syndrome of menopause. BJOG: An International Journal of Obstetrics & Gynaecology. 2022; 129(12).
25. Photiou L, Lin MJ, Dubin DP, et al. Review of non-invasive vulvovaginal rejuvenation. Journal of the European Academy of Dermatology and Venereology. 2020; 34(4):716–726.
26. Pitsouni E, Grigoriadis T, Falagas M, et al. Microablative fractional CO2 laser for the genitourinary syndrome of menopause: power of 30 or 40 W? Lasers in Medical Science. 2017; 32(8):1865–1872.

27. Politano CA, Costa-Paiva L, Aguiar LB, et al. Fractional CO2 laser versus promestriene and lubricant in genitourinary syndrome of menopause: a randomized clinical trial. Menopause. 2019; 26(8):833–840.
28. PRISMA.Availableat:https://prismastatement.org/documents/PRISMA_2020_flow_diagram_new_SRs_v1.docx. Accessed November 25, 2023.
29. RejuvaMed Skin Clinic. CO2 Laser Vaginal Rejuvenation - RejuvaMed Health & Wellness. Available Accessed November 25, 2023.
30. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. Journal of Sex & Marital Therapy. 2000; 26(2):191–208.
31. Ruanphoo P, Bunyavejchevin S. Treatment for vaginal atrophy using microablative fractional CO2 laser. Menopause. Published Ahead of Print, 2020.
32. Salvatore S, Leone Roberti Maggiore U, Athanasiou S, et al. Histological study on the effects of microablative fractional CO2 laser on atrophic vaginal tissue. Menopause. 2015; 22(8):845–849.
33. Salvatore S, Pitsouni E, Grigoriadis T, et al. CO2 laser and the genitourinary syndrome of menopause: a randomized sham-controlled trial. Climacteric. 2020; 24(2):187–193.
34. Sarmento ACA, Costa APF, Vieira-Baptista P, et al. Genitourinary Syndrome of Menopause: Epidemiology, Physiopathology, Clinical Manifestation and Diagnostic. Frontiers in Reproductive Health. 2021; 3.
35. Sokol ER, Karram MM. An assessment of the safety and efficacy of a fractional CO2 laser system for the treatment of vulvovaginal atrophy. Menopause. 2016; 23(10):1102–1107.
36. Skerrett P. The FDA needs to take another look at laser-based 'vaginal rejuvenation.' STAT. 2022.
37. Tadir Y, Gaspar A, Lev-Sagie A, et al. Light and energy-based therapeutics for genitourinary syndrome of menopause: Consensus and controversies. Lasers in Surgery and Medicine. 2017; 49(2):137–159.
38. Wilailak S, Manonai J, Sillaphakit C, et al. Validation of the Thai Version of ICIQ-VS (International Consultation on Incontinence Questionnaire - Vaginal Symptoms) in Thai Women. Ramathibodi Medical Journal. 2015; 38(4):1–13.
39. Zerbinati N, Serati M, Origoni M, et al. Microscopic and ultrastructural modifications of postmenopausal atrophic vaginal mucosa after fractional carbon dioxide laser treatment. Lasers in Medical Science. 2014; 30(1):429–436.