


Review

# Carbon Dioxide Laser Vulvovaginal Rejuvenation: A Systematic Review

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**Abstract:** Genitourinary syndrome of menopause (GSM) causes significant symptomatic aggravation that affects the quality of life (QoL). Vulvovaginal atrophy (VVA), the hallmark of GSM, is managed with topical non-hormonal therapy, including moisturizers and lubricants, and topical estrogen application. Patients not responding/being unsatisfied with previous local estrogen therapies are candidates for a noninvasive modality. Carbon dioxide (CO<sub>2</sub>) laser therapy, especially the fractionated type (FrCO<sub>2</sub>), has drawn considerable attention over the past two decades as a non-invasive treatment for GSM. This systematic review describes the accumulated evidence from 40 FrCO<sub>2</sub> laser studies (3466 participants) in GSM/VVA. MEDLINE, Scopus and Cochrane databases were searched through April 2021. We analyze the effects of FrCO<sub>2</sub> laser therapy on symptoms, sexual function, and QoL of patients with GSM/VVA. As shown in this review, FrCO<sub>2</sub> laser therapy for GSM shows good efficacy and safety. This modality has the potential to advance female sexual wellness. Patient satisfaction was high in the studies included in this systematic review. However, there is a lack of level I evidence, and more randomized sham-controlled trials are required. Furthermore, several clinical questions, such as the number of sessions required that determine cost-effectiveness, should be addressed. Also, whether FrCO<sub>2</sub> laser therapy may exert a synergistic effect with systemic and/or local hormonal/non-hormonal treatments, energy-based devices, and other modalities to treat GSM requires further investigation. Lastly, studies are required to compare FrCO<sub>2</sub> laser therapy with other energy-based devices such as erbium:YAG laser and radiofrequency.

**Keywords:** genitourinary syndrome of menopause; vaginal atrophy; vulvovaginal atrophy; atrophic vaginitis; vaginal rejuvenation; vulvovaginal rejuvenation; carbon dioxide laser; vaginal laser therapy



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## 1. Introduction

### 1.1. Genitourinary Syndrome of Menopause (GSM)

The female genital and lower urinary tracts share the exact embryologic origin and respond to estrogen [1]. GSM is a chronic condition that affects the vulva, vagina, and lower urinary tract [2]. The revised nomenclature replaces the terms vulvovaginal atrophy (VVA), urogenital atrophy, and atrophic vaginitis [2]. GSM is diagnosed based on symptoms and pelvic examination. Laboratory findings, in particular vaginal pH, can be helpful. GSM symptomatology results from estrogen decline in the vaginal mucosa that reduced epithelial thickness, lamina propria, and muscular layer, as well as connective tissue changes, i.e., decreased collagen and elastin content and decreased blood flow. These effects make the vulvovaginal tissues vulnerable to trauma during “sexual intercourse” and gynecology examination [3,4].

Genital dryness is the most frequent and bothersome symptom [5]. In sexually active women, the main complaints are decreased lubrication and dyspareunia [6]. Physical findings include low resilience, vaginal pallor, fragile walls, absence of hymenal remnants, and flattening of the vagina walls [2,7,8]. Vulvar manifestations include thinning of tissue, with increased vulnerability to minimal contact, burning sensation, and itching [9]. Urinary symptoms include painful urination, urinary urgency, urge and stress urinary incontinence (SUI), and repeated urinary tract infections [4,10].

### 1.2. Vulvovaginal Rejuvenation

Vaginal rejuvenation refers to procedures that primarily reduce the width of the vagina for reasons of function and well-being [11]. Vaginal rejuvenation has been gaining interest and popularity as a tool to restore vaginal anatomy and function and address both aesthetic and functional issues [12,13]. Emerging noninvasive procedures for ameliorating symptoms of GSM include energy-based devices, such as lasers and radiofrequency (RF), and injectable agents, such as fillers and platelet-rich plasma (PRP) therapy [14]. Among these techniques, fractionated CO<sub>2</sub> (FrCO<sub>2</sub>) laser (10,600 nm) technology is a therapeutic approach for GSM, and there is a wide range of commercially available FrCO<sub>2</sub> laser devices advertised for this indication. However, no CO<sub>2</sub> laser device has been granted FDA approval for GSM. The treatment aims at restoring premenopausal vaginal function [14,15].

The American College of Obstetricians and Gynecologists' (ACOG) committee opinion on vaginal "rejuvenation" indicated that it is not "medically indicated" due to a lack of evidence regarding effectiveness and safety [16]. Additionally, the Royal Australian and New Zealand College of Obstetricians and Gynecologists disapproved of the conduction of vaginal surgery or laser practices, lacking evidence supporting effectiveness and safety, other than well-conducted clinical trials [17]. Furthermore, the US Food and Drug Administration (FDA) released a strict warning about the utilization of "energy-based devices" to alter vaginal tissue; it insisted that such practices could severely hurt women and more robust data are required [18]. Nevertheless, the FDA warning did not include sufficient data to address safety or efficacy [13].

### 1.3. Study Objectives and Design

The aim of this systematic review is to assess the available evidence regarding the safety and efficacy of FrCO<sub>2</sub> laser therapy in vulvovaginal rejuvenation. The population is peri- and postmenopausal women with symptoms and clinical signs of GSM, with/without a history of breast or gynecological cancer. The intervention is FrCO<sub>2</sub> laser treatment of vaginal and/or vulvar tissue. Furthermore, we searched for studies comparing this intervention to other GSM/VVA therapies such as topical estrogen, lubricant, pelvic floor exercise, and other energy-based modalities. The outcomes were subjective, objective, or cosmetic.

## 2. Methods

We conducted an evidence-based, systematic review of CO<sub>2</sub> laser studies for GSM/VVA following the *Preferred Reporting Items for Systematic Reviews and Meta-analysis* (PRISMA) guidelines in April 2021. We searched for articles in MEDLINE, Scopus, and Cochrane databases using the search items 'genitourinary syndrome menopause' OR 'vulvovaginal atrophy' OR 'atrophic vaginitis' AND 'laser therapy' OR 'carbon dioxide laser'.

Inclusion criteria were: articles in full text, articles in English language, articles that assess the efficacy of FrCO<sub>2</sub> laser therapy in the management of peri and postmenopausal women with signs and symptoms of GSM/VVA, and sample size > 15 patients. The length of follow up was any period. Studies comparing this intervention with other therapies such as topical estrogen, vaginal lubricant, pelvic floor exercise, or other energy-based modalities were included.

Exclusion criteria were: small sample size (<15 patients), review articles, opinion letters, studies focusing on other lasers or RF, urinary incontinence such as SUI, or pelvic

organ prolapse. The risk of bias in individual studies was assessed at study and outcome levels, and studies with a high risk of bias were excluded. Studies were screened by title and abstract, and the entire text of the collected studies was reviewed. Also, 12 articles were added from a hand search of the reference lists of the eligible publications. All authors reviewed the eligible articles and evaluated the study design and risk of bias. Disagreements among authors were discussed until a consensus was reached.

Data recorded were: name of first author, year of publication, name of laser device, type of study, number and characteristics of participants, therapeutic protocol, follow up period, side effects, and primary and secondary outcomes. Primary outcomes included a subjective evaluation of GSM/VVA symptoms (dryness, dyspareunia, itching, burning, frequency and urgency of urination, dysuria, burning sensation when urinating) and objective assessment of GSM/VVA clinical signs. Secondary outcomes included an assessment of sexual function and quality of life (QoL) and cosmetic outcome.

### 3. Results

The flow chart of study selection is shown in Figure 1. Forty studies with a total of 3466 participants were eligible [19–58]. Major characteristics and outcomes of the eligible studies are shown in Table 1. The studies are randomized clinical trials (RCTs) (n = 5) [37,46,47,54,57], prospective cohort (n = 26), retrospective (n = 8), and case series (n = 1). High quality (level II) evidence was included in 26 studies [19–22,24–32,34–36,38,41,45,48,49,51–53,55,56]. Eight studies included level III evidence [23,33,39,40,42,44,50,58]. In a handful of studies FrCO<sub>2</sub> was compared to vaginal estrogen cream and/or vaginal lubricant [37,46,47]. Seven studies included breast cancer survivors (BCS) [23,24,36,39,40,45,58]. Only 4 studies evaluated the aesthetic outcome of CO<sub>2</sub> laser therapy on GSM patients [22,27,30,41]. Up to 3 sessions 4–6 weeks apart were performed. Twenty-eight studies (70%) included ≤6 months follow-up and only 11 studies (27.5%) included ≥12 months follow-up.

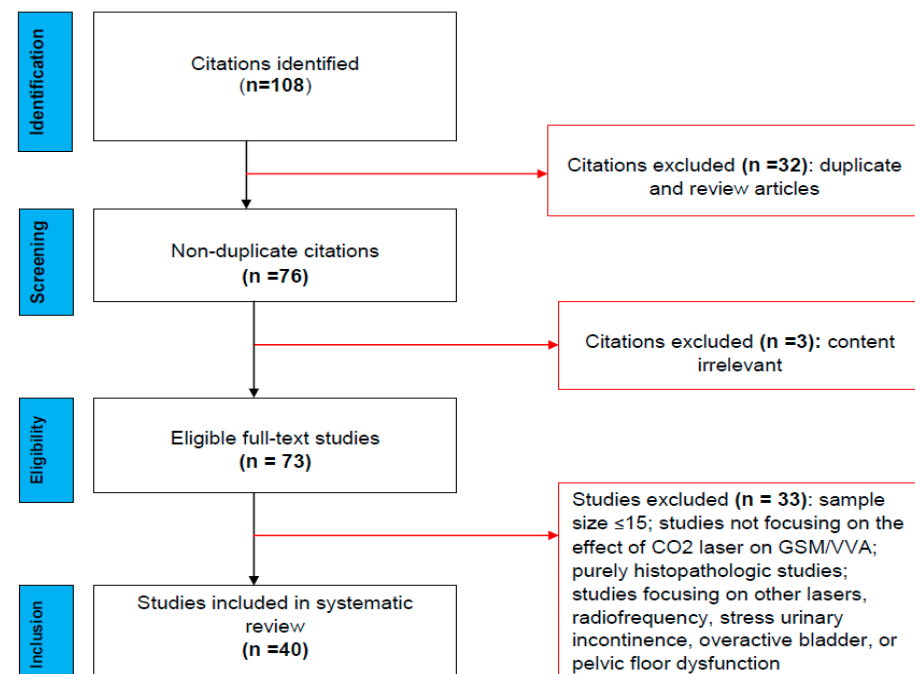


Figure 1. Flow diagram of literature search and study selection.

Table 1. CO<sub>2</sub> laser studies for vulvovaginal rejuvenation.

First Author, Year [ref]	Device Name	Study Type, Participants	Level of Evidence	Efficacy	Follow-up (mos)	Adverse Effects
Salvatore et al. 2014 [19]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (VVA), n = 15	II	Dyspareunia impr ( $p < 0.001$ ), other VVA symptoms ( $p < 0.05$ ); VHIS ( $p < 0.001$ ): FSFI in all domains ( $p < 0.001$ ); SF-12: physical ( $p < 0.001$ ), mental ( $p = 0.048$ )	3	None
Salvatore et al., 2014 [20]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (VVA), n = 50	II	Vaginal dryness, burning, itching, dyspareunia impr ( $p < 0.001$ ); VHIS and SF-12 ( $p < 0.001$ ); 84% of pts satisfied	3	None
Salvatore et al., 2014 [21]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 77	II	VVA symptoms impr ( $p < 0.001$ ); total FSFI ( $p < 0.001$ ); SF-12: physical ( $p = 0.013$ ), mental ( $p = 0.001$ ); 17/20 pts able to resume sexual function	3	None
Perino et al. 2015 [22]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 48	II	Impr vaginal dryness, burning, itching, dyspareunia (all $p < 0.0001$ ); 91.7% of pts “satisfied” or “very satisfied”; cosmetic outcome: complete vaginal resurfacing at 1-mo fu	1	None
Pagano et al. 2016 [23]	SmartXide2 V2LR, Monalisa Touch	Retrospective cohort (VVA), n = 26, BCS	III	Impr dyspareunia, dryness, itching, sensitivity during sexual intercourse ( $p < 0.0001$ )	1	None
Pieralli et al. 2016 [24]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (VVA), n = 50, BCS	II	Impr dyspareunia ( $p < 1.86 \times 10^{-22}$ ), VHIS ( $p < 0.0001$ ); 52% pts satisfied at 11 mos	≤25	None
Pitsouni et al., 2016 [25]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 53	II	Impr dyspareunia, dryness, burning, itching, dysuria, VMV, VHIS, FSFI; satisfaction with procedure impr (PGI-I)	3	Mild irritation of the introitus.
Sokol et Karram, 2016 [26]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (VVA), n = 30 (3 lost at fu)	II	Impr burning sensation ( $p = 0.018$ ), itching ( $p = 0.001$ ), vaginal dryness ( $p < 0.001$ ), dyspareunia ( $p < 0.001$ ), dysuria ( $p < 0.035$ ), VHIS & FSFI ( $p < 0.001$ ); 96% of pts “satisfied” or “extremely satisfied”	3	Mild-to-moderate pain, minimal bleeding.

Table 1. Cont.

First Author, Year [ref]	Device Name	Study Type, Participants	Level of Evidence	Efficacy	Follow-up (mos)	Adverse Effects
Arroyo, 2017 [27]	CO <sub>2</sub> RE Intima	prospective cohort (VVA), n = 21 perimenopausal	II	VHI impr ( $p < 0.01$ ); "sexual gratification" increased; all pts satisfied; impr "vaginal rejuvenation" (94%)	8	Mild discomfort, itching (most common).
Athanasioe et al, 2017 [28]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 55	II	Impr dyspareunia, dryness, VHIS (adjusted $p < 0.001$ ); 41% of pts regained normal sexual activity	1	Mild irritation of the introitus.
Behnia-Willison et al., 2017 [29]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 102	II	Impr GSM symptoms ( $p < 0.001$ ); sexual function scores impr over time ( $p = 0.005$ ), including dyspareunia ( $p = 0.002$ ), sexual issues ( $p = 0.001$ )	24	Post-coital UTIs, vaginal discharge/infection, postmenopausal bleeding, lower pelvic pain
Filippini, et al. 2017 [30]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (VVA), n = 386 postmenopausal	II	Complete improvement of dryness, vaginal introitus pain, burning sensation, dyspareunia, itching, soreness after 3 Rxs; cosmetic effect "hypertrophic vulvar dystrophy" after 1st Rx and at 1-mo fu	12	Mild burning, discomfort during probe movement, minimum blood-serum secretions for 1–2 days, vulvar pain
Pagano et al. 2017 [31]	The FemiLift CO <sub>2</sub> Laser.	Prospective cohort (VVA), n = 33, postmenopausal; VVA (n = 16) and/or SUI (n = 17)	II	Dryness, burning, dyspareunia, VHIS impr ( $p < 0.01$ ); 90 % of pts satisfied with procedure, reported impr QoL	3	None
Pieralli et al. 2017 [32]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (VVA), n = 184 (128 spontaneous & 56 oncological menopause)	II	At 12, 18, 24 mos: 72%, 63%, 25% of pts satisfied, respectively; between 18–24 mos: decrease in patient satisfaction	24	None
Pitsouni et al., 2017 [33]	SmartXide2 V2LR, Monalisa Touch	Retrospective case-control (GSM), n = 50, 30-W (n = 25) vs. 40-W (n = 25)	III	Impr dyspareunia, dryness, itching/burning, FSFI, VMV, VHIS (all $p < 0.001$ ); no differences between 30- and 40-W power groups	1	Mild irritation, burning sensation at the introitus.

Table 1. Cont.

First Author, Year [ref]	Device Name	Study Type, Participants	Level of Evidence	Efficacy	Follow-up (mos)	Adverse Effects
Siliquini et al. 2017 [34]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (VVA), n = 87 postmenopausal	II	VAS, VHI, VVHI impr at end of Rx and during fu ( $p < 0.001$ ); DIVA impr ( $p < 0.001$ ); 37.7% of pts very satisfied, 52.9% satisfied	15	None
Sokol et Karram, 2017 [35]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 30	II	Pain ( $p = 0.01$ ), burning sensation ( $p = 0.007$ ), itching ( $p = 0.002$ ), vaginal dryness ( $p < 0.0001$ ), dyspareunia ( $p < 0.0001$ ), VHIS ( $p < 0.0001$ ), FSFI ( $p < 0.0001$ ) impr; no difference in SF-12; 92% of pts “satisfied” or extremely satisfied at 12-mo fu	12	Mild to moderate pain following therapy and minimal bleeding
Becorpi et al. 2018 [36]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 20, BCS	II	Impr VHIS ( $p = 0.000$ ), VRS ( $p$ range: 0.000–0.012), FSFI ( $p = 0.003$ ); no difference in FSDSr ( $p = 0.074$ )	1	Not specified
Cruz et al. 2018 [37]	SmartXide2 V2LR, Monalisa Touch	RCT (GSM), n = 45, CO <sub>2</sub> (n = 15) vs. vaginal estriol (n = 15) vs. CO <sub>2</sub> + vaginal estriol (n = 15) comparison	I	All groups: VHIS impr ( $p < 0.01$ ); laser + estriol group, and laser only group: impr dryness ( $p < 0.001$ ), dyspareunia ( $p = 0.009$ ), burning ( $p = 0.002$ ); estriol group: dryness ( $p < 0.001$ ); laser + estriol group: total FSFI impr ( $p = 0.02$ )	5	None
Eder, 2018 [38]	AcuPulse System, FemTouch Handpiece	Prospective cohort (VVA), n = 28 postmenopausal	II	VHIS and most VVA symptoms impr ( $p < 0.05$ ) at 1-mo post-first Rx and during fu; FSFI ( $p < 0.05$ )	6	Vaginal bleeding (one episode)
Gittens et Mullen, 2018 [39]	SmartXide2 V2LR, Monalisa Touch	Retrospective observational (GSM), n = 25, postmenopausal (n = 17), BCS (n = 8)	III	Impr VVA symptoms, FSDS-R, total FSFI, and all FSFI domains post-3 Rxs; no difference in sexual function improvement between postmenopausal pts and BCS treated with endocrine Rx	1.5	Not specified
Pagano et al., 2018 [40]	SmartXide2 V2LR, Monalisa Touch	Retrospective cohort (VVA), n = 82, BCS	III	Sensitivity during sexual intercourse, Impr vaginal dryness, itching, dyspareunia, dysuria ( $p < 0.001$ for all), bleeding, probe insertion ( $p = 0.001$ for both), movement-related pain ( $p = 0.011$ )	1	Persistent discomfort (3 pts discontinued Rx)

Table 1. Cont.

First Author, Year [ref]	Device Name	Study Type, Participants	Level of Evidence	Efficacy	Follow-up (mos)	Adverse Effects
Samuels et Garcia, 2018 [41]	CO <sub>2</sub> RE Intima	Prospective cohort (VVA), n = 40 postmenopausal	II	Vaginal dryness, itching, dyspareunia impr ( $p < 0.05$ ), VHIS ( $p < 0.001$ ), FSFI ( $p < 0.001$ ); 50% of pts “very satisfied”; cosmetic outcome: improvement in labial and vulvar tissue	12	Itching, swelling, vulvar discomfort, burning on urination, vaginal fungal infection.
Athanasίου et al. 2019 [42]	SmartXide2 V2LR, Monalisa Touch	Retrospective cohort (GSM), n = 94	III	Vaginal dryness, dyspareunia impr ( $p < 0.001$ for both), FSFI: ( $p < 0.001$ ); no difference between 4 and 5 Rxs	12	None
Eder, 2019 [43]	AcuPulse System, FemTouch Handpiece	Case series (VVA), n = 20	IV	VHIS, VAS, total FSFI impr ( $p < 0.05$ ); 90% of pts were satisfied	24	None
Filippini et al., 2019 [44]	SmartXide2 V2LR, Monalisa Touch	Retrospective cohort (GSM), n = 645	III	Dyspareunia, vaginal orifice pain, dryness, itching, burning impr ( $p < 0.0001$ )	1	None
Pearson et al., 2019 [45]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort., n = 26 (postmenopausal BCS with VVA)	II	Vaginal dryness, itching, dyspareunia, dysuria ( $p < 0.001$ ), burning ( $p = 0.003$ ), total FSFI impr ( $p \leq 0.001$ )	3	Not specified.
Politano, et al., 2019 [46]	SmartXide2 V2LR, Monalisa Touch	RCT (GSM), n = 72, CO <sub>2</sub> laser vs. vaginal promestriene vs. vaginal lubricant comparison	I	VHIS, VMI significantly higher in laser group than promestriene cream and vaginal lubricant ( $p < 0.001$ ); FSFI: impr desire and lubrication domains in laser group; total FSFI: no differences among groups	3.5	None
Paraiso et al., 2019 [47]	SmartXide2 V2LR, Monalisa Touch	RCT (GSM), n = 69 (7 lost at follow up); laser (n = 30) vs. estriol cream (n = 32) comparison	I	Laser group: 85.5% of pts “better” or “much better”, 78.5% “satisfied” or “very satisfied”; estriol cream group: 70% “better” or “much better”, and 73.3% “satisfied or very satisfied”; FSFI did not differ between groups; high vaginal maturation in estriol group ( $p = 0.02$ )	6	None
Tovar-Huamani et al. 2019 [48]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 60	II	Impr vaginal dryness, itching, burning, dyspareunia, dysuria, VHIS (all $p < 0.001$ ), FSFI ( $p = 0.001$ ), VMV ( $p < 0.0001$ )	4	dysuria and urinary frequency (one patient).

Table 1. Cont.

First Author, Year [ref]	Device Name	Study Type, Participants	Level of Evidence	Efficacy	Follow-up (mos)	Adverse Effects
Adabi et al. 2020 [49]	The fractional micro ablativ CO <sub>2</sub> laser system (Smixel)	Prospective cohort (VVA), n = 140, postmenopausal	II	VHIS: vaginal resilience, fluid, epithelial integrity, and lubrication impr ( $p < 0.0001$ ) FSFI: impr only in arousal and satisfaction status; QoL: impr somatic, social function, mental health components	1	None
Angioli et al., 2020 [50]	SmartXide2 V2LR, Monalisa Touch	Retrospective cohort (VVA), n = 165	III	Impr vaginal dryness (66%), burning (66%), dyspareunia (59%), pain at introitus (54%), itching (54%) (all $p < 0.00001$ )	1	None
Ghanbari et al., 2020 [51]	SmartXide2 V2LR, Monalisa Touch	Prospective observational (VVA), n = 47	II	Impr vaginal dryness, dyspareunia, vaginal discharge, itching (all $p < 0.001$ ).	2	None
Li et al., 2020 [52]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 162; laser (n = 108) vs. estriol cream (n = 54)	II	Laser group: VHIS ( $p < 0.01$ ), VAS ( $p < 0.001$ ) impr; control group: VHIS ( $p < 0.05$ ), VAS ( $p < 0.001$ ). At 3-, 6-mo fu: no difference between groups ( $p < 0.05$ ).	12	None
Marin et al., 2020 [53]	Aphrodite	Prospective cohort (VVA), n = 50 (25 menopausal + 25 non-menopausal)	II	Impr FSFI and QoL ( $p < 0.05$ for both) at 3- and 6-mo fu	6	Mild itching, vaginal discharge, vaginal edema, "heating sensation".
Ruanphoo et Bunyavejchevin, 2020 [54]	SmartXide2 V2LR, Monalisa Touch	Double-blind RCT (VVA), n = 88 postmenopausal; laser (n = 44) vs. sham (n = 44)	I	Impr VHIS ( $p < 0.001$ ), VAS ( $p = 0.03$ ); more "very satisfied or satisfied" pts in laser group ( $p = 0.002$ )	3	Vaginal inflammation, pain post-procedure, vaginal bleeding.
Takacs et al., 2020 [55]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (VA), n = 52 (34 postmenopausal, 18 pre-menopausal)	II	Impr vaginal dryness in both premenopausal and postmenopausal groups ( $p < 0.01$ )	1	Not specified



Table 1. Cont.

First Author, Year [ref]	Device Name	Study Type, Participants	Level of Evidence	Efficacy	Follow-up (mos)	Adverse Effects
Sindou-Faurie et al. 2020 [56]	SmartXide2 V2LR, Monalisa Touch	Prospective cohort (GSM), n = 46	II	Impr vaginal dryness ( $p = 6.34 \times 10^{-6}$ ), dyspareunia ( $p = 0.001$ ), sensitivity during intercourse ( $p = 0.001$ ); pts able to achieve ( $p = 0.026$ ) and maintain ( $p = 0.018$ ) lubrication during coitus	3	“Vaginal evisceration” in a BCS
Salvatore et al. 2020 [57]	SmartXide2 V2LR, Monalisa Touch	Double-blinded RCT (GSM), n = 58, laser (n = 28) vs. sham (n = 30)	I	Laser group: vaginal dryness, dyspareunia, itching, burning, dysuria, total FSFI impr; sham group: vaginal dryness, itching, and burning impr; dyspareunia & sexual dysfunction significantly lower in laser than sham group ( $p < 0.05$ )	4	None
Siliquini et al., 2021 [58]	SmartXide2 V2LR, Monalisa Touch	Retrospective cohort (GSM), n = 135, postmenopausal, BCS (n = 45), healthy women (n = 90)	III	Both groups: VHI VVHI, dyspareunia, and vaginal dryness impr; improvement lasted up to 12-mo fu and was slower in BCS than healthy women	12	None

**Abbreviations:** BCS, breast cancer survivors; DIVA, day-by-day impact of vaginal aging; FSDSr, female sexual distress scale revised; FSFI, Female Sexual Function Index; fu, follow-up; GSM, genitourinary syndrome of menopause; PGI-I, global impression of improvement; impr, significant improvement/significantly improved; mo, month; QoL, quality of life; SF-12, short form-12; RCT, randomized controlled trial; Rx, treatment; SUI, stress urinary incontinence; VAS, visual analog scale; VHIS, vaginal health index score; VMI, vaginal maturation index; VMV, vaginal maturation value; VRS, verbal rating scale; VVA, vulvovaginal atrophy; VVHI, vulvovaginal health index.

Eligible studies showed only a low or negligible risk of bias. Selective reporting within a study was not identified. Publication bias, observer bias, bias relating to sponsorship from laser manufacturers, and the placebo effect are unlikely given the large number of adequately powered studies including RCTs with well-documented benefits. Studies utilized established subjective and objective instruments to quantify the improvement in symptoms and vaginal health. Subjective instruments included visual analog scale (VAS), verbal rating scale (VRS), and day-by-day impact of vaginal aging (DIVA). Objective instruments included vaginal health index score (VHIS) and vulvovaginal health index (VVHI). Various degrees of improvement of GSM symptoms were reported across all studies. There was no significant difference in the outcome between BCS and physiologic menopause patients [39].

Twenty-one studies (52.5%) evaluated sexual function and showed a significant improvement in total female sexual function index (FSFI) score post-treatment [19,21,25,26,29,33,35–39,41–43,45–49,53,57]. Patient satisfaction was evaluated through several instruments including the global impression of improvement (PGI-I). Patient satisfaction regarding the procedure was evaluated in 13 studies (32.5%) [20,22,24–27,31,32,34,41,43,47,54]. The effect of CO<sub>2</sub> laser therapy on quality of life (QoL) was evaluated in 6 studies [19,21,22,35,49,53]. Twenty-one studies (52.5%) reported that there were no adverse effects and 15 (37.5%) only mild adverse effects.

## 4. Discussion

### 4.1. GSM Management

GSM can cause significant symptomatic aggravation and reduce self-esteem and confidence [59,60]. It can significantly compromise the QoL of postmenopausal women on a quotidian basis [61]. Furthermore, it has a negative effect on the sexual health of patients [62]. If untreated, GSM will likely worsen [10]. GSM is underdiagnosed, which is most commonly due to the failure of communication between health care providers. Patients often feel embarrassed and think that the condition due to aging. Furthermore, women are usually uninformed about the available therapies for GSM [62]. Therefore, enhanced contact and rapport between the patient and healthcare provider is crucial to patient education and therapy success [63]. The aim of treatment is the restoration of vaginal and vulvar tissue [64]. Topical non-hormonal therapy, including moisturizers and lubricants, is first-line therapy. Regular sexual activity is recommended [65]. Topical estrogen application may be beneficial in moderate and severe cases and could restore premenopausal histology. The effect is long-standing [65,66].

### 4.2. CO<sub>2</sub> Laser Mechanism of Rejuvenation

GSM is a major indication of noninvasive vulvovaginal rejuvenation. Patients not responding/being unsatisfied with previous local estrogen therapies are candidates for a noninvasive modality. FrCO<sub>2</sub> is the most commonly used minimally invasive modality for vulvovaginal rejuvenation. The CO<sub>2</sub> laser light is absorbed by water, its chromophore, and transformed into thermal energy that results in tissue vaporization [67]. The laser energy application on vaginal tissue increases the temperature to 40 to 42 °C. FrCO<sub>2</sub> laser delivers energy in microthermal zones. Columns of untreated skin tissue remain in between the microthermal zones and start a rapid tissue repair process that enhances the healing thus minimizing the risk of scarring [68,69]. As an inflammatory stage develops immediately after vulvovaginal treatment, most providers recommend waiting at least 2–3 days before resuming sexual activity. CO<sub>2</sub> laser-induced tissue vaporization leads to collagen shrinkage, synthesis of new collagen, and increased vessel formation and growth factor production [3,4]. Histopathology of postmenopausal women after FrCO<sub>2</sub> laser treatment demonstrated increased thickness of the vaginal epithelium with the formation of new papillae, increased extracellular matrix synthesis, increased angiogenesis, neocollage-

nesis, ne elastogenesis [22,32,70,71], and increased glycogen content [70]. Salvatore and colleagues showed enhanced vaginal tissue remodeling without damage to surrounding tissue [72]. FrCO<sub>2</sub> laser therapy decreases vaginal pH gradually, increases lactobacillus, and restores normal vaginal flora [73].

This systematic review analyzes the effects of CO<sub>2</sub> laser therapy on symptoms, sexual function, and QoL.

#### 4.3. Clinical Efficacy of CO<sub>2</sub> Laser Therapy for GSM

A significant improvement of vaginal status and GSM symptoms such as dyspareunia, vaginal dryness, itch or burning, and dysuria was documented across all studies. Along the same lines, vaginal health scores such as VHI and VHIS improved in all studies. The beneficial effects of therapy were noted already after the first laser session [34]. Symptomatic improvement was maintained in the follow-up period [29,34].

FrCO<sub>2</sub> laser therapy was compared with topical hormonal treatment and/or vaginal lubricant in 3 RCTs [37,46,47]. The study by Cruz et al. compared FrCO<sub>2</sub> laser with vaginal estriol and combination therapy groups [37]. VHIS improved significantly in all groups. The estriol group improved regarding vaginal dryness but the other groups showed improvement also in dyspareunia and burning. The combination group showed significant FSFI improvement while the laser group worsening of pain domain of FSFI. In the study by Politano et al., FrCO<sub>2</sub> laser was compared with vaginal promestriene and vaginal lubricant [46]. VHIS and VMI scores were significantly higher post-treatment in the laser group than promestriene and lubricant groups. However, total FSFI score did not differ among the three groups, although desire and lubrication domains improved in the FrCO<sub>2</sub> group. In the study by Paraiso et al. [47], patient satisfaction was higher in the laser than estrogen cream group but there was no difference in FSFI.

Data on the aesthetic outcome are scarce because only a few studies described the appearance of the vulvovaginal area after CO<sub>2</sub> laser therapy. Complete vaginal resurfacing and hypertrophy of the vulvar tissues was noted 1-month post-treatment [22,30]. The improvement of vulvar and labial tissues could be maintained up to 5 months post-treatment [41]. It is noteworthy that 94% of patients reported an improvement in vaginal tightening [27].

#### 4.4. CO<sub>2</sub> Laser Therapy for GSM: Effects on Sexual Function

Sexual function improved significantly post-therapy, as evidenced by an increased total FSI score. Improvement in sexual function is possibly related to a reduction of dyspareunia and improved lubrication and vaginal tightness following treatment [21,29]. A significant improvement in total FSFI score was documented even after one laser session [41]. Interestingly, the FSFI score increased for a period up to 24 months post-therapy [29,43]. Most studies showed an improvement in all FSFI domains. Forty-one percent of patients regained normal sexual function in one study [28], and 85% of sexually inactive patients resumed sexual activity in another [21]. Sexual activity can be resumed 1 to 3 days following the procedure, with no particular activity restriction [26,30].

#### 4.5. CO<sub>2</sub> Laser Therapy for GSM: Adverse Effects, QoL, and Patient Satisfaction

Adverse effects were generally mild and included irritation of the introitus [25], itching [27,41,53], mild burning sensation, pain during probe movement [30], scant bleeding [26,35,38], dysuria [41,48], vaginal discharge [53], and vaginal infection [41]. The presence of only mild complications in our review and relevant databases (MAUDE, Bloomberg Law) contradicts the FDA safety warning regarding vaginal laser therapy [74]. Some complications could have been reported only to the FDA. As indicated by Guo et al., there are insufficient data to understand whether the adverse events represent a lack of efficacy, natural progression of disease, inappropriate device use, or true device-related harm, as the majority of post-treatment complaints are the symptoms of GSM for which the patients likely sought treatment [74]. The FDA warning may have been intended to prevent

the marketing of vaginal laser treatments for cosmetic reasons or indications that are not well-defined. However, vaginal laser therapy for cosmetic purposes should not be equated with laser treatment of a highly impactful medical condition (GSM) for which there are only few therapeutic options [74]. Healthcare providers should engage affected women in the decision-making process when considering vaginal laser therapy for GSM [74].

A significant improvement in QoL was documented in five studies [19,21,22,49,53]. Both physical and mental components of SF-12 instrument improved [19,21,49]. However, the study by Sokol and Karam did not show any effect of therapy on QoL [35]. QoL improvement was maintained up to 15 months post-therapy [34]. A very high level of patient satisfaction with the procedure was noted up to 8 months post-therapy [20,22,26,27,47], and most patients (52%) were 'satisfied' or 'very satisfied' at 11 months [24]. However, patient satisfaction fell from 63% to 25% between 18 and 24 months [32].

#### 4.6. Limitations

There was a small number of RCTs, and only a handful of studies included cosmetic outcome. Many reports are limited by a short follow-up (i.e., <6 months in 70% of studies). No studies compared head-to-head FrCO<sub>2</sub> to other energy-based modalities such as erbium:YAG laser or RF. Lastly, the studies included in this report used the same FrCO<sub>2</sub> technology. The results of this technology may not be applied to other emerging laser devices marketed for GSM that use different CO<sub>2</sub> technologies (e.g., differing energy settings and handpieces) that may affect the laser-tissue interaction.

### 5. Conclusions and Future Directions

CO<sub>2</sub> laser therapy for GSM shows good efficacy and safety. This modality has the potential to advance female sexual wellness. Patient satisfaction was high in the studies included in this systematic review. However, more randomized, sham-controlled trials are required. Furthermore, there is a large gap in level I evidence [75]. The number of sessions required has not been standardized because studies were performed in different populations and inclusion criteria varied significantly among the studies. More research into the number of sessions required would help determine the cost-effectiveness of the procedure. Objective standards pertaining to time to orgasm, vulvovaginal appearance, vaginal laxity, vaginal lubrication, and changes that occur in the vaginal wall are also lacking [75]. Lastly, the improvement in clinical findings should be confirmed with histopathologic studies to provide more robust data [76].

There are insufficient data to compare the efficacy of FrCO<sub>2</sub> laser therapy with topical hormonal and non-hormonal treatments. In two RCTs included in this systematic review, FrCO<sub>2</sub> seemed to fare better [46] or was associated with higher patient satisfaction [47] but the effect on FSFI did not differ from that of topical treatment. Further studies may help identify groups of patients that are likely to respond better to FrCO<sub>2</sub> than topical treatments. Whether FrCO<sub>2</sub> laser therapy may exert a synergistic effect with systemic and/or local hormonal/non-hormonal treatments, energy-based devices and other modalities (e.g., PRP) to treat GSM requires further investigation.

Lastly, there is a lack of studies comparing FrCO<sub>2</sub> laser therapy with other energy-based devices such as erbium:YAG laser and RF for vulvovaginal rejuvenation. There is an ongoing RCT on 88 postmenopausal patients that compares FrCO<sub>2</sub> to photothermal erbium:YAG laser for GSM with a 12-month follow-up period [77]. A comparison of FrCO<sub>2</sub> with RF is worth pursuing especially as transcutaneous, temperature-controlled RF yielded recently excellent results in female genital appearance, sexual dysfunction, and SUI [78]. Patient satisfaction was high in the study. RF is a nonablative technology whereas FrCO<sub>2</sub> causes sloughing of the vaginal epithelium; therefore, the recovery time before the patient can undertake sexual activity may be longer with FrCO<sub>2</sub> than RF therapy. A head-to-head comparison between FrCO<sub>2</sub> laser and RF is required regarding adverse effects, healing/recovery time before sexual activity can be resumed, number of sessions needed, and cost involved.

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