



# CO<sub>2</sub> laser therapy for genitourinary syndrome of menopause with sham comparator in randomized controlled trials: A systematic review

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**Citation:** Hariani AW, Kurniawati EM, Hardianto G. CO<sub>2</sub> laser therapy for genitourinary syndrome of menopause with sham comparator in randomized controlled trials: a systematic review. *Pelviperineology*. 2026;45(1):5-11

## ABSTRACT

To critically evaluate the efficacy of fractional CO<sub>2</sub> laser therapy for genitourinary syndrome of menopause (GSM) by systematically reviewing evidence exclusively from sham-controlled randomized controlled trials (RCTs). A systematic review was conducted following preferred reporting items for systematic review and meta-analyses guidelines. Major scientific databases were searched for sham-controlled RCTs comparing fractional CO<sub>2</sub> laser to a sham procedure for GSM treatment. The primary outcomes analysed were patient-reported symptom improvement, changes in sexual function, and histological changes in the vaginal epithelium. Seven RCTs, encompassing a total of 319 participants, met the inclusion criteria. While a subset of trials reported statistically significant improvements in sexual function and reductions in symptoms like dryness and dyspareunia compared to sham, an equal number of trials found no significant difference between the active and sham interventions. Only one study included the use vaginal histology as a primary outcome and found no significant difference in epithelial remodelling between the laser and sham groups. While fractional CO<sub>2</sub> laser therapy has yet to be established as a routine clinical option for GSM, its potential remains promising. The current evidence highlights the need for further large-scale, multi-centre, long-term trials with standardized protocols to fully explore and confirm its therapeutic benefits.

**Keywords:** Genitourinary syndrome of menopause; vaginal atrophy; menopause; CO<sub>2</sub> laser

## INTRODUCTION

Genitourinary syndrome of menopause (GSM) is a condition that affects the majority of postmenopausal women, with estimates suggesting that up to 50% or more experience its manifestations.<sup>1</sup>

This syndrome was caused by the decline in estrogenic levels following menopause, which leads to various anatomical and physiological changes in the vulva, vagina, and lower urinary tract.<sup>2</sup> The symptoms of GSM include dryness of the vagina, burning sensation, irritation, dyspareunia, and various urinary

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**Received:** 30 October 2025 **Accepted:** 13 January 2026 **Publication Date:** 24 April 2026



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issues such as urgency and recurrent infections. GSM is often chronic and progressive if left untreated, potentially leading to a significant decline in quality of life and sexual function.<sup>3</sup>

The impact of GSM was observed to be more than physical discomfort, it also affects women's intimate relationships, self-esteem, and overall well-being.<sup>4</sup> Many women that had GSM do not consult a clinician due to embarrassment or the misconception that these symptoms are an inevitable part of aging.<sup>5</sup> Current treatment for GSM ranges from non-hormonal options like lubricants and moisturizers for milder symptoms<sup>6</sup> to hormonal therapies, primarily local oestrogen application, which directly address the underlying estrogenic deficiency and are considered highly effective for moderate to severe symptoms.<sup>7</sup> However, some women may have contraindications to hormonal treatments, such as a history or a present hormone-sensitive cancers, or may prefer non-hormonal alternatives due to concerns about side effects.<sup>4,8,9</sup>

In recent years, energy-based devices, particularly fractional CO<sub>2</sub> laser therapy, have emerged as a novel, non-hormonal treatment option for GSM. The proposed mechanism of action involves a laser delivering controlled micro-ablative thermal energy to the vaginal tissue. This process can stimulate tissue remodelling, including the formation of new collagen, elastin production, and revascularization.<sup>10</sup> The final aim of CO<sub>2</sub> laser therapy is to restore vaginal epithelial thickness, elasticity, and lubrication. Athanasiou et al.,<sup>11</sup> reported that CO<sub>2</sub> laser therapy provides a significant improvement, even in the absence of GSM, up to a 12 month follow-up.

Despite its increasing use and anecdotal reports of success, the efficacy of vaginal CO<sub>2</sub> laser therapy for GSM remains uncertain.<sup>12</sup> This uncertainty lies in the relationship between the histological changes induced by the laser and the patient-reported symptomatic improvements. While some studies have reported increased epithelial thickness and collagen, others, including sham-controlled RCTs,<sup>13</sup> have found no significant difference between the active and sham laser groups.<sup>14</sup> Therefore, this systematic review aims to critically evaluate the effect of vaginal CO<sub>2</sub> laser treatment compared to sham laser treatment on validated measures of vaginal histological changes and patient-reported symptom improvements in postmenopausal women with atrophic vagina.

## MATERIAL AND METHODS

### Eligibility Criteria

This systematic review was conducted in accordance with the preferred reporting items for systematic review and meta-

analyses 2020 guidelines. The primary research question was: "What is the effect of vaginal CO<sub>2</sub> laser treatment when compared to sham laser treatment in women with GSM in histological and quality of life?".

The research question was formulated using the PICO framework, Population (P): Women diagnosed with GSM; Intervention (I): CO<sub>2</sub> laser treatment; Comparison (C): sham laser treatment as a placebo; and Outcome (O): improvement in histological and quality of life aspects.

Studies included in this analysis were full-text, randomised controlled trial peer-reviewed studies that reported improvements in histological and quality of life aspects. Studies that included non-GSM-related vaginal pathologies, non-English studies, lacked data, reviews, editorials, letters, conference abstracts, or case reports were excluded.

### Information Sources

A comprehensive electronic search (date) was conducted in multiple academic digital databases, including PubMed, Scopus, Virtual Health Library, as well as grey literature sources, to reduce publication bias via Open Access Thesis and Dissertation Repositories.

### Search Strategy

The literature search was conducted using a combination of MeSH terms and free-text keywords related to GSM, Atrophic Vagina, and CO<sub>2</sub> laser therapy. The following search strategy used were: ("Genitourinary Syndrome of Menopause" OR "Atrophic Vagina" OR "vaginal atrophy" OR "vulvovaginal atrophy") AND ("CO<sub>2</sub> Laser" OR "Laser Therapy" OR "Laser Treatment"). Any necessary adjustment were made for each database category to adapt the search term. The search was done on June 16<sup>th</sup>, 2025.

### Selection Process

Two independent reviewers with relevant expertise conducted the study selection. All retrieved records will be imported to EndNote 20 (Clarivate Analytics, Philadelphia, USA) for reference management. Duplicate entries will be removed using two separate methods. First, automatic duplicates were detected by EndNote 20, and second, manual screening was performed using Microsoft Excel.

The first study selection was done by title and abstract reviews. Articles that meet the initial eligibility criteria will proceed to a full-text review to determine final inclusion. Additionally, when a reviewer finds articles in the selection process that raise doubts, the article will proceed to the next round of review.

## Data Collection

From eligible studies, general data will be extracted including authorship, publication year, study design, and sample characteristics (such as sample size, age, menopausal status, baseline GSM severity, comorbidities, and prior GSM treatments). Detailed information regarding the CO<sub>2</sub> laser intervention (device, parameters, session details) and the specifics of the comparator, particularly for sham procedures, will also be systematically recorded.

For the primary and secondary outcomes, data will be collected regarding the vaginal maturation index, including assessment methodology and scores, and vaginal pH measurements. We will also extract total and domain scores for the female sexual function index (FSFI), overall and component scores for the vaginal health index (VHI). Additionally, we will obtain visual analog scale (VAS) scores for key GSM symptoms including dryness, dyspareunia, itching, and burning. For all these measures, baseline values, post-treatment values, and change scores will be recorded.

## RESULTS

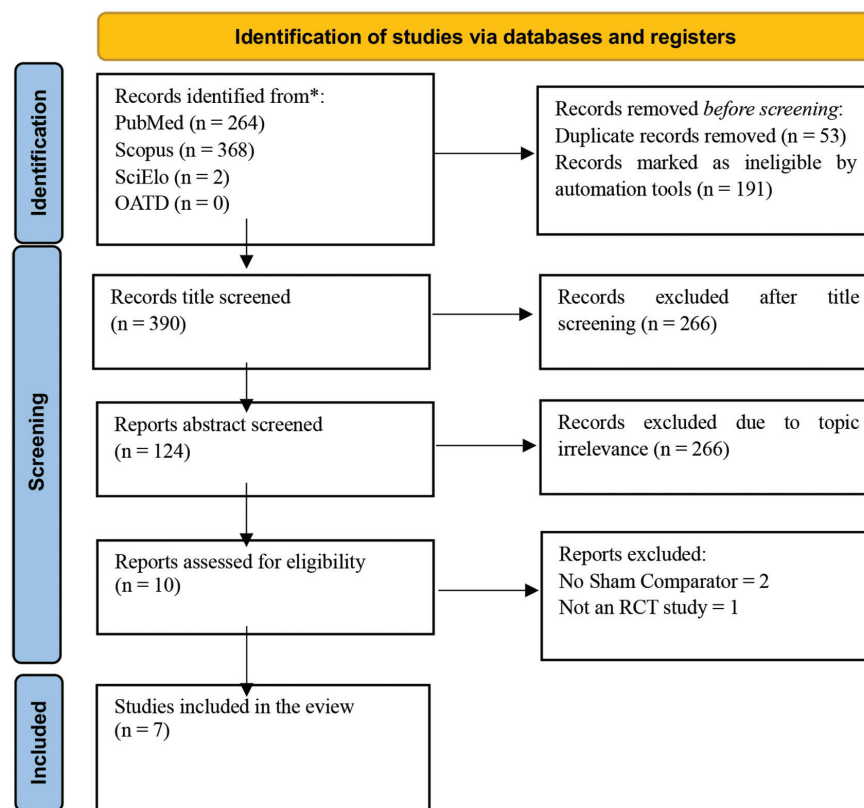
The literature search resulted in a total of 634 studies. Initially, automatic duplicate detection was performed using EndNote

(n=191), followed by manual duplication detection to identify further instances of duplication (n=53). The initial exclusion of title relevance resulted in the exclusion of 266 articles, while 390 articles continued to undergo abstract reading. It is essential to note that when the title is ambiguous, it will proceed to the next round. Abstract reading screened 124 articles, and 10 articles were included in the full-text reading, with three studies excluded due to no sham comparator (n=2) and not being a randomised controlled trial study (n=1). The database selection flowchart shown in Figure 1 and the summary of included study shown in Table 1.

## Study Characteristics

Seven studies were included in this review, with a total of 163 observed in the treatment arm and 156 in the sham arm.<sup>14-20</sup> Two studies included an additional condition of the cohort with gynecologic and breast cancer survivors.<sup>16,20</sup> The most commonly used device is the SmartXide2 V2LR (n=4), followed by MonaLisa Touch (n=2) and Femilift (n=1). The post-treatment measurement averaged at 3.5 months, ranging from 1 to 6 months.

One study reported the histological changes in GSM patients,<sup>14</sup> which summarizes that there is no significant difference in the



**Figure 1.** Database selection flowchart based on PRISMA reviews

RCT: randomized controlled trial; PRISMA: preferred reporting items for systematic review and meta-analyses

microscopic features of the vaginal epithelium following either laser or sham treatment ( $p=0.2$ ) and in the VAS scale as well ( $p=0.17$ ).

The overall results of various variables reported in the studies are reported in Table 2<sup>14-20</sup> and Table 3.<sup>18-20</sup> The findings are mixed, resulting in differing conclusions across studies. Most importantly, three studies indicated that fractional CO<sub>2</sub> laser therapy did not demonstrate a significant advantage over sham for primary bothersome symptoms.<sup>17,19,20</sup> Jaber et al.,<sup>20</sup> trial in breast cancer survivors found no significant difference between three laser treatments and sham for dyspareunia and intercourse dryness. Cruff and Khandwala<sup>17</sup> reported no significant difference in patient improvement in GSM-related dyspareunia, with an underpowered study. Lastly, Page et al.,<sup>19</sup> concluded that the treatment response for laser and sham at 4 months offers no measurable long-term benefits.

Conversely, other studies have reported significant benefits for laser treatments compared to sham treatments. Salvatore et al.<sup>18</sup> concluded that the CO<sub>2</sub> laser was better than sham in reducing dryness, dyspareunia, and improving FSFI scores. Ruanphoo

and Bunyavejchevin<sup>15</sup> reported significantly improved VHI and VAS scores compared to the sham group. A more detailed examination from the Quick et al.<sup>21</sup> study in gynaecological cancer survivors also reveals improvements in FSFI scores, as well as some objective improvements in vaginal pH, moisture, and elasticity.

## DISCUSSION

The current systematic review was conducted to evaluate the efficacy of fractional CO<sub>2</sub> laser therapy for GSM treatment by exclusively analysing evidence from sham-controlled RCTs. Overall, the data aggregated from this study includes seven clinical trials with a total of 319 participants. It was observed that the studies did not yield a definitive conclusion, but instead presented an evidentiary conflict of findings. There were inconsistencies in outcomes across the studies, preventing an explicit endorsement of fractional CO<sub>2</sub> laser treatments.

The initial introduction of CO<sub>2</sub> laser therapy for GSM was largely driven by prospective and case series studies. These early, uncontrolled studies reported significant improvements and

**Table 1. Summary of included studies**

Author (year)	Additional conditions	Device	Post treatment measurement
Ruanphoo and Bunyavejchevin <sup>15</sup>	None	SmartXide2 V2LR, DEKA, Florence, Italy	3 months
Quick et al. <sup>16</sup>	Gynecologic cancer survivors	MonaLisa Touch, DEKA, Florence, Italy	1 month
Cruff and Khandwala <sup>17</sup>	None	MonaLisa Touch, DEKA, Florence, Italy	6 months
Salvatore et al. <sup>18</sup>	None	SmartXide2 V2LR, DEKA, Florence, Italy	4 months
Li et al. <sup>14</sup>	None	SmartXide2 V2LR, DEKA, Florence, Italy	2 months
Page et al. <sup>19</sup>	None	SmartXide2 V2LR, DEKA, Florence, Italy	3 months
Jaber et al. <sup>20</sup>	Breast cancer survivors	FemiLift	6 months

**Table 2. Summary of the included studies on VHI, VAS, FSFI, and UDI-6 values**

Author (year)	Sham									
	n	Age	Baseline				Post			
			VHI	VAS	FSFI	UDI-6	VHI	VAS	FSFI	UDI-6
Ruanphoo and Bunyavejchevin <sup>15</sup>	44	59.84±7.49	14.66±2.91	2.02±0.4	-	-	16.08±3.27	2.06±0.49	-	-
Quick et al. <sup>16</sup>	8	56.8±5.95	-	-	-	-	-	Δ-1	Δ-0.3	Δ-21
Cruff and Khandwala <sup>17</sup>	12	59	11.5	80	11.3	33.3	Δ5	Δ-0.31	Δ6.6	Δ-18.8
Salvatore et al. <sup>18</sup>	30	57±6.8	-	-	9.7±7.8	17.4±21.5	-	-	12.1±8.3	14.7±21.3
Li et al. <sup>14</sup>	24	<b>Histological data</b>								
Page et al. <sup>19</sup>	29	56.2±6.3	10.7±3.56	++	11.2±6.64	-	10.7±3.56	++	14.3±6.96	-
Jaber et al. <sup>20</sup>	9	47	11.73±2.12	4.59±2.02++	13.58±7.29	-	14.7±4.6	2.97±1.89++	13.18±9.48	-

Table 2. Continued

Treatment									
n	Age	Baseline				Post			
		VHI	VAS	FSFI	UDI-6	VHI	VAS	FSFI	UDI-6
44	61.73±8.01	14.18±3.39	2.27±0.4	-	-	17.45±2.61*	1.83±0.51*	-	-
10	56 ±11.17	-	-	-	-	-	Δ-3	Δ6.5	Δ-14.6
11	61	10.5	81	9.3	54.2	Δ3	Δ-19	Δ6.4	Δ18.8
30	58.4±6	-	-	11.4±8.2	24±22.1	-	-	23.8±6.6*	15.9±17.4*
22	Histological data								
28	57.4±7.07	11.7±3.68	++	10.3±6.65	-	14.6±4.67	++	13.9±8.35	-
18	45	12.89±2.78	4.67±2.06 ++	11.37±7.52	-	16.67±3.88	3.38±1.75++	15.2 ±8.59	-

Δ: difference between observations on baseline and post; \*: significant difference between baseline and post; ++: a detailed observation was reported; VHI: vaginal health index; FSFI: female sexual function index; VAS: visual analog scale; UDI-6: urogenital distress inventory-6

high patient satisfaction rates.<sup>22</sup> For example, Di Donato et al.,<sup>23</sup> reported significant improvements in various aspects, including VHIS and reduced pH, in their prospective observational cohort study. In our study inclusion, the trial by Salvatore et al.<sup>18</sup> concluded that the CO<sub>2</sub> laser was superior to sham treatment for improving the FSFI score, and Ruanphoo and Bunyavejchevin<sup>15</sup> found that laser treatment led to a significantly enhanced VHI and VAS when compared to the sham group.

On the contrary, Studies Page et al.,<sup>19</sup> Jaber et al.,<sup>20</sup> and Cruff and Khandwala<sup>17</sup> all concluded that fractional CO<sub>2</sub> laser therapy offered no significant benefit over the sham intervention for the most bothersome symptoms of GSM, including dyspareunia. While valuable for generating initial hypotheses and monitoring patients' improvement over time, such study designs are susceptible to bias, particularly performance bias and the placebo effect, especially when dealing with subjective, quality-of-life-related symptoms.<sup>24</sup> It is considered that using sham-controlled RCTs research, a methodologically stringent and clinically realistic appraisal can be observed in the therapy's efficacy can be observed.

The findings of this review align with the trend of evidence observed in a broader CO<sub>2</sub> GSM therapy literature. Early meta-analysis, which pooled data from observational studies alongside non-sham-controlled trials, tended to report positive effects. For example, Filippini et al.,<sup>12</sup> included 2022 studies, and found that there was a significant improvement in GSM symptoms and FSFI scores, but appropriately cautioned that the overall quality of evidence was "very low" or "low" due to the amount of non-randomized designs, which can induce bias. This chronological progression of evidence can be observed as an initial excitement based on lower-quality and biased evidence. However, a more rigorous analysis using sham-controlled trials needs to be done. Clinically, changes in GSM were observed in the vulvar appearance, including alterations in tissue thickness due to

the loss of fat, labia agglutination, and a significant reduction in pubic hair.<sup>25</sup> Histologically, GSM causes dysfunction in the mucosa of the urinary tract and vagina, resulting in decreased flexibility, elasticity, strength, and sensitivity of the mucosa. Specifically, the endometrium undergoes hypoplastic changes, along with extensive de-epithelialization. Uneven thinning of the transitional epithelium on the urothelium was also noted, accompanied by moderate oedema. In the vagina, severe atrophy and thinning of the vaginal mucosa are evident, often associated with a decrease in *Lactobacillus* prevalence, leading to the alkalization of vaginal secretions.<sup>26</sup>

The therapeutic rationale for the fractional CO<sub>2</sub> laser is to induce a specific biological mechanism of action. The technology is designed to deliver controlled micro-ablative thermal energy to the vaginal tissue, creating a micro-injury that stimulates the wound-healing process.<sup>27,28</sup> This process can induce a tissue remodelling, including neocolagenesis, neo-elastinogenesis, and neo-angiogenesis, which aim to restore the thickness, elasticity, and physiological function of the vaginal epithelium.<sup>29,30</sup> The findings for this review, however, are contrary to the premise. Although the search also targeted sham-controlled histological evidence, only Li et al.,<sup>14</sup> observed the vaginal histology as the primary outcome measured. In this methodologically rigorous double-blind, sham-controlled study, direct comparison of vaginal biopsies taken before and after the intervention. It was found that there is no statistically significant difference in any microscopic features between active and sham laser groups. Further studies focusing on the histological aspect improvement need to be done.

Future studies should incorporate large-scale, multi-centre RCTs, as such trials are necessary to provide adequate statistical power to detect clinically meaningful differences and minimize the impact of single-centre biases. Furthermore, a standardized protocol for CO<sub>2</sub> laser therapy must be developed, including

**Table 3. Studies measuring detailed observations using the visual analogue scale**

	Sham									
	Pre					Post				
	Dryness	Burning	Itching	Dyspareunia	Dysuria	Dryness	Burning	Itching	Dyspareunia	Dysuria
Page et al. <sup>19</sup>	4.07±3.63	3.48±3.07	3.24±2.61	8.62±2.29	1.64±2.6	4.07±3.75	2.1±2.76	1.69±2.24	6.45±3.32	1.21±2.53
Salvatore et al. <sup>18</sup>	7.5±1.9	4.6±3.4	3.1±3.2	8.7±1.4	0.9±1.6	5.6±2.9*	3.7±3.4	1.8±2.6*	7.6±1.9	0.9±1.2
Jaber et al. <sup>20</sup>	7.67±3.44	2.67±2.61	2.7±2.96	9±1.55	2.4±3.2	4.53±3.72	1.07±1.58	1.27±1.49	6.82±3.16	0.6±1.35
Treatment										
	Pre					Post				
	Dryness	Burning	Itching	Dyspareunia	Dysuria	Dryness	Burning	Itching	Dyspareunia	Dysuria
	4.28±3.63	3.03±3.03	2.1±2.76	8.24±2.82	1.32±2.64	3.58±3.38	2±2.93	1.86±2.63	5.93±3.54	0.72±1.79
	8±1.7	3.6±3	3.9±3.1	8.6±1.5	1.6±2.4	2.4±2.9*	1.4±2.4*	1±2.1*	2.6±2.6*	0.6±1.5*
	5.26±4.03	2.89±3.23	3.26±2.94	8.88±1.82	2.44±3.24	4.16±3.53	1.78±1.99	2±2.52	7.25±3.15	1.83±2.36

\*: significant difference between baseline and post-treatment

the device, energy settings, pulse characteristics, and treatment schedule. Detailed reporting of these protocols is essential to allow a homogenous comparison across studies.

### CONCLUSION

In conclusion, this systematic review of seven sham-controlled randomized trials highlights the potential of fractional CO<sub>2</sub> laser therapy in treating GSM, despite considerable methodological heterogeneity, including differences in CO<sub>2</sub> laser devices, treatment parameters, follow-up periods (1-6 months), and patient populations (e.g., inclusion of cancer survivors). While some smaller trials have shown subjective advantages of CO<sub>2</sub> laser over a sham procedure (e.g., VHI, FSFI, VAS), this study reveals a lack of clear and consistent efficacy in treating dyspareunia and vaginal dryness. Importantly, the one research that specifically looked at objective parameters showed no discernible histological advantage. The observed improvements in specific trials underscore the importance of innovative approaches and the need to build on this foundation with rigorous future studies.

### FOOTNOTES

#### Contributions

Surgical and Medical Practices: E.M.K., G.H., Concept: A.W.H., E.M.K., G.H., Design: A.W.H., E.M.K., G.H., Data Collection or Processing: A.W.H., E.M.K., G.H., Analysis or Interpretation: A.W.H., E.M.K., G.H., Literature Search: A.W.H., E.M.K., G.H., Writing: A.W.H., E.M.K., G.H.

### DISCLOSURES

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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