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REVIEW ARTICLE

Obstetrics

Physical methods for the treatment of genitourinary syndrome of menopause: A systematic review

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Abstract

Background: Genitourinary syndrome of menopause (GSM) negatively affects sexual function and quality of life. Techniques like laser and radiofrequency are being used to manage GSM, particularly in women with contraindications for hormone therapy.

Objectives: To verify whether the physical methods of laser and radiofrequency can be recommended as safe and effective options for the treatment of GSM/urinary urgency or incontinence in pre- and postmenopausal women.

Search strategy: Databases were comprehensively searched using combinations of the following keywords in any language: "postmenopause"; "genitourinary syndrome of menopause"; "vaginal atrophy"; "radiofrequency"; and "laser."

Selection criteria: Full articles of case-control, cross-sectional, cohort, randomized clinical trials, and quasi-randomized or controlled clinical trials were included.

Data collection and analysis: All authors independently evaluated the design of the studies for quality of reporting, risk of bias, and quality of evidence.

Main results: Of the included 49 studies, 37 were on the CO_2 laser, 10 on the Erbium laser, and two on radiofrequency.

Conclusions: Laser and radiofrequency therapy could be promising and safe therapeutic options for GSM/urinary incontinence. However, the study findings cannot be generalized until new randomized clinical trials are performed that confirm the strength of the evidence. This review has been registered with PROSPERO: CRD42020141913.

KEYWORDS
atrophy, erbium, female urogenital diseases, laser therapy, menopause, radiofrequency

1 | INTRODUCTION

Genitourinary syndrome of menopause (GSM) is a new term created to replace vulvovaginal atrophy (VVA). It is characterized by symptoms ranging from genital (dryness, burning, and irritation) and sexual changes (lack of lubrication, discomfort/pain, impaired function) to urinary symptoms (urgency, dysuria).[1,2] During this period, there is a decrease in circulating estrogen, which provokes thinning of the vaginal epithelium and a reduction in its collagen content, hyalinization, and elastin content, thereby increasing the connective tissue density and reducing the vascularity of the vagina. This can lead to burning, fissuring, dyspareunia, and postcoital bleeding.[3]

The most utilized and effective treatment for symptoms of GSM is topical estrogen. This can be administered in several forms, including tablets, creams, suppositories, and rings. However,

non-pharmacological approaches are also beneficial, mainly in women with contraindications to the use of hormones or those who simply do not want to use them. Intravaginal laser therapy was recently introduced and has been proposed for the treatment of GSM and/or urinary incontinence.[1,4]

A microablative fractional CO_2 laser is one of the newly proposed energy-based devices, along with an erbium photothermal yttrium-aluminum-garnet (Er:YAG) laser and radiofrequency. Current data suggest that the CO_2 laser, via the vaginal remodeling pathway, alleviates symptoms of GSM, as defined by the North American Menopause Society (NAMS) and the International Society for the Study of Women's Sexual Health (ISSWSH). In particular, improvements in dryness, incontinence, dyspareunia, itching/burning, sexual function, dysuria, and urinary frequency/urgency have been reported consistently in studies assessing the short-term efficacy of CO_2 laser therapy.[4,5]

Radiofrequency is another physical method for the treatment of GSM. It involves cutting and coagulating biological tissues using a high-frequency alternating current, which instantly raises the intracellular temperature to 100°C, thus causing expansion and rupture of the cellular membrane. The thermal effects of radiofrequency result in the denaturation of collagen, promoting the immediate and effective contraction of its fibers, activating fibroblasts, and leading to neocollagenesis, reorganization of collagen fibers, and subsequent remodeling of the tissue. There are different types of radiofrequency; the most popular is transcutaneous temperature-controlled radiofrequency (TTCRF).[6-8]

The aim of the present systematic review was to verify whether the physical methods of laser and radiofrequency can be recommended as safe and effective options for the treatment of GSM.

2 | MATERIALS AND METHODS

The present study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[9]

A literature search was carried out using the following databases: PubMed; Embase; Scopus; Web of Science; the Cochrane Central Register of Controlled Trials (Library); CINAHL; and clinical trial databases (www.trialscentral.org, www.controlled-trials.com, and clinicaltrials.gov). The gray literature was searched using appropriate databases (e.g. OpenGrey). The final search of the electronic literature was conducted on April 30, 2020. There were no language restrictions. The following search terms were used: "postmenopause"; "genitourinary syndrome of menopause"; "vaginal atrophy"; "radiofrequency"; and "laser." A detailed example of the search strategy (PubMed) is illustrated in Table 1. The inclusion criteria for the articles in the present analysis were as follows: full-text articles of case-control, cross-sectional, cohort, and randomized clinical trials (RCT), and quasi-randomized or controlled clinical trials (the inclusion of non-randomized studies on intervention effects [NRSI] in the review is justified by the lack of sufficient published clinical trials on the topic for the question to be answered); published in peer-reviewed journals, clinical trial databases, or gray literature; compared the efficacy of intravaginal laser or radiofrequency to that of no treatment, placebo, and vaginal estrogen in the management of GSM in pre- and postmenopausal women. The present analysis included pre- and postmenopausal women with induced menopause or natural menopause (12 consecutive months of spontaneous amenorrhea without apparent cause) with levels of plasma gonadotropin and estradiol in the postmenopausal range (follicle-stimulating hormone [FSH] > 40 U/L; estradiol <25 pg/mL), one or more VVA symptoms, symptoms of GSM with/without urinary incontinence, and previous breast cancer. All protocols of the primary studies were available. The exclusion criteria were as follows: studies that used a treatment option other than laser or radiofrequency, and those in which outcomes were assessed in a manner other than that recorded in the present protocol. Any discrepancies during the review were resolved by consensus of all participating authors.

Dyspareunia and dryness were assessed using the Visual Analog Scale (VAS) 0–10, VAS 0–5, and VAS 0–3; while VAS-10 was used to assess burning, itching, and dysuria. Frequency and urinary incontinence were assessed using different methodologies, such as micturition diaries and questionnaires (Overactive Bladder-Questionnaire short form [OAB-Q SF], the International Consultation on Incontinence Questionnaires [ICIQ-FLUTS; filling domain], and the Urinary Distress Inventory-6 [UDI-6]). Urinary incontinence was assessed using micturition diaries, UDI-6, and ICIQ-UI Short Form [ICIQ-UI SF].

Vaginal atrophy was assessed using the Vaginal Health Index (VHI) questionnaire, which consists of five measures: elasticity; volume of fluid volume; pH; epithelial integrity; and moisture. Data regarding adverse events and drop-outs due to side effects were also evaluated.

A data search was performed by the authors (ACAS and JFL), and if there was no common decision regarding the inclusion or exclusion of a study, a third author (AKG) was consulted to reach a consensus. A standardized data extraction form was used to collect the following

TABLE 1 PubMed search strategy

Number	Search items
1	Postmenopause
2	Postmenopausal women
3	Genitourinary syndrome of menopause
4	Vaginal atrophy
5	Vulvovaginal atrophy
6	Or/1-6
7	Radiofrequency
8	Radiofrequency therapy
9	Laser
10	Laser therapy
11	Or/7-11
12	6 and 11

TABLE 2 Characteristics of the studies included in the systematic review

Author, Year	Country	Study design	Interventions	Patients (n)	Mean age (years)	Inclusion criteria	Therapeutic protocol	Follow-up
Salvatore, 2014[13]	Italy	Prospective	CO_2 laser	15	57.3	Women being sexually active, with dyspareunia related to VVA, age >50 years, absence of menstruation for ≥12 months, and not responding/being unsatisfied with previous local estrogen therapies.	3 laser therapies	0, 4, 8, and 12 weeks
Salvatore, 2014[14]	Italy	Prospective	CO_2 laser	49	59.6	Women being sexually active, with dyspareunia related to VVA, age >50 years, absence of menstruation for ≥12 months, and not responding/being unsatisfied with previous local estrogen therapies.	3 laser therapies	0,4,8, and 12 weeks
Gambacciani, 2015[15]	Italy	Prospective longitudinal	1.Erbium:YAG laser 2. Estriol	62 (43/19)	60.9–63	Presence of GSM in healthy postmenopausal women with levels of plasma gonadotropin and estradiol in the postmenopausal range (FSH >40 U/L; estradiol <25 pg/mL) and negative cervical smear.	3 laser therapies (30 days)	4 and 24 weeks
Gambacciani, 2015[16]	Italy	Prospective	Erbium:YAG laser	65	62.9	Postmenopausal women, suffering from GSM, FSH >40 U/L, estradiol <25 pg/mL.	3 laser therapies (30 days)	1 month
Perino, 2015[17]	Italy	Prospective	CO_2 laser	48	56	Menopausal status, one or more vulvovaginal symptoms, and non-response to previous estrogen or local therapies.	3 laser therapies (30 days)	0 and 30 days
Salvatore, 2015[18]	Italy	Prospective	CO^2 laser	77	60.2	Symptoms of VVA; age ≥50 years; absence of menstruation for ≥12 months; not responding/being unsatisfied with previous local estrogen therapies; wishing to maintain an active sexual life.	3 laser therapies (4 weeks)	12 weeks
Baggish, 2016[19]	USA	Prospective cohort	CO_2 laser	23	67	Postmenopausal women diagnosed via microscopic evaluation with vaginal atrophy and who were symptomatic.	3 laser therapies (4–6 weeks)	6 and 12 months
Gaspar, 2016[20]	Argentina	Comparative cohort	1.Erbium:YAG laser 2. Estriol	50	55–53.3	Mensured estradiol level of ≤20 pg/mL and symptoms of GSM dyspareunia, vaginal dryness, vaginal burning or irritation, and chronic leukorrhea.	3 laser therapies (8 weeks) 3 laser therapies (3 weeks)	6 months
Leibaschoff, 2016[21]	Colombia	Prospective, descriptive, double-blind, randomized controlled trial	1. TTCRF 2. Placebo	20	55–56.9	Early stages of SUI, positive cough stress test, non-previous treatments, voluntary participation, impact of SUI on quality of life, SUI-related sexual dysfunction, no prolapse associated POP >1 anterior compartment, menopause.	3 RF therapies (4 weeks)	12 weeks
Murina, 2016[22]	Italy	Prospective	CO_2 laser	70	30.1	Women presenting with vulvar pain and/or burning plus dyspareunia and/or vestibular atrophy in whom previous therapeutic intervention was unsuccessful or produced unsatisfactory outcomes.	3 laser therapies (30 days)	4 months

(Continues)

TABLE 2 (Continued)

Author, Year	Country	Study design	Interventions	Patients (n)	Mean age (years)	Inclusion criteria	Therapeutic protocol	Follow-up
Pagano, 2016[23]	Italy	Retrospective	CO_2 laser	26	42	Women aged 20–62 years affected by BC, with symptoms of VVA due to CT/HRT-related menopause. Interruption of VVA treatment at least 30 days before the new treatment.	3 laser therapies (30–40 days)	30 and 60 days
Perino, 2016[24]	Italy	Prospective	CO_2 laser	30	56	Menopausal status, one or more vulvovaginal symptoms, non-response to previous estrogen or local therapies, and diagnosis of overactive bladder syndrome.	3 laser therapies (30 days)	0 and 30 days
Pieralli, 2016[25]	Italy	Prospective descriptive cohort	CO_2 laser	50	53.3	Oncological menopause, VVA dyspareunia, negative cervical smear.	3 laser therapies (30 days)	0 and 30 days
Pitsouni, 2016[26]	Greece	Prospective	CO_2 laser	53	57.2	Menopause, ≥1 symptom of GSM with moderate-severe intensity and clinical signs of GSM.	3 laser therapies (30 days)	0 and 12 weeks
Sokol, 2016[27]	USA	Prospective	CO_2 laser	30	58.6	Women with complaints of GSM, non-smoking. With bothersome symptoms of VVA, have less than stage 2 prolapse, and any procedures in the anatomical area for the previous 6 months. Use of vaginal creams, moisturizers, lubricants, or homeopathic preparations was not permitted.	3 laser therapies (6 weeks)	0 and 3 months
Vicariotto, 2016[28]	Italy	Prospectively, exploratory, open-label	DQRF	23	41.7–60.4	Age <54 years and premenopausal. Had at least one full-term vaginal delivery, and currently have negative pregnancy tests and a normal cervical smear. To be in a stable monogamous heterosexual relationship, to have reasonable sexual activity, and to have no evidence of significant POP.	5 sessions (14 ± 1 days)	30, 60 days
Athanasiou, 2017[29]	Greece	Prospective	1. CO_2 laser 2. CO_2 laser 3. CO_2 laser	55	57	Postmenopausal women with dyspareunia, of moderate to severe intensity, willing to maintain or resume sexual activity.	1.3 laser therapies (30 days) 2. 4 laser therapies (30 days) 3. 5 laser therapies (30 days)	3, 6, 12 months
Arroyo, 2017[30]	Spain	Prospective	CO_2 laser	21	45	Perimenopausal women presenting symptoms of VVA (vaginal dryness, irritation, soreness, or dyspareunia associated with this condition).	3 laser therapies (3–4 weeks)	12 and 24 weeks

(Continues)

TABLE 2 (Continued)

Author, Year	Country	Study design	Interventions	Patients (n)	Mean age (years)	Inclusion criteria	Therapeutic protocol	Follow-up
Cruz, 2017[31]	Brazil	Randomized clinical trial	1. Laser CO_2 + placebo estriol 2. Laser CO_2 + estriol 3. Sham laser CO_2 + estriol	45	55.7–55.9	Aged 45–70 years who presented with amenorrhea for 24 months or longer and at least one moderate symptom of VVA.	2 laser therapies (0 and 4 weeks)	8 and 20 weeks
Gambacciani, 2017[32]	Italy	Prospective	Erbium:YAG laser	37	50.8	GSM in women with plasma levels of gonadotropin and estradiol in postmenopausal range (FSH >40 U/L; estradiol <25 pg/mL) and negative cervical smear.	3 laser therapies (30 days)	6, 12, and 18 months
Isaza, 2017[33]	Colombia	Prospective	$TACO_2L$	161	53.38	Postmenopausal women (aged 45–65 years) with a diagnosis of mild SUI, with genital prolapse of POP Quantification stage >I in the anterior compartment and patients who were not adequately classified because of previous surgery.	3 laser therapies (30–45 days)	12, 24, and 36 months
Pitsouni, 2017[34]	Greece	Retrospective case-control	1. CO_2 laser 30 W 2. CO_2 laser 40 W	50 (25/25)	56.3–56.8	Postmenopausal women with severe intensity of dyspareunia and vaginal dryness.	3 laser therapies (30 days)	1 and 3 months
Siliquini, 2017[35]	Italy	Prospective	CO_2 laser	87	58.6	Menopausal status (amenorrhea for at least 12 months or for 6 months with serum levels of estradiol ≤30 pg/mL and FSH ≥50 IU/L); negative cervical smear in the 12 months before the study; symptoms of VVA (vaginal dryness and/or dyspareunia and/or absence of sexual intercourse).	3 laser therapies (30 days)	Visit (T0), at baseline (T1), at week 4 (T2), at week 8 (T3), after 3 months since the last laser application (T4), after 6 months (T5), after 9 months (T6), after 12 months (T7) and after 15 months (T8)
Sokol, 2017[36]	USA	Prospective	CO_2 laser	30	58.6	Women with complaints of GSM, non-smoking. With symptoms of VVA, have less than stage 2 POP and any procedures in the anatomical area for the previous 6 months. Use of vaginal creams, moisturizers, lubricants, or homeopathic preparations was not permitted.	3 laser (6 weeks)	3 and 6 months, and 1 year
Athanasiou, 2018[4]	Greece	Retrospective	CO_2 laser	94	57	Postmenopausal women with at least one symptom of GSM of moderate to severe intensity, received 3–5 laser therapies, had at least 6 months of follow-up, normal gynecological examination, normal cervical smear.	3 laser therapies (30 days)	1, 3, 6, and 12 months

(Continues)

TABLE 2 (Continued)

Author, Year	Country	Study design	Interventions	Patients (n)	Mean age (years)	Inclusion criteria	Therapeutic protocol	Follow-up
Becorpi, 2018[37]	Italy	Prospective	CO_2 laser	20	58.2	Menopausal status, diagnosis of vaginal atrophy, patients with previous BC, and negative smear test performed within 1 year of selection visit.	3 laser therapies (30 days)	3 months
Blaganje, 2018[38]	Slovenia	Randomized controlled trial	1.Erbium:YAG laser 2. Sham group	114	39.95	Premenopausal (age range 35–65 years), sexually active with at least one vaginal delivery and a diagnosis of SUI who signed informed consent were included in this study.	1 laser therapy	3 months
Eder, 2018[39]	USA	Prospective	CO_2 laser	28	60.1	Sexual activity or desire for sexual activity, menopausal status, and one or more VVA-related symptoms. VHI scores ≤5, systemic steroid or hormonal use in previous 3 months, active genital infection, recurrent urinary tract infections, abnormal cervical smears, or POP >II.	3 laser therapies (4 weeks)	1, 3, and 6 months
Gambacciani, 2018[40]	Italy	Prospective, longitudinal	1.Erbium:YAG laser 2. Estriol	254 (205/49)	61.2–62	Presence of GSM in women with plasma levels of gonadotropin and estradiol in the postmenopausal range (FSH >40U/L; estradiol <25 pg/mL) and negative cervical smear.	3 laser therapies (30 days)	24 months
Gaspar, 2018[41]	Argentina	Prospective	Erbium:YAG laser	29	66	Clinical urinary symptoms of GSM, cytological proof of <5%of vaginal superficial cells and vaginal pH >5. VLPP <60 cm of H_2O was considered as type III SUI.	2 laser therapies (3 weeks)	3 and 6 months
Mohajeri, 2018[42]	Iran	Prospective	CO_2 laser	31	63.5	Postmenopausal women who had either urgency incontinence, urinated ≥8 times during daytime and ≥1 times during night-time, ≥1 episodes of urinary urgency incontinence, and experienced a feeling of urgency per 24 h.	3 laser therapies (30 days)	0, 1, 2, and 3 months
Mothes, 2018[43]	Germany	Retrospective	Erbium:YAG laser	16	71	Grade I SUI, urgency without an anatomic cause for residual volume, grade I prolapse/complaint of vaginal laxity, and symptoms of VVA (itching, dryness, burning, discomfort, sexual impairment) and GSM.	1 laser therapy	6 weeks
Mothes, 2018[44]	Germany	Prospective	Erbium:YAG laser	71	60.65	Urgency with no anatomic cause for residual volume (cystocele), grade I prolapse/ vaginal laxity, symptoms of vaginal atrophy and/or GSM.	1 laser therapy	6 weeks
Pagano, 2018[45]	Italy	Retrospective	CO_2 laser	82	44	Women affected by BC and VVA induced or worsened by adjuvant CT and/or HT. Cervical smear tests had to be negative and sexually active.	3 laser therapies (30 days)	4 months

(Continues)

TABLE 2 (Continued)

Author, Year	Country	Study design	Interventions	Patients (n)	Mean age (years)	Inclusion criteria	Therapeutic protocol	Follow-up
Samuels, 2018[46]	USA	Prospective	CO_2 laser	40	34	Absence of menstruation for at least 12 months; unresponsive/dissatisfied with local HRT; desire to maintain sexual activity and experiencing sexual activity at least once a month.	3 laser therapies (30 days)	1, 3, 6, and 12 months
Singh, 2018[47]	Singapore	Prospective cohort	CO_2 laser	45	59.7	Women with signs and symptoms of overt urogenital atrophy.	3 laser therapies 0, 1, 2, 3, and 6 months	3 and 6 months
Arêas, 2019[48]	Brazil	Open, prospective, therapeutic intervention	Erbium:YAG laser	24	53.7	History of BC, complaints of dyspareunia and/or vaginal dryness, and to have had no menstruation for at least 1 year.	3 laser therapies (30 days)	6 months
Bence, 2019[49]	Hungary	Prospective	CO_2 laser	51	57	VVA, mild exertion or urge incontinence, subjective vaginal width sensation, and pelvic subsidence causing complaints (stage I or II pelvic subsidence based on a scale POP).	3 laser therapies (4–6 weeks)	6 weeks
Filippini, 2019[50]	Italy	Retrospective multicenter	CO_2 laser	645	56	Menopausal status (18–75 years), >1 vulvovaginal symptom and VAS evaluation before and after the treatment. 3–4 CO2 laser treatments, VVA, no uncontrolled psychiatric disorders, no symptomatic genital infections, no stenosis, trauma, or necrosis of the urethra.	3–4 laser therapies	0 and 1 month
Murina, 2019[51]	Italy	Retrospective single center	CO_2 laser	33	55	Postmenopausal women presenting with vulvar pain and/or burning plus dyspareunia related to GSM and vestibular atrophy, in whom previous therapeutic intervention was unsuccessful or produced unsatisfactory outcomes.	3 laser therapies (30/60 days)	3 months
Paraiso, 2019[52]	USA	Multicentered, randomized single-blinded clinical Trial	1.CO_2 laser 2. Estrogen cream (Premarin)	62 (33/29)	61	Menopausal women with absence of menstruation for at least 12 months and reported bothersome vaginal dryness of ≥7 cm on VAS.	1.3 laser therapies (6 weeks) 2. 0.5 g IV daily (14 days) followed by 0.5 g twice weekly (24 weeks)	Baseline and at 3 at 6 weeks (laser 2) and 3 months (laser 3).
Pearson, 2019[53]	Australia	Prospective	CO_2 laser	26	55	Women aged >18 years with a history of stage I–III BC who have symptomatic VVA.	3 laser therapies (4 weeks)	0, 4, 8, and 12 weeks

(Continues)

TABLE 2 (Continued)

Author, Year	Country	Study design	Interventions	Patients (n)	Mean age (years)	Inclusion criteria	Therapeutic protocol	Follow-up
Politano, 2019[1]	Brazil	Randomized clinical trial	1.CO_2 laser 2.Promestriene IV 10 mg 3. Vaginal lubricant	72	50	Postmenopausal women aged >50 years.	3 laser therapies (30 days)	14 weeks
Sipos, 2019[54]	Hungary	Prospective cohort	CO_2 laser	40	58	Postmenopausal, with least 12 consecutive months of amenorrhea without any other obvious reason or consistently elevated FSH blood levels of ≥30 mIU/mL.	3 laser therapies (4 weeks)	4 weeks
Tovar-Huamani, 2019[55]	Peru	Prospective uncontrolled before and after	CO_2 laser	60	55	A minimum of 1 year of amenorrhea, no previous HRT, with symptoms of VVA, with changes at the vaginal mucosa related to hypoestrogenism confirmed.	3 laser therapies (30 days)	1 and 3 months
Adabi, 2020[2]	Iran	Prospective	CO_2 laser	140	56.8	Sexual activity at least once a month, cessation of menstruation for at least 12 months, and symptoms not alleviated by the previous local estrogen therapy.	3 laser therapies (4 weeks)	0 and 3 months
Aguiar, 2020[56]	Brazil	Randomized clinical trial	CO_2 laser	72	57.28	Women aged ≥50 years, who were amenorrhoeic for at least 1 year, with symptoms related to GSM, and who did not use THR for at least last 6 months previously and any kind of medication for OAB.	3 laser therapies (30 days)	0 and 2 weeks
Alexiades, 2020[57]	USA	Prospective self-controlled open-label	CO_2 laser	18	54	Healthy female aged ≥35 years; absence of menstruation ≥12 months; with VVA; unresponsive/dissatisfied with previous local estrogen therapy; desire to maintain sexual activity and experiencing sexual activity at least once a month; cervical smear with HPV PCR normal; negative urinalysis and normal internal and external vaginal examination.	3 laser therapies (30 days)	1, 3, 6, and 12 months
Takacs, 2020[58]	Hungary	Prospective cohort	CO_2 laser	34	63	Presence of vaginal dryness (VAS for vaginal dryness >1).	3 laser therapies (4 weeks)	4 weeks

Abbreviations: BC, breast cancer; CT, chemotherapy; DQRF, low-energy dynamic quadripolar radiofrequency; FSH, follicle-stimulating hormone; GSM, genitourinary syndrome of menopause; HRT, hormone replacement therapy; IV, intravaginally; OAB, oral anti-muscarinics or oral β3adrenoceptor agonists; POP, pelvic organ prolapse; SUI, stress urinary incontinence; $TACO_2L$, long-term effect of thermoablative fractional CO_2 laser; TTCRF, non-ablative, monopolar transcutaneous temperature controlled radiofrequency; VA, vaginal atrophy; VAS, Visual Analog Scale;VHI, Vaginal Health Index; VLPP, Valsalva leak point pressure; VVA, vulvovaginal atrophy; YAG, Yttrium-aluminum-garnet.

TABLE 3 Outcomes of the studies included in the systematic review

Author, year	Outcomes measured	Outcomes	Side effects
Salvatore, 2014[13]	The VHI was used to make an objective evaluation of female urogenital health.	Dyspareunia was improved in 100% of patients using the treatment. The intensity of dyspareunia significantly decreased from baseline to 12-week follow-up ($P < 0.001$). All other symptoms of VVA significantly improved at the same follow-up.	No AEs related to the laser procedure was recorded.
Salvatore, 2014[14]	VVA was assessed during the study using subjective (VAS) and objective (VHI) measures.	Laser treatment was effective in improving symptoms of VVA at 12-week follow-up, as well as the VHI.	No AEs were recorded during the study period.
Gambacciani, 2015[15]	GSM was evaluated either with subjective (VAS) and objective (VHI) measures. In addition, in patients experiencing SUI, the degree of incontinence was evaluated with the ICIQ-UI SF.	Treatment induced a significant decrease of VAS of both vaginal dryness and dyspareunia ($P < 0.01$), with a significant ($P < 0.01$) increase of VHI. Treatment was associated with a significant ($P < 0.01$) improvement of ICIQ-SF scores.	Treatment was well tolerated, with <3% of patients discontinuing treatment due to AEs.
Gambacciani, 2015[16]	Symptoms of GSM were evaluated either with subjective (VAS) and objective (VHI) measures. In addition, from mild-moderate SUI, the degree of incontinence was evaluated with the ICIQ-UI SF.	Treatment induced a significant decrease of VAS of both vaginal dryness, dyspareunia ($P < 0.01$) and a significant ($P < 0.01$) increase of VHI). In addition, induced a significant ($P < 0.01$) improvement of ICIQ-SF scores.	The treatment was well tolerated with <2% of patients discontinuing treatment due to AEs.
Perino, 2015[17]	The VHI was used to evaluate the vaginal status of the women, and VAS was used to evaluate the subjective intensity of symptoms of VVA.	Data indicated a significant improvement in symptoms of VVA ($P < 0.0001$). Moreover, VHI scores were significantly higher at T1 ($P < 0.0001$).	No AEs due to fractional CO_2 laser treatment occurred.
Salvatore, 2015[18]	A 10-point VAS was used to measure the overall satisfaction with sexual life and the intensity of symptoms of VVA.	17 (85%) out of 20 (26%) women, not sexually active because of severity of VVA at baseline, regained a normal sexual life. There was also a significant improvement in each symptoms of VVA.	—
Baggish, 2016[19]	The VHI was used for evaluating elasticity; fluid volume; pH; epithelial integrity; and moisture. All symptoms were measured via a 10-point VAS.	22 women who complained of dryness and discomfort had these symptoms alleviated and vaginal microscopic exam showed significant changes in color, elasticity. 20 women had elimination of urgency and urinary frequency, and 18 had alleviation of dyspareunia.	No patient reported any discomfort during or after each treatment session.
Gaspar, 2016[20]	Analysis of VAS was performed for assessment of the severity of the following symptoms of GSM.	There was a statistically significant ($P < 0.05$) reduction of all the symptoms in both groups up to the 6-month follow-up; the relief of symptoms was more prominent in the laser group at all follow-ups. The effect of the laser treatment remained statistically significant at the 12- and 18-month follow-up.	Side effects were minimal and of transient nature in both groups.
Leibaschoff, 2016[21]	SUI was subjectively evaluated with subjective UDI−6 and with the ICIQ-UI SF before and after TTCRF treatments and objectively with cough stress test. Vaginal health was evaluated with the VHI score, and dyspareunia and dryness with the VAS.	Was associated with significant ($P < 0.01$) improvement of ICIQ-SF and UDI−6 scores. VHI scores significantly treatment group. The VAS values in the control group did not show any significant changes during the treatment period.	TTCRF was well tolerated with no complications reported in study participants.

(Continues)

TABLE 3 (Continued)

Author, year	Outcomes measured	Outcomes	Side effects
Murina, 2016[22]	A VAS of pain was chosen to evaluate improvement.	For VAS, a statistically significant improvement was noted after three sessions of vestibular fractional CO_2 laser treatment.	No AEs from fractional CO_2 laser treatment were noted.
Pagano, 2016[23]	The severity of symptoms of VVA was assessed with a VAS based on a score of 0–10, where 0 indicates "absence of symptoms" and 10 indicates a symptom "as bad as it could be."	Treatment resulted in a significant regression of symptoms of VVA and procedure-related discomfort vs baseline ($P < 0.001$ in almost all cases).	No AEs were observed or reported by women.
Perino, 2016[24]	Vaginal status using VHI, subjective intensity of symptoms of VVA using VAS and micturition diary were evaluated.	A statistically significant improvement in symptoms of VVA was observed and in VHI ($P < 0.0001$). A significant improvement was also identified in the micturition diary, in a number of urge episodes and OAB-q ($P < 0.0001$). Of the 30 patients, nine suffered from episodes of incontinence and had improved.	No AEs due to fractional CO_2 laser treatment occurred.
Pieralli, 2016[25]	The VHI score was chosen as the system to evaluate the presence of VVA and its improvement after the treatment. Intensity of dyspareunia was evaluated using VAS.	Data indicated a significant improvement in VVA dyspareunia. Moreover, VHI scores were significantly higher 30 days after treatment. Of patients, 76% were satisfied or very satisfied with the treatment results.	No AEs due to fractional CO_2 laser treatment occurred.
Pitsouni, 2016[26]	The primary outcomes were VMV and VHI. Secondary outcomes included symptoms of GSM, ICIQ-FLUTS and ICIQ-UI SF, UDI−6.	VHI increased significantly. There was a significant decrease in dryness, dyspareunia, burning, itching, dysuria, frequency, urgency, urgency incontinence, stress incontinence, and scores on the ICIQ-FLUTS, ICIQ-UI SF, and UDI−6.	All participants completed the study protocol without any serious side effects. Only a temporary mild irritation of the introitus was noted: it started immediately after the laser treatment, lasted up to 2 h, and resolved spontaneously.
Sokol, 2016[27]	VAS was used to assess symptoms of VVA; VHI scores were completed before each treatment and at follow-up.	Average improvement in VAS was 1.7 3.2 for pain, 1.4 2.9 for burning, 1.4 1.9 for itching, 6.1 2.7 for dryness, 5.1 3.0 for dyspareunia, and 1.0 2.4 for dysuria. Improvements in average VHI were statistically significant ($P < 0.001$).	2 women reported mild-to-moderate pain lasting 2–3 days and 2 reported minor bleeding lasting <1 day, but none were discontinued due to the occurrence of AEs.
Vicariotto, 2016[28]	VAS for symptoms of VVA/GSM and overall satisfaction with sexual life were used.	Clinically and statistically significant improvements were observed for mean VAS scores of most symptoms of VVA/GSM.	No AEs, including thermal burns or injuries, were reported during or after treatments in either arm of the study.
Athanasiou, 2017[29]	A 10-point VAS was used for overall sexual satisfaction. VHI was used for the evaluation of vaginal health.	After the third, fourth, and fifth laser sessions, respectively: dyspareunia completely regressed in 27%, 58%, and 81% of participants; dryness completely regressed in 36%, 66%, and 86%; and VHI regained non-atrophic values in 80%, 96%, and 100%.	None of the participants had any serious AEs. Some reported a mild irritation at the introitus during the procedure and/or immediately after. This resolved spontaneously.
Arroyo, 2017[30]	Evaluation change in VHI at 12 weeks after the final treatment. Change in VHI at 24 weeks after the final treatment and subject assessments of changes in symptoms of VVA and sexual gratification.	At 12 weeks after the third treatment, 82% of the patients showed a statistically significant improvement in VHI ($P = 0.05$). Improvement in VHI remained significant at 6–8 months after treatments ($P = 0.01$).	There were no treatment complications, AEs were limited a patient with a mild urinary infection after her first treatment that resolved completely after a weekly course of oral antibiotics.

(Continues)

TABLE 3 (Continued)

Author, year	Outcomes measured	Outcomes	Side effects
Cruz, 2017[31]	Both VHI and VVA were assessed at weeks 0, 8, and 20. Participants rated symptoms of VVA symptoms on a VAS of 0–10.	Average score of VHI was significantly higher at weeks 8 and 20 in all study arms. At week 20, the laser +vaginal estriol arm also showed incremental improvement of VHI score ($P < 0.01$). Laser and laser +vaginal estriol groups showed a significant improvement of dyspareunia, burning, and dryness, and the estriol arm only of dryness ($P < 0.001$).	—
Gambacciani, 2017[32]	Vas was used to assess vaginal dryness and dyspareunia. The VHI evaluates the appearance of the vaginal mucosa.	From baseline values of 8.5 1.0 cm, vaginal dryness VAS scores were 4.4 to 1.2 cm after the third treatment and 5.5 1.5 cm 12 months after the treatment ($P < 0.01$ vs basal values). VHI, from baseline values of 8.1 to 1.3, was 21.0 1.4 after the third treatment and 18 1.8 12 months from the last laser application ($P < 0.01$ vs basal values).	No AEs were recorded during the study.
Isaza, 2017[33]	The ICIQ-UI SF was used to evaluate SUI before and after treatment.	Treatment was associated with a significant improvement in ICIQ-UI SF scores and 1-h pad weight test at 12 months (both $P < 0.001$), 24 months (both $P < 0.001$), and 36 months (both $P < 0.001$).	$TACO_2L$ treatment was well tolerated, and no side effects were observed during the study period.
Pitsouni, 2017[34]	Dyspareunia, dryness, and itching/burning were assessed using VAS 0–10. VHI was used to evaluate clinical findings. ICIQ-FLUTS was used to assess dysuria, urinary frequency at daytime, nocturia, and urgency.	Statistically significant improvement of dyspareunia, dryness, itching/burning, VHI was observed for both powers. In between-group comparison, improvement of these outcomes was not statistically significantly different.	AEs in both groups included a related to the laser-application irritation-burning sensation of mild intensity at the introitus. No serious AEs were related.
Siliquini, 2017[35]	Subjective measures included VAS for both vaginal dryness and dyspareunia. Objective measures included VHI.	Treatment induced significant improvement in the VAS score. After treatment, VHI indicated no VVA and this improvement was long-lasting. Multivariate analysis showed that the time of follow-up was correlated with better VHI ($P < 0.001$).	Most patients were satisfied with laser therapy and no serious AEs due to fractional CO_2 laser occurred.
Sokol, 2017[36]	Vaginal pain, burning, itching, dryness, dyspareunia, and dysuria were graded with VAS. VHI scoring questionnaires were completed before each treatment and at follow-up.	Average improvement in VAS scores for all symptom categories was statistically significant at 3 months and remained so up to 1 year, except dysuria. Improvement in average VHI was also statistically significant ($P < 0.0001$).	None were discontinued or withdrew due to an AE.
Athanasiou, 2018[4]	VAS for dyspareunia, dryness, and itching/burning. ICIQ-FLUTS: Filling Domain and ICIQ-UI SF for lower urinary tract symptoms and UDI–6.	All GSM symptoms improved statistically significantly. Intensity of dyspareunia and dryness decreased from 9 and 8 at baseline to 0 and 0, 1 month after last laser therapy (all $P < 0.001$), respectively. The positive laser effect remained unchanged throughout the 12 months of follow-up.	There were no AEs reported at the various follow-up periods.
Becorpi, 2018[37]	VHI for vaginal health.	For VHI, a statistically significant improvement was recorded after the laser treatment.	No AEs were reported.
Blaganje, 2018[38]	ICIQ-UI SF was used as the primary outcome measure.	3 months after treatment, the ICIQ-UI SF was significantly more improved in the laser group than in the sham control group.	No serious AEs were reported.

(Continues)

TABLE 3 (Continued)

Author, year	Outcomes measured	Outcomes	Side effects
Eder, 2018[39]	At each study visit, VHI score and VVA severity of symptoms were recorded.	1 month after the first laser treatment, the mean VHI score was significantly improved, and improved further at 3 and 6 months after all treatments. Almost all symptoms of VVA were significantly improved at 1 month after the first treatment.	AEs reported during the study were of moderate severity and were unrelated to the procedure.
Gambacciani, 2018[40]	Subjective (VAS) and objective (VHI) measures were used to evaluate GSM. In addition, in patients experiencing SUI, the degree of incontinence was evaluated with the ICIQ-UI SF.	Laser treatment induced a significant ($P < 0.01$) decrease in VAS for both vaginal dryness and dyspareunia, as well an increase in VHI ($P < 0.01$). In addition, treatment improved mild-moderate SUI.	<3% of patients discontinued treatment due to AEs.
Gaspar, 2018[41]	The primary clinical outcome measures were subjective assessment of the severity of urinary symptoms of GSM; a VAS scale assessed dysuria, frequency, and urgency. The severity of a patient's incontinence was assessed using ICIQ-UI SF and the 1-h pad test.	The average baseline VAS values for dysuria, urgency, and frequency were 66, 58, and 49, respectively. ICIQ-SF improved by an average of 64% at 3 months and by 40% at 6 months. The 1-h pad test showed a reduction of the quantity of leaked urine by 59% at 3 months and by 42% at 6 months. All urinary symptoms of GSM improved.	AEs were mild and transient.
Mohajeri, 2018[42]	The study measures were urgency, frequency, nocturia, leakage, ICIQ-OAB, UDI−6, which were examined at baseline and every month thereafter up to the end of the laser treatment sessions.	Significant differences occurred in the ICIQ-OAB score and urgency ($P < 0.05$). Laser therapy led to marked improvements in the UDI−6 score only at the third month ($P = 0.001$).	—
Mothes, 2018[43]	Follow-up included VHI.	Evaluation was performed after 8.3 ± 2.5 weeks. Pre-laser VHI scored 16 ± 4.6 and post-laser VHI 20 ± 3 with $P = 0.01$. Patients were satisfied in 94% (n = 15) regarding symptom relief.	—
Mothes, 2018[44]	Determination of the VHI by speculum examination.	In patients with GSM, pre- and post-treatment VHI differed significantly (15.3 ± 4.5 vs 19.9 ± 2.8 ($P < 0.001$, Student t-test).	—
Pagano, 2018[45]	Both the severity of symptoms of VVA and procedures related to discomfort were assessed with VAS.	Pre- vs post-treatment differences in mean VAS scores were significant for sensitivity during sexual intercourse, vaginal dryness, itching/stinging, dyspareunia and dysuria ($P < 0.001$ for all), bleeding ($P < 0.001$), probe insertion ($P < 0.001$), and movement-related pain ($P < 0.011$).	No patient reported systemic AEs of the laser treatment nor were any observed.
Samuels, 2018[46]	The VHI, a quantitative assessment of vaginal health. VAS was used to measure discomfort associated with insertion of the probe, rotation/retraction of the probe, and laser application. A validated questionnaire on UI (ICIQ-UIF).	VHI improved significantly after the first treatment and was maintained with mean improvement at the 6- and 12-month follow-ups. Vaginal symptoms of dryness, itching, and dyspareunia improved significantly at all evaluations.	No AEs were reported at any of the follow-ups.

(Continues)

TABLE 3 (Continued)

Author, year	Outcomes measured	Outcomes	Side effects
Singh, 2018[47]	Patients were evaluated for reduction of signs and symptoms, and the VHI was used to reassess the patients at 3- and 6-month follow-ups after the last session of laser therapy.	27 patients with dryness who completed follow-up reported a reduction of dryness, and 17 patients with dyspareunia reported a reduction of dyspareunia. A VAS for scoring severity of symptoms could not be used for all patients, as many of them were not well-educated and had difficulty answering the questions.	There were no side effects or complications reported, except for a few patients reporting discomfort during insertion of the probe and some reporting vaginal soreness.
Arêas, 2019[48]	Vaginal health was assessed before each laser session using the VHI.	Vaginal health improved, as shown by an increased overall score ($P < 0.001$). The effect size was large between pre- and post-treatment scores for vaginal elasticity, fluid volume, epithelial integrity, and moisture.	Complications recorded during laser treatment included vaginal candidiasis and acute cystitis after the first session. These complaints were successfully treated before the second session.
Bence, 2019[49]	VHI was determined, recording the condition of the vagina in five aspects. Subjective complaints were assessed by patients on a VAS–10.	The improvement of VHI and VAS score was statistically significant between all sessions.	No serious side effects were reported in any of the cases
Filippini, 2019[50]	Physical chemical examination of urine, urinalysis, VAS (0–10) evaluation of vaginal atrophy and related symptoms, pH testing with optional VHI evaluation.	In all the parameters examined (dyspareunia, vaginal orifice pain, dryness/atrophy, itching, burning, pH), statistically significant data were found between the pre- and post-treatment.	No side effects were observed in any of the laser sessions.
Murina, 2019[51]	At the first assessment, symptoms of dryness, burning/pain, and dyspareunia were evaluated on a VAS–10.	There was a statistically significant reduction of all the symptoms in both groups up to the 3-month follow-up.	Side effects included a sensation of mild-to-moderate pain in 12 patients, as well as slight transient edema after laser treatment (and 8% in laser group).
Paraiso, 2019[52]	The primary outcome of this study was to compare subjective improvement of vaginal dryness using the VAS for GSM. Secondary outcomes included comparisons between groups of the VHI, and the UDI–6.	VAS scores for vaginal dryness did not differ between groups. VAS scores for the other symptoms of GSM (vaginal burning, vaginal itching, and dysuria) did not differ between the two groups. Mean differences in UDI scores were also not different between groups.	Ten AEs were either mild or moderate and included vaginal bleeding, pain, and/or discharge; breast tenderness; urinary tract infection; migraine; and abdominal cramping.
Pearson, 2019[53]	Symptomatic improvement of VVA at 12 weeks by VAS.	There was a significant improvement in each of the symptoms of VVA: dryness ($P < 0.001$), itch ($P < 0.001$), burning ($P = 0.003$), dysuria ($P < 0.001$), and dyspareunia ($P < 0.001$).	—
Politano, 2019[1]	Vaginal maturation and VHI score.	CO_2 laser group (mean score 18.68) with promestriene (15.11) and lubricant (10.44) groups ($P < 0.001$).	There were no AEs associated with any of the treatments.
Sipos, 2019[54]	Patients were asked to complete the UDI–6 to assess urinary bother.	UDI–6 scores were not significantly different after the first treatment compared with baseline. However, each subsequent treatment resulted in further, statistically significant improvement in symptom scores.	—

(Continues)

TABLE 3 (Continued)

Author, year	Outcomes measured	Outcomes	Side effects
Tovar-Huamani, 2019[55]	Subjective (VAS) and objective (VHI; OAB-qSF were used during the study period to assess CO_2 fractionated laser treatment outcomes compared to baseline.	Treatment was effective to improve GSM symptoms after three sessions (VHI).	No AEs were evidenced
Adabi, 2020[2]	The evaluation of improvement in vaginal health was realized with the VHI; the ICIQ evaluated UI.	The frequency of UI, enuresis, urgency, and the leak improved significantly ($P < 0.05$). Among the scale variables for urinary function, it was seen that the urgency impact had no improvement. All vaginal indices improved ($P < 0.05$).	No AEs were experienced by patients.
Aguiar, 2020[56]	Urinary symptoms were assessed using validated questionnaires, the ICIQ-UI SF, and the ICIQ-OAB.	There was a significant reduction in the total ICIQ-UI SF score in the intragroup comparison, of the CO_2 laser group ($P = 0.004$). This group also showed a statistically significant reduction in nocturia ($P = 0.031$). Regarding the total ICIQ-OAB score, the results of the CO_2 laser group were superior to those of the lubricant group in the intergroup comparison ($P = 0.038$).	No AEs were observed or reported in any of the treatment groups.
Alexiades, 2020[57]	VHI was used to assess changes in vaginal elasticity, fluid volume, vaginal pH, epithelial integrity, and moisture.	Treatment resulted in statistically significant improvements as compared with baseline at all post-treatment and follow-up intervals to 12 months in VHI ($P \leq 0.003$).	No AEs were associated with treatment.
Takacs, 2020[58]	Participants reported the intensity of the symptom of vaginal dryness using a 10-point VAS. The scale's left extremity indicates the complete absence of symptoms (0) and the right extremity indicates the worst possible symptom (10).	The vaginal dryness VAS was higher in postmenopausal women compared with premenopausal cases ($P < 0.01$). In both the premenopausal and postmenopausal groups, vaginal dryness scores improved significantly from baseline after the three treatments.	—

Abbreviations: AE, adverse event; GSM, genitourinary syndrome of menopause; ICIQ, International Consultation on Incontinence Questionnaires; ICIQ-FLUTS, Incontinence Questionnaire of Female Urinary Tract Symptoms; ICIQ-OAB, International Consultation on Incontinence Overactive Bladder; ICIQ-UI SF, ICIQ-Urinary Incontinence Short Form; ICIQ-VS, Consultation on Incontinence Questionnaire – Vaginal Symptoms; OAB-Q SF, Overactive Bladder Questionnaire Short Form; SUI, stress urinary incontinence; UDI-6, Urogenital Distress Inventory; UI, urinary incontinence; VAS, Visual Analog Scale; VHI, Vaginal Health Index; VVA, vulvovaginal atrophy.

data: names of authors; year of publication; country of origin; study design; sample, age (in years); inclusion criteria; therapeutic protocol; follow-up; and outcome measures. Data extraction was performed by three independent raters (CM, KSM, and APFC). In case the authors detected duplicate or secondary publications in the systematic review that involved the same populations, the researchers responsible for those studies were contacted to confirm the duplicated data, thus ensuring that duplicated data were not used in the systematic review. All authors independently evaluated the design of each study for quality of reporting, risk of bias, and quality of evidence. Quality of reporting was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[10] The risk of bias assessment was performed using the Newcastle-Ottawa Quality Assessment Scale for observational studies [11] and the Cochrane Collaboration risk of bias tool for randomized clinical trials.[12] Any discrepancies were resolved by consensus. As data were extracted and described, heterogeneity between the outcomes did not allow for pooling data and performing a subgroup analysis or meta-analysis. The results are displayed in Tables 2–5.

3 | RESULTS

The flowchart of the studies that comprise the present review are described in Figure 1. After searching the databases, 1993 articles were identified, of which 171 were excluded due to repetition. After reviewing titles and abstracts of articles, 1753 records were excluded, resulting in 69 records for full-text review. After reviewing the full-text articles, an additional 20 records were excluded. This process resulted in 49 articles,[1,2,4,13-58] which were further reviewed using a hand-searching approach. Table 2 displays all the selected studies. Of these, 37 were about the CO_2 laser,[1,2,4,13,14,17-19,22-27,29-31,33-37,39,42,45-47,49-58] 10 were about the Erbium laser,[15,16,20,32,38,40,41,43,44,48] and two were about

TABLE 4 Quality assessment of the included studies using the Newcastle Ottawa Scale[a]

Newcastle – Ottawa	Selection				Comparability	Outcome			
Item	1	2	3	4	1	1	2	3	Total
Salvatore, 2014[13]	☆	-	☆	-	☆	-	☆	☆	☆☆☆☆☆
Salvatore, 2014[14]	☆	-	☆	-	☆	-	☆	☆	☆☆☆☆☆
Gambacciani, 2015[15]	☆	☆	☆	-	☆	☆	-	☆	☆☆☆☆☆☆
Gambacciani, 2015[16]	☆	☆	☆	-	☆	☆	-	☆	☆☆☆☆☆☆
Perino, 2015[17]	☆	☆	☆	-	☆☆		-	☆	☆☆☆☆☆☆
Salvatore, 2015[18]	☆	☆	☆	-	☆	-	☆	☆	☆☆☆☆☆☆
Baggish, 2016[19]	☆	-	☆	-	☆	☆	☆	☆	☆☆☆☆☆☆
Gaspar, 2016[20]	☆	☆	☆	-	☆☆	☆	☆	-	☆☆☆☆☆☆☆
Murina, 2016[22]	☆	-	☆	-	☆	☆	-	☆	☆☆☆☆☆
Pagano, 2016[23]	☆	-	☆	-	☆	☆	-	-	☆☆☆☆
Perino, 2016[24]	-	-	☆	☆	☆☆	☆	-	-	☆☆☆☆☆
Pieralli, 2016[25]	☆	-	☆	-	☆	☆	-	-	☆☆☆☆
Pitsouni, 2016[26]	☆	-	☆	-	☆☆	☆	☆	☆	☆☆☆☆☆☆☆
Sokol, 2016[27]	☆	-	☆	-	☆	☆	-	☆	☆☆☆☆☆
Vicariotto, 2016[28]	-	-	☆	-	☆	☆	☆	☆	☆☆☆☆☆
Athanasiou, 2017[29]	☆	-	☆	-	☆	☆	-	☆	☆☆☆☆☆
Arroyo, 2017[30]	☆	☆	☆	-	☆	-	☆	-	☆☆☆☆☆
Gambacciani, 2017[32]	☆	-	☆	-	☆☆	☆	☆	☆	☆☆☆☆☆☆☆
Isaza, 2017[33]	☆	-	☆	-	☆	-	☆	☆	☆☆☆☆☆
Pitsouni, 2017[34]	☆	-	☆	☆	☆☆	☆	☆	☆	☆☆☆☆☆☆☆☆
Siliquini, 2017[35]	☆	-	☆	☆	☆☆	☆	☆	☆	☆☆☆☆☆☆☆☆
Sokol, 2017[36]	☆	-	☆	-	☆	☆	-	☆	☆☆☆☆☆
Athanasiou, 2018[4]	☆	-	☆	-	☆	☆	☆	☆	☆☆☆☆☆☆
Becorpi, 2018[37]	☆	-	☆	-	☆	☆	☆	-	☆☆☆☆☆
Eder, 2018[39]	☆	-	☆	☆	☆	☆	-	☆	☆☆☆☆☆☆
Gambacciani, 2018[40]	☆	-	☆	-	☆	-	☆	☆	☆☆☆☆☆
Gaspar, 2018[41]	☆	-	☆	-	☆	☆	-	-	☆☆☆☆
Mohajeri, 2018[42]	☆	-	-	☆	☆	-	-	☆	☆☆☆☆
Mothes, 2018[43]	☆	-	☆	☆	☆	☆	-	☆	☆☆☆☆☆☆
Mothes, 2018[44]	☆	-	☆	☆	☆	☆	-	☆	☆☆☆☆☆☆
Pagano, 2018 [45]	☆	-	☆	☆	☆	☆	-	☆	☆☆☆☆☆☆
Samuels, 2018[46]	☆	-	☆	-	☆	☆	☆	☆	☆☆☆☆☆☆
Singh, 2018[47]	☆	-	-	-	☆	☆	-	☆	☆☆☆☆
Arêas, 2019[48]	☆	-	☆	-	☆	☆	-	☆	☆☆☆☆☆
Bence, 2019[49]	☆	-	☆	-	☆	☆	-	-	☆☆☆☆
Filippini, 2019[50]	☆	☆	-	-	☆☆	☆	☆	☆	☆☆☆☆☆☆☆
Murina, 2019[51]	☆	-	☆	-	☆	☆	-	☆	☆☆☆☆☆
Pearson, 2019[53]	☆	-	☆	-	☆	☆	-	☆	☆☆☆☆☆
Sipos, 2019[54]	☆	-	☆	☆	☆	-	-	-	☆☆☆☆
Tovar-Huamani, 2019[55]	☆	☆	-	☆	☆	☆	☆	-	☆☆☆☆☆☆
Adabi, 2020[2]	☆	-	☆	☆	☆	☆	-	-	☆☆☆☆☆
Alexiades, 2020[57]	☆	-	☆	-	☆	☆	☆	-	☆☆☆☆☆
Takacs, 2020[58]	☆	-	☆	☆	☆	☆	☆	-	☆☆☆☆☆☆

[a]Newcastle - Ottawa Quality Assessment Scale: 0–3 = poor; >3–6 = fair; >6–8 = good; >8–9 = excellent.[10]

TABLE 5 Quality assessment of the included studies using the Cochrane risk of bias tool.[a]

Study/Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Leibaschoff, 2016[21]	+	+	+	+	?	?	?
Cruz, 2017[31]	+	+	+	?	+	+	-
Blaganje, 2018[38]	+	+	+	+	+	+	?
Paraiso, 2019[52]	+	?	+	?	+	+	?
Politano, 2019[1]	+	+	+	+	+	+	+
Aguiar, 2020[56]	+	+	-	-	+	+	+

[a]Cochrane Collaboration risk of bias tool: - high risk of bias; ? unclear risk of bias; + low risk of bias.[11]

radiofrequency.[21,28] Outcomes of the studies included in the systematic review are shown in Table 3.

In the 37 studies on the CO_2 laser,[1,2,4,13,14,17-19,22-27,29-31,33-37,39,42,45-47,49-58] a total of 2513 women were included (mean age 55.04 years). A total of 22 studies were prospective,[2,13,14,17,18,22,24,26,27,29,30,33,35-37,39,42,46,49,53,55,57] six were retrospective,[4,23,34,45,50,51] five were cohort,[19,25,47,54,58] and four were randomized clinical trials.[1,31,52,56] Most of these studies were conducted in Italy (n = 13)[13,14,17,18,22-25,35,37,45,50,51] followed by the USA (n = 7),[19,27,36,39,46,52,57] Greece (n = 4),[4,26,29,34] Brazil (n = 3),[1,31,56] Hungary (n = 3),[49,54,58] Iran (n = 2),[2,42] Colombia (n = 1),[33] Spain (n = 1),[30] Singapore (n = 1),[47] Australia (n = 1),[53] and Peru (n = 1).[55]

All the treatment protocols in these studies involved three sessions of laser[1,2,4,13,14,17-19,22-27,29-31,33-37,39,42,45-47,49-58]; however, the interval between sessions varied from 30 days[1,4,13,14,17,22-25,28,29,33-35,37,42,45-47,51,55-57] to 4 and 6 weeks,[2,18,19,27,30,31,36,39,49,52-54,58] and one study did not specify this data.[50] The assessment of outcomes were in the range of 0–24 weeks and 0–36 months after laser treatment.

The studies evaluated vaginal status using the VHI[1,13,14,17,19,24-27,29-31,34,35,37,39,46,47,49,50,52,55,57] and the subjective intensity of the symptoms of VVA using a VAS.[4,14,17-19,22-25,27,29,31,34,35,45-47,49-53,55,58] For the measurement of frequency, urgency, nocturia, and leakage, the ICIQ-OABqSF[24,42,55,56] and UDI-6[4,26,42,52,54] were used. Validated questionnaires on urinary incontinence, ICIQ-UIF SF,[2,4,26,33,46,56] and ICIQ-FLUTS[4,26,34] were also used. No adverse events due to fractional CO_2 laser treatment took place: only a temporary mild irritation of the introitus was noted, which started immediately after the laser treatment and resolved spontaneously.

In the 10 studies on Er:YAG lasers,[15,16,20,32,38,40,41,43,44,48] a total of 722 women were included (mean age 58.27 years). The treatment protocol in most of the studies involved three sessions[15,16,20,32,40,41,48] of laser treatment, while in only three studies, it involved one session.[38,43,44] Outcomes were assessed at 4, 6, 12, and 24 weeks up to 1, 3, 6, and 24 months after laser treatment. Seven studies were prospective,[15,16,32,40,41,44,48] one was cohort,[20] one was retrospective,[43] and one was a randomized clinical trial.[38] Most of the studies were conducted in Italy (n = 4),[15,16,32,40] followed by Argentina (n = 2),[20,41] Germany (n = 2),[43,44] Brazil (n = 1),[48] and Slovenia (n = 1).[38]

In these studies, GSM was evaluated either with subjective (VAS)[15,16,20,32,40,41] or objective (VHI) measures.[15,16,32,40,43,44,48] In addition, patients with stress urinary incontinence (SUI) with a degree of incontinence were evaluated with the ICIQ-UI SF.[15,16,38,40,41] Treatment was well tolerated and no significant adverse effects were observed.

In the two studies on radiofrequency,[21,28] 43 women were included (mean age 53.5 years). One study was a prospective, descriptive, double-blind randomized controlled trial,[21] and the other was prospective, exploratory, and open label.[28] One study was from Italy[28] and the other from Colombia.[21] In these studies, the treatment protocol involved three [21] and five [28] sessions of radiofrequency.

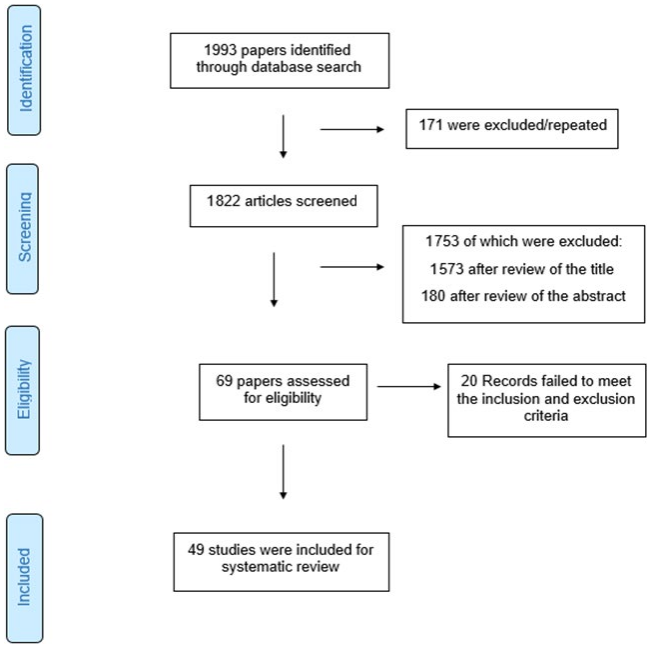

FIGURE 1 Flow diagram of the search process

Assessment of outcomes was performed 30 and 60 days [28] and 12 weeks [21] after the last session of radiofrequency.

In these two studies, urinary symptoms were evaluated, and SUI was subjectively evaluated with subjective UDI-6[21] and with the ICIQ-UI SF.[21] Vaginal health was evaluated using the VHI score and VAS for dryness and dyspareunia.[21,28] None of the studies presented significant adverse effects.

4 | DISCUSSION

The present study found vast evidence to support the hypothesis that laser therapy is effective and safe in postmenopausal women with GSM/urinary incontinence. However, there is little evidence to support the hypothesis that radiofrequency therapy is safe and effective for GSM.

Previous reviews that assessed randomized controlled trials and observational studies also found evidence suggesting that laser treatment improves vaginal health, vaginal atrophy, and symptoms of urinary incontinence.[3,59-61] However, it is believed that no previous review has been conducted on studies using radiofrequency.

It should be noted that Pitsouni et al.[3] conducted a meta-analysis of the efficacy of laser therapy for postmenopausal women with GSM with/without urinary incontinence. Jha et al.[59] also conducted a systematic review and meta-analysis on the impact of vaginal laser treatment for GSM in survivors of breast cancer. The authors of these studies used inclusion criteria that were different from those used in the present study, and thus their search was less comprehensive. It is important to note that most reviews are focused on assessing sexual function,[60,61] which was not the objective of the present study. Finally, it is important to note that none of the reviews previously carried out addressed data on the use of radiofrequency.

The CO_2 laser was among the first gas lasers to be developed and is still one of the most commonly used lasers, as it has the largest body of scientific evidence detailing the efficacy of its use in the treatment of GSM. Therefore, it is not unexpected that the studies included in the present review were predominantly focused on the microablative fractional CO_2 laser. The CO_2 laser seems to be an efficacious therapy for the management of all symptoms of GSM up to 12 months after treatment, irrespective of the number of sessions of laser therapy. The VHI score was significantly improved. There was an improvement in elasticity, volume of fluid, pH, epithelial integrity, and vaginal moisture. VAS scores were significant for sensitivity, itching/stinging/ vaginal dryness, dyspareunia, and dysuria.[1,2,4,13,14,17-19,22-27,29-31,33-37,39,42,45-47,49-58]

Treatment with the Er:YAG laser showed that this method could be effective, practical, and safe, and the effects are rapid and sustained for at least 12 months. Application of the Er:YAG laser is associated with an improvement in VVA, and such treatment induced a significant decrease in VAS, an increase of VHI, and a significant improvement in urinary incontinence. This treatment is more pronounced and lasts longer than treatment with topical estriol.[15,16,20,32,38,40,41,43,44,48] The results obtained in the present review are in line with the results obtained in previous reviews,[3,59-61] where it was observed that the CO_2 / YAG laser may be effective in treating GSM, reducing the severity of symptoms of VVA, restoring the vaginal mucosa, and thus improving the quality of life of these women. The studies also pointed out that laser therapy in the urological area can be a useful substitute and a promising complement for therapies that are not well accepted by patients, such as the administration of hormones, pelvic floor exercises, or surgery. It should be emphasized that the reviewers agree on the low quality of the studies involved, which limits the confidence in the results and confirms the need for further studies.

TTCRF seems a safe and effective non-surgical option for the treatment of mild to moderate SUI and other symptoms related to GSM, while the dynamic quadripolar radiofrequency therapy promotes rapid and persistent vaginal rejuvenation based on subjective improvement in symptoms including dysuria and urinary incontinence in menopausal women. In both treatments, significant improvements were observed in the mean VAS score and for symptoms of VVA.[21,28] Little is known about the effectiveness of the use of radiofrequency in the treatment of GSM/urinary incontinence, since, as has already been reported in the present review, the current literature on this topic is still sparse. Some available studies indicate that intravaginal, non-ablative, and energy-based devices appear to be a promising alternative for the treatment of mild to moderate symptoms related to GSM.[6,7]

Treatments using laser and radiofrequency could be considered safe, with no severe side effects; however, moderate to mild side effects were observed. It is important to highlight the lack of these data in some studies, which casts doubt on the actual safety of the treatment.

It is important to clarify that the present study had some limitations. The majority of the identified studies were not randomized clinical trials. Hence, the possible placebo effect of the treatment cannot be ruled out. The assessment of the risk of bias was performed using the Newcastle-Ottawa scale (on the study and outcome level) and demonstrated that the average quality was good (5.46/9), with studies by Pitsouni et al.[34] and Siliquini et al.[35] being very good (8/9). Quality assessment of the individual studies using the Newcastle Ottawa Score is shown in Table 4. The studies exhibited some type of weakness in all domains. In the selection domain, the main weaknesses were the lack of description of the derivation of the exposed population and the lack of description of unexposed groups. In the comparability domain, the main weakness was the lack of sufficient description of the groups. In the results domain, a lack of independent blind evaluation and insufficient follow-up time for the results to occur were observed. However, the clinical trials presented moderate to low risk of bias. Quality assessment of the clinical trial using the Cochrane risk of bias is shown in Table 5.

The main flaws observed in the studies were the lack of blinding of both the patients as well as researchers involved in the study and outcome assessment. Consequently, the findings of the present study cannot be generalized until new randomized clinical trials are performed to confirm the strength of the evidence.

5 | CONCLUSION

In conclusion, laser and radiofrequency therapy could be promising and safe options for non-pharmaceutical therapies for GSM/urinary incontinence in both clinical and pathophysiological aspects. However, the quality of the body of evidence is "low" or "very low," and the possible placebo effect of the treatment has not yet been ruled out or estimated, since there are limited data regarding the use of radiofrequency in women with GSM/urinary incontinence. It is essential that there should be well-designed controlled studies with standardized settings and therapeutic protocols with a long duration of follow-up and consistent outcome evaluations, comparing laser and radiofrequency therapy to placebo or other treatment modalities and/or evaluating the pathway and mechanism of action on the vaginal mucosa so that safe conclusions can be derived.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors made substantive intellectual contributions to the development of this manuscript. ACAS and AKS contributed to the study conception and design and conceptualized the review approach. JFL, KSM, CM, and APFC contributed to the screening, study selection, data charting, and data extraction. ACAS and AKS wrote the manuscript. All authors provided detailed comments on earlier drafts and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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