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REVIEW

The evidence behind the use of LASER for genitourinary syndrome of menopause, vulvovaginal atrophy, urinary incontinence and lichen sclerosus: A state-of-the-art review

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Abstract

In recent years, LASER has been introduced as a minimally invasive treatment for a broad range of vaginal and vulvar symptoms and diseases. However, the efficacy and safety of vaginal and vulvar LASER has continuously been questioned. The aim of this study is to create an overview of the current literature and discuss the controversies within the use of LASER for genitourinary syndrome of menopause, vulvovaginal atrophy, urinary incontinence and lichen sclerosus. A search string was built in PubMed. The search was commenced on August 25, 2021 and closed on October 27, 2021. Two authors screened the studies in Covidence for inclusion according to the eligibility criteria in the protocol. The data were extracted from the studies and are reported in both text and tables. This review included 114 papers, of which 15 were randomized controlled trials (RCTs). The effect of LASER as a vaginal treatment was investigated for genitourinary syndrome of menopause in 36 studies (six RCTs), vulvovaginal atrophy in 34 studies (four RCTs) and urinary incontinence in 30 studies (two RCTs). Ten studies (three RCTs) investigated the effect of vulvar treatment for lichen sclerosus. Half of the included RCTs, irrespective of indication, did not find a significant difference in improvement in women treated with vaginal CO_2 or Er:YAG LASER compared with their respective controls. However, most non-comparative studies reported significant improvement after exposure to vaginal or vulvar LASER across all indications. Included studies generally had a short follow-up period and only a single RCT followed their participants for more than 6 months post treatment. Adverse events were reported as mild and transient and 99 studies including 51 094 patients provided information of no serious adverse events. In conclusion, this review found that the effect of vaginal and vulvar LASER decreases with higher study quality where potential biases have been eliminated. We therefore stress that all patients who are treated with vaginal or vulvar LASER should be carefully monitored and that LASER for those

Abbreviations: AE, adverse event; Er:YAG, erbium:yttrium-aluminum-garnet; GSM, genitourinary syndrome of menopause; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire - Urinary Incontinence—Short Form; IQR, interquartile range; LASER, light amplification by stimulated emission of radiation; LS, lichen sclerosus; Nd:YAG, neodymium-doped:yttrium-aluminum-garnet; RCT, randomized controlled trial; SAE, severe adverse event; UI, urinary incontinence; VAS, Visual Analog Scale; VVA, vulvovaginal atrophy.

indications as a treatment should be kept on a research level until further high-quality evidence is available.

KEYWORDS
atrophy, CO_2 LASER, genitourinary syndrome, incontinence lichen, vaginal LASER

1 | INTRODUCTION

Female urogenital disorders affect the quality of life in several ways, physically, socially, emotionally and sexually, as detected in a study which found that more than 45% of postmenopausal women experience bothersome symptoms related to genitourinary syndrome of menopause (GSM), possibly having a negative impact on quality of life. This reflects the importance of an innovative approach within the therapeutic field of urogenital diseases.[1]

The diagnostic term GSM was introduced in 2014 by North American Menopause Society and refers to vaginal, sexual and urinary symptoms caused by an estrogen deficiency in menopausal women and cancer survivors. This new diagnostic term has not replaced the diagnostic term vulvovaginal atrophy (VVA), which is characterized by vaginal dryness, burning, itching and pain. In many women, VVA and urinary incontinence (UI) occur at the same time.[2,3] Types of UI comprise stress UI, urge UI and mixed UI. UI may be associated with estrogen deficiency, which leads to a change in the metabolism of the connective tissue and pelvic floor dysfunction.[4] Treatment of symptoms related to the estrogen deficiency consist of hormonal treatment (estrogen, dehydroepiandrosterone (DHEA), etc.) and non-hormonal treatment (lifestyle changes, moisturizers, etc.); however, women with relative contraindications to hormonal therapy are seeking non-hormonal options such as light amplification by stimulated emission of radiation (LASER) technology. Studies have suggested that LASER technology may also help patients who suffer from vulvar lichen sclerosus (LS).[5,6]

LASER has been used as a minimally invasive technology for a selection of diseases and symptoms within the gynecologic field for some years. Carbon dioxide (CO_2) LASER was one of the earliest LASERs to appear in the 1960s, along with the erbium:yttrium-aluminum-garnet (Er:YAG) LASER and the neodymium-doped:yttrium-aluminum-garnet (Nd:YAG) LASER.[7] In July 2018, the U.S. Food and Drug Administration released an alert about adverse events (AE) related to the vaginal LASER based on 14 cases of vaginal burns, scarring, acute and chronic pain.[8,9] In 2019, Preti et al. released a best practice document questioning the clinical trials and evidence behind the use of LASER in gynecology. Today, LASER is not recommended for general gynecologic use.[10]

Vaginal and vulvar LASER are performed with a handpiece and each of the impulses is fired by the treating operator, who decides the number of impulses; the treatment takes only a few minutes. The LASER generates small impulses which exit through a small window affecting the mucosa of the tissue.[11] Previous cohort studies (Table 1) reported the histologic and immunologic effects of LASER, which encompass a change in epithelial proliferation and cellularity.[12–20] Biopsies have shown that the lamina propria in the vaginal mucosa developed neo-angiogenesis[12,14–17,20] and neo-collagenesis,[14,15] representing a higher concentration of cytokines and fibroblasts.[12,14–19] Nevertheless, these studies do not differentiate between regeneration and healing from LASER, which questions the durability of the LASER effect. In a randomized controlled trial (RCT), Mackowa et al. investigated the histology in menopausal animals and concluded that Er:YAG LASER was not better than sham-LASER and was inferior to estrogen replacement for increasing epithelial thickness.[21]

Key message

LASER technology is not yet recommended for routine treatment of genitourinary syndrome of menopause, vulvovaginal atrophy, urinary incontinence or lichen sclerosus, as high-quality studies, including RCTs, are missing within the field. However, in the more than 50 000 women having LASER in studies, no serious short-term adverse events are described.

This review aimed to identify the evidence behind gynecologic LASER for the indications GSM, VVA, UI and LS.

2 | MATERIAL AND METHODS

This review is an exploratory investigation of the evidence available on vaginal and vulvar LASER.

2.1 | Eligibility criteria

The authors set up an internal protocol to use as a guideline for the review, listing the criteria and outcomes for this review. The eligibility criteria for this state-of-the-art review adhered to the principals of PICO—participants, interventions, comparison and outcome. Studies that investigated the effect of any vaginal and vulvar LASER on women with symptoms of GSM, VVA, UI or LS were eligible for inclusion. No outcome restrictions were applied. Only original studies were included; unpublished work, editorials, conference abstracts, reviews and meta-analysis were excluded. Likewise, in vivo studies on animals, histologic cohort studies, and studies of the effect of radiofrequency treatment were excluded.

TABLE 1 Histologic and immunologic findings

Indication	LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years)[b]; menopause status	Treatment settings	No. treatments, interval	Conclusion	Adverse events
GSM	CO_2	Pagano et al. (2021)[12]	Italy	Cohort	N/A	20	58.7 ± 6.6; Postmenopausal	Internal: 30 W, stack 1–3. External: 24 W, stack 1	3 sessions, 1 months	Remodeling of vulvar connective tissue, improvement in vulvar epithelium trophism, and neovascularization	N/A
		Athanasiou et al. (2016)[13]	Greece	Cohort	3 months, first	53	57.2 ± 5.4; Postmenopausal	40 W, stack 1–3	3 sessions, 1 months	Significant reduction in vaginal pH, increase in *Lactobacillus* morphotypes and improvement in vaginal epithelia	No SAE. Transient: mild irritation of the introitus
UI	Er:YAG	Lapii et al. (2017)[14]	Russia	Cohort	2 months, last	98	49.0 ± 12.5; N/A	2940 nm	2 sessions, 1–1.5 months	Neo-collagengenesis. Elastogenesis. Neo-angiogenesis. Reduction of epithelial degeneration and atrophy. Improvement in fibroblast population	N/A
		Lapii et al. (2017)[15]	Russia	Cohort	2 months, last	18	49 ± 12.5; N/A	2940 nm	N/A	Significant improvement in Ki-67-labeled nuclei. Epithelial proliferative activity. Neocollagenogenesis. Neoangiogenesis. High concentration of elastic fibers	N/A

(Continues)

TABLE 1 (Continued)

Indication	LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years)[b]; menopause status	Treatment settings	No. treatments, interval	Conclusion	Adverse events
VVA	CO_2	Salvatore et al. (2018)[16]	Italy	Cohort	N/A	1	63; Postmenopausal	30 W	1 session	Thicker epithelium, and cells are larger. Connective tissue different; numerous papillae, richer in blood vessels, and many fibroblasts	N/A
		Zerbinati et al. (2014)[17]	Italy	Other	2 months, last	5	57 (54–63); Postmenopausal	100 mJ	1 session	Improvement in fibroblasts and rough endoplasmatic reticulum. Thicker epithelium. Large amount of glycogen. Improvement in capillaries	No SAE
		Becorpi et al. (2018)[18]	Italy	Cohort	1 months, last	20	58.2; Postmenopausal	30 W, stack 1	N/A	High remodeling status in vaginal epithelium is demonstrated by the significant changes in inflammatory and modulatory cytokine patterns. No significant change in the bacteria	N/A
		Salvatore et al. (2015)[19]	Italy	Cohort	N/A	5	63 (57–71); Postmenopausal	30 W	1 session	Changes in the epithelium and lamina propria in relation to mild ablative effects, fibroblasts activation, modifications of collagen, elastic fibers, and mucopolysaccharides in the lamina propria	N/A
	Er:YAG	Gaspar et al. (2020)[20]	Argentina	Cohort	6 months, last	10	60.6 ± 6.82; Postmenopausal	6.0 J/cm^2	2 sessions, 1 months	Improvement in epithelial thickness. Significant improvement in glycogen load, new papillae and neo-angiogenesis in lamina propria with capillaries reaching the epithelium	No SAE

General characteristics, findings, and adverse events in included studies. The table is sorted by (1) treatment indication, (2) LASER type, (3) year of publication and (4) author name.

Abbreviations: cm^2, square centimeter(s); CO_2, Carbon Dioxide LASER; Er:YAG, Erbium:Yttrium-Aluminum-Garnet LASER; GSM, genitourinary syndrome of menopause; J, joule; mJ, milijoule; N/A, not available or not applicable; SAE, severe adverse event(s); UI, urinary incontinence; VVA, vulvovaginal atrophy; W, watt.

[a]Follow-up is reported as time from initial treatment session (first) or final treatment session (last).

[b]Age is reported in mean ± SD unless otherwise specified.

Language restrictions were applied and only studies in English were included.

2.2 | Search strategy

The search string was generated in the PubMed database. The search terms were branched in treatment-associated search terms and symptom- and disease-associated search terms (Table 2). The PubMed search was commenced August 25 and closed October 27, 2021. Titles and abstracts and were screened by two authors (OEM and SEC) to meet the eligibility criteria listed above. Subsequently, the two authors performed a full-text screening on the papers. The reference lists of systematic reviews and meta-analyses identified through the initial database search were also screened to find additional studies. The authors used Covidence for the screening process.[22] If any discrepancies about the eligibility criteria occurred, the papers were re-screened until consensus was reached. Two authors (OEM and SEC) performed the data extraction.

3 | RESULTS

A total of 114 papers were included according to the eligibility criteria listed above. Of these, 111 studies investigated GSM, VVA, UI, and LS symptoms as primary indication (Tables 3–6); 15 RCT,[23–37] 87 cohort studies,[38–124] eight case reports,[125–132] one case-control study,[133] including a total of 9000 women, not accounting for overlap between the studies. Additionally, three cross-sectional studies focused solely on the characteristics of AEs.[134–136] The full screening process is shown in Figure 1.

Of the included studies, 81 studies investigated CO_2 -LASER from different manufacturers.[23–31,33,35,36,38–58,66–93,95–104,122–125,128–131,133,136] Twenty-eight studies investigated Er:YAG LASER from different manufacturers.[32,34,59–65,94,107–121,127,132,135] Three studies reported on CO_2 or Er:YAG simultaneously.[105,126,134] One study investigated the effect of CO_2 -LASER in combination with a platelet-rich plasma injection.[106] A single study investigated the effect of a Nd:YAG LASER.[37] The most common energy setting reported for internal CO_2 LASER application is 30–40 W and for the Er.YAG LASER 3–10 J/cm^2. Year of publication ranged from 1997 to 2021, with a median (interquartile range [IQR]) of articles published in 2019 (2017–2020).

TABLE 2 The search string in PubMed

Treatment		Indication
Vaginal LASER OR CO_2 LASER OR Energy based device OR Fractional CO_2 LASER OR	AND	Atrophy PR Lichen OR Incontinence OR Genitourinary Syndrome

(((((((Fractional CO_2 LASER) OR (energy based devices)) OR (CO_2 LASER)) OR (LASER therapy)) OR (Vaginal LASER)) AND (Incontinence)) OR ((((((Fractional CO_2 LASER) OR (energy based devices)) OR (CO_2 LASER)) OR (LASER therapy)) OR (Vaginal LASER)) AND (lichen sclerosus))) OR ((((((Fractional CO_2 LASER) OR (energy based devices)) OR (CO_2 LASER)) OR (LASER therapy)) OR (Vaginal LASER)) AND (Vaginal atrophy)) OR ((((((Fractional CO_2 LASER) OR (energy based devices)) OR (CO_2 LASER)) OR (LASER therapy)) OR (Vaginal LASER)) AND (genitourinary syndrome)).

3.1 | Genitourinary syndrome of menopause

Thirty-six studies on the effect of vaginal LASER on GSM were identified through this review (Table 3).[23,24,26–28,38–65,70,125,133] The studies included 4220 women with study sizes ranging from 4 to 1081 women with a median (IQR) of 60.5 (42.25–75.25) women. Among these studies, 29 studies investigated the effect of CO_2 LASER,[23–28,38–58,125,133] counting six RCTs including 336 women[23–28], and 21 cohort studies including 2251 women.[38–58] Seven cohort studies including 1579 women investigated the effect of Er:YAG.[59–65]

Three RCTs with a total of 137 women who received either CO_2 LASER or sham LASER reported no significant between-group difference in subjective and objective measures at a follow-up of 1–12 months.[23,24,26] In contrast, Salvatore et al. used CO_2 LASER or sham LASER on 58 women and found a significantly higher improvement in visual analog scale (VAS) at the 1-month follow-up in the CO_2 group compared with sham LASER.[25] Two RCTs of 141 women compared LASER with estrogen treatment using the Vaginal Health Index Score, Vaginal Maturation Index (VMI), and Female Sexual Function Index (FSFI); Politano et al. found a significant between-group improvement at a 14-week follow-up favoring the LASER group,[28] whereas Paraiso et al.[27] found no significant difference in improvement at a 6-month follow-up.

In observational studies, data from 2089 women exposed to CO_2 LASER[38,40–58] and 1579 women exposed to Er:YAG[59–61,64,65,137,138] showed improvement across outcome measures of subjective and objective symptom severity, sexual function and UI symptoms. Of 3880 women exposed to either CO_2 or Er:YAG in observational studies, 940 were followed for 12 months or more.[39,40,42,44,47,53,55,60–62]

3.2 | Vulvovaginal atrophy

Thirty-four studies examining the effect of vaginal LASER on VVA were identified through this review (Table 4).[29–32,66–94,126] The studies include 2464 women with study sizes ranging from 2 to 386 women with a median (IQR) of 46 (28.25–86.5) women. Among these studies, 31 studies investigated the effect of CO_2 LASER[29–31,66–93] and two studies the effect of Er:YAG.[32,94] Four RCTs included 188 women[29–32] and 29 cohort studies included 2274 women;[66–94] a case report of two cases included one case treated with CO_2 and one with Er:YAG for VVA.[126]

Two RCTs randomized 70 women to topical hormone treatment, CO_2 LASER or a combination of these; no significant histologic [29] or

TABLE 3 Genitourinary syndrome of menopause

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years);[b] menopause status	Treatment settings
CO_2	Cruff & Khandwala (2021)[23]	USA	RCT	6 months, first	34	Median (IQR): LASER = 61 (54–66), sham = 59 (56–65); Postmenopausal	Internal: 30 W, stack 1–3. External: 26 W, stack 1
	Li et al. (2021)[24]	Australia	RCT	12 months, first	85	57 ± 8; Postmenopausal	40 W, stack 2
	Quick et al. (2021)[26]	USA	RCT	4 weeks, last	18	56.3 ± 8.98; N/A	Internal: 30 W, stack 1–3 External: 26 W, stack 1
	Paraiso et al. (2020)[27]	USA	RCT	6 months, last	69	61 ± 7; Postmenopausal	Internal: 30 W, stack 1–3 External: 26 W, stack 1
	Salvatore et al. (2020)[25]	Italy	RCT	1 months, last	58	LASER = 57.0 ± 6.9, sham = 58.4 ± 6.0; Postmenopausal	Internal: 30 W, stack 1–3. External: 24 W, stack 1
	Politano et al. (2019)[28]	Brazil	RCT	14 weeks, last	72	1: 57.83 ± 5.01. 2: 57.21 ± 5.26. 3: 56.79 ± 5.33; Postmenopausal	40 W, stack 2
	Bretas et al. (2021)[38]	Brazil	Cohort	20 weeks, first	14	54.4 ± 4.5; Postmenopausal	60 mJ (1st), 75 mJ (2nd) and 90 mJ (3rd).
	Li et al. (2021)[39]	China	Cohort	12 months, last	162	56.56 ± 7.59; Postmenopausal	35–40 W, stack 1 or 2
	Quick et al. (2021)[40]	USA	Cohort	12 months, last	67	57.4 ± 9.5; Postmenopausal	Internal: 30 W, stack 1 and 3 External: 26 W, stack 1
	Ruffolo et al. (2021)[41]	Italy	Cohort	16 weeks, first	61	A: 57.18 ± 5.27 B: 58.07 ± 7.21	30 W, stack 1–3
	Siliquini et al. (2021)[42]	Italy	Cohort	12 months, last	135	BC: 60.62 ± 8.18. No BC: 58.37 ± 8.40; Postmenopausal	Internal: 40 W, stack 1–3. External: 15–35 W, stack 1–2

No. treatments, interval	Comparison	Outcome	Conclusion	Adverse events
3 sessions, 6 weeks	Sham LASER	Primary: 2-stage improvement in GSM symptoms. Secondary: VHIS, FSFI, DIVA, UDI-6, modified PGI-I and VAS for GSM	No significant difference between improvement in sham vs LASER at 6 months, but the study lacked power	No SAE
3 sessions, 1 months	Sham LASER (1:1)	Primary: VAS for symptom severity and VSQ. Secondary: QoL, SS, VHIS, vaginal histology, and cytology	No significant between-group difference in change in overall VAS, VAS for most severe symptom or VSQ score, but scores improved in both groups at follow-up	No SAE. AE: LASER ($n = 16$) vs sham ($n = 17$); vaginal pain/discomfort (44% vs 68%), spotting (30% vs 5%), lower urinary tract symptoms or confirmed UTI (15% vs 5%), and vaginal discharge (11% vs 11%). Upper UTI in LASER group ($n = 1$)
3 sessions, 1 months	Sham LASER (1:1)	Primary: VAS*. Secondary: VuAS, FSFI, UDI-6, objective vaginal symptoms	No significant difference in overall VAS* from baseline to follow-up between active vs sham group	No SAE. AE: discharge ($n = 3$), dryness ($n = 3$), pain ($n = 1$), inflammation ($n = 2$), flank pain ($n = 1$) (unrelated)
3 sessions, 6 weeks	Vaginal estrogen (1:1)	Primary: VAS for GSM symptoms. Secondary: VHIS, VMI, Quality of Life FSFI, DIVA and UDI-6.	No significant difference in any VAS scores from baseline to follow-up between treatment groups	No SAE. AE: Vaginal bleeding ($n = 2$), vaginal pain ($n = 1$), vaginal discharge ($n = 1$), UTI ($n = 1$)
3 sessions, 1 months	Sham LASER (1:1)	Primary; VAS for dryness and dyspareunia. Secondary: FSFI, UDI-6	Significantly lower VAS for dryness and dyspareunia in the LASER group compared with sham LASER	No SAE. Transient: mild irritation of the vulva ($n = 28/28$ active)
3 sessions, 1 months	1) CO_2 LASER, 2) intravaginal promestriene, 3) vaginal lubricant (1:1:1)	Primary: VHIS and VMI Secondary: FSFI	Significant difference in improvement in VHIS, with highest score in the LASER group, then promestriene and lastly lubricant	NO SAE or AE
3 sessions, 1 months	B&A treatment	Primary: VHIS, FSFI, ICIQ-SF and histologic analyses of the vaginal wall	Significant improvement in VHIS, FSFI and ICIQ-SF cores but not in vaginal pH at week 20	No SAE. Transient: dysuria ($n = 2$), vaginosis ($n = 2$)
2–3 sessions, 4 ± 1 week	Topical estriol cream ($n = 54$)	Primary: VHIS and VAS for GSM symptoms	No significant between-group difference in VAS and VHIS. VHIS were significantly better at 12 months than at baseline for both groups	No SAE
3 sessions, 30–45 days	B&A treatment	Primary: FSFI and FSDS-R	Significant improvement in FSFI and FSDS-R scores was found at 12 months, but FSFI still indicated sexual problems	No SAE
3 sessions, 1 months	Symptoms before menopause (A) vs postmenopausal (B).	Primary: UDI-6 and ICIQ-SF. Secondary: VAS for VVA symptoms	Significant improvement in postmenopausal contra menopausal. Significant improvement in VVA symptoms	No SAE. Transient: vaginal burning ($n = 3$)
3 sessions, 1 months	BC and no BC	Primary: VHI, VVHI, VAS (dyspareunia and dryness), procedure-related pain	Significant improvement in VHI and VAS in both groups	No SAE

(Continues)

TABLE 3 (Continued)

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years);[b] menopause status	Treatment settings
	Sindou-Faurie et al. (2021)[43]	France	Cohort	3 months, last	46	57.3 ± 11.1; Postmenopausal ($n = 43$)	30–35 W, N/A
	Veron et al. (2021)[44]	France	Cohort	18 months, last	46	Median (IQR): 56.6 (47–59.4); Postmenopausal	26 to 40 W, stack 1–3
	Filippini et al. (2020)[45]	Italy	Cohort	Open, yearly follow-up	645	Median: 56 ± 7.9; Postmenopausal	Internal: 40 W, stack 1–2. External: 30 W, stack 1
	Takacs et al. (2020)[46]	USA	Cohort	6 weeks, last	52	Premenopausal: 46 ± 6. Postmenopausal: 63 ± 6	30 W, stack 1
	Athanasiou et al. (2019)[47]	Greece	Cohort	12 months, last	94	Median (IQR) 3: 57 (45–71), 4: 57 (44–71), 5: 57 (52–61); Postmenopausal	Internal: 30–40 W, stack 1–3. External: 24 W, stack 1
	Gittens et al. (2019)[48]	USA	Cohort	N/A	25	55.2 ± 9.5; Postmenopausal	N/A
	Murina et al. (2019)[49]	Italy	Cohort	3 months, last	72	1: 56 ± 6.1, 2: 55 ± 5.9; Postmenopausal	30 W, stack 2
	Quick et al. (2019)[50]	Germany	Cohort	1 months, last	64	57.4 ± 9.5; N/A	30 W, stack 1–3
	Tovar-Huamani et al. (2019)[51]	Perú	Cohort	1 months, last	60	Median (IQR): 55 (49–69); Postmenopausal	40 W, N/A
	Athanasiou et al. (2017)[52]	Greece	Cohort	1 months, last	55	57 ± 14; Postmenopausal	N/A
	Behnia-Willison et al. (2017)[53]	Australia	Cohort	24 months, last	102	61 ± 7; Postmenopausal	30 W, stack 2
	Lang et al. (2017)[54]	USA	Cohort	Mean of 31.7 ± 21 weeks, last	368	62 ± 8; 90% postmenopausal	N/A
	Sokol et al. (2017)[55]	USA	Cohort	1 year, last	30	58.6 ± 8.8; Postmenopausal	30 W, stack 1–3

No. treatments, interval	Comparison	Outcome	Conclusion	Adverse events
3 sessions, 1 months	B&A treatment	Primary: QoL, VAS, and FSFI	Significant improvement in dryness and stress urinary incontinence	N/A
3 sessions, 1 months	B&A treatment	Primary: SF12, FSFI, and Ditrovie score. Secondary: Vaginal pH and maturity pattern on SMEAR	Significant improvement in FSFI. Improvement in Ditrovie scale	No SAE. Transient: vaginal bleeding ($n = 3$)
3 sessions, N/A	B&A treatment	Primary: VAS	Significant improvement in VAS symptoms dryness, dyspareunia, burning, pain and itching	No SAE or AE
3 sessions, 1 months	B&A treatment	Primary: VAS and Vaginal Maturation Values	Significant improvement in VAS for both groups	N/A
N/A	3, 4 or 5 sessions	Primary: VAS, FSFI, ICIQ, and UDI-6	Significant improvement in all groups in VAS and FSFI. Differences between 4 and 5 sessions not found	No SAE
3 sessions, N/A	B&A treatment	Primary: FSFI, WBFS, FSDS-R	Significant improvement in every domain of FSFI, WBFS, and FSDS-R	No SAE
3 sessions, 1 months	1) LASER + ospemifene and 2) LASER only	Primary: VHS and VAS	Significant overall within-group improvement. Dryness and dyspareunia significant higher in LASER + ospemifene group vs LASER group	No SAE. Transient: mild to moderate pain and edema
3 sessions, 1 months	B&A treatment	Primary: VAS and SAE. Secondary: FSFI, UDI	Improvement in VAS, FSFI, and UDI	No SAE. Transient: vaginal discharge ($n = 69$) and vaginal dryness ($n = 30$)
3 sessions, 1 months	B&A treatment	Primary: VAS. Secondary: FSFI, and VHI	Improvement in VAS for GSM symptoms	N/A
3–5 sessions, 1 months	3, 4 or 5 sessions	Primary: VAS. Secondary: VHIS and cytological evaluation	Significant improvement after 3rd session. Significant improvement in VAS and FSFI after 4th session, no difference between 4th and 5th	No SAE. Transient: mild irritation at the introitus
3 sessions, 6 weeks	B&A treatment	Primary: GSM symptoms frequency and severity. Secondary: APFQ	Significant improvement in GSM symptoms at 2–4-month follow-up and 12–24-month follow-up	No SAE. AE: UTI ($n = 3$), vaginal infection ($n = 2$), pain ($n = 3$), genital herpes breakout ($n = 1$), bleeding ($n = 2$)
3 sessions, N/A	B&A treatment	Primary: vaginal dryness, sexual function, and PGI	Significant improvement in vaginal dryness. 86% satisfied with the treatment	No SAE. AE: urinary tract symptoms ($n = 5$), vaginal pain/burning ($n = 2$), vaginal itching ($n = 1$), dyspareunia ($n = 1$)
3 sessions, 6 weeks	B&A treatment	Primary: VAS. Secondary: FSFI, and VHI	Significant improvement in VAS the first year (except dysuria), VHIS and FSFI.	No SAE. Transient: pain ($n = 2$) and bleeding ($n = 2$)

(Continues)

TABLE 3 (Continued)

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years);[b] menopause status	Treatment settings
	Murina et al. (2016)[56]	Italy	Cohort	4 months, last	70	N/A; Menopausal ($n = 33$)	30 W, stack 2
	Pitsouni et al. (2016)[57]	Greece	Cohort	4 weeks, last	53	57.2 ± 5.4; Postmenopausal	30 W, stack 1–3
	Sokol et al. (2016)[58]	USA	Cohort	3 months, last	30	58.6 ± 8.8; Postmenopausal	30 W, stack 1–3
	Pitsouni et al. (2017)[133]	Greece	Case-Control	1 months, last	50	30W = 56.3 ± 5.1. 40W = 56.8 ± 3.6; Postmenopausal	30 and 40 W, stack 1–3
	Gordon et al. (2019)[125]	USA	Case Report	N/A	4	58, 61, 65 and 68 y; Postmenopausal	N/A
Er:YAG	Gambacciani et al. (2020)[59]	Italy	Cohort	24 weeks, last	1081	54.3 ± 3; Postmenopausal	6.0 J/cm^2
	Gambacciani et al. (2018)[60]	Italy	Cohort	24 months, last	254	LASER = 61.2 ± 7.2. LT = 62.0 ± 7.5; Postmenopausal	6.0 J/cm^2
	Mothes et al. (2018)[63]	Germany	Cohort	6 weeks, last	16	71 ± 7; Postmenopausal	Phase 1: 15–35 J/cm^2. Phase 2: 3–9 J/cm^2
	Gambacciani & Levancini (2017)[61]	Italy	Cohort	18 months, last	43	50.8 ± 8.1; Postmenopausal	6.0 J/cm^2
	Gaspar et al. (2017)[62]	Argentina	Cohort	18 months, first	50	LASER = 55.0 ± 6.7. Estriol = 53.5 ± 5.7; Postmenopausal	Total: 1000–1500 J
	Gambacciani & Levancini (2015)[64]	Italy	Cohort	4 weeks, last	65	62.9 ± 8.1; Postmenopausal	3 and 8.5 J

No. treatments, interval	Comparison	Outcome	Conclusion	Adverse events
N/A	B&A treatment	Primary: VAS, Marinoff score, and efficacy	Significant improvement in VAS, Marinoff and efficacy. Improvement gradually increased through 4 months of follow-up	No SAE
3 sessions, 1 months	B&A treatment	Primary: VMV and VHIS. Secondary: FSFI, ICIQ-FLUTS, ICIQ-UI SF, UDI-6, KHQ	Significant improvement in VMV and VHIS at follow-up	No SAE. Transient: mild irritation at the introitus
3 sessions, 6 weeks	B&A treatment	Primary: VAS. Secondary: VHI, dilator size, FSFI, SF-12, difficulty in performing treatment, PGI 5 scale	Significant improvement in VAS for all categories of symptoms	No SAE. Transient: mild to moderate pain ($n = 2$), minor bleeding ($n = 1$)
3 sessions, 1 months	30 W ($n = 25$) vs 40 W ($n = 25$)	Primary: VAS (dyspareunia + dryness). Secondary: VAS (other GSM symptoms) FSFI, ICIQ-FLUTS, VMV and VHIS	No significant between-group differences in VAS, but within-group improvement was significant	No SAE. Transient: mild irritation, burning sensation
3 sessions, N/A	N/A	N/A	Case series of complications following treatment of GSM with CO_2 LASER	Fibrosis, scarring, agglutination and penetration injury following CO_2 LASER treatment
2–3 sessions, 1 months	B&A treatment	Primary: FSFI and FSDS-R.	Significant improvement in FSFI and FSDS-R scores	No SAE
3 sessions, 1 months	Local treatments (LT): hormonal or non-hormonal ($n = 49$)	Primary: VAS and VHIS. Secondary: ICIQ-UI SF	Significant improvement in VAS and VHIS until 12 and 18 months respectively. VAS was significantly improved in the LASER group compared with LT at 6 months	No SAE or AE
N/A	B&A treatment	Primary: subjective satisfaction, vaginal pH, VHI	Significant improvement in VHI, but not in pH and 94% of patients were satisfied	No SAE
3 sessions, 30 days	B&A treatment	Primary: VAS and VHIS.	Significant improvement in VAS and VHIS up to 12-month follow-up, but not after 18 months	No SAE or AE
3 sessions, 3 weeks + 2 weeks pretreatment with estriol	Topical estriol (1:1)	Primary: Biopsies, MV, Vaginal pH, VAS (dyspareunia, dryness, irritation, and leukorrhea)	Significant reduction in VAS at 18-month follow-up in the LASER group only. Overall bigger improvement in the LASER group on all outcomes	No SAE. Transient: mild to moderate pain (4%), edema, pain ($n = 1$), spotting ($n = 1$)
3 sessions, 30 days	B&A treatment	Primary: VAS and VHIS. Secondary: ICIQ-UI SF	Significant improvement in VAS and VHIS	No SAE. Transient: "bad experience" at first application ($n = 3$)

(Continues)

TABLE 3 (Continued)

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years);[b] menopause status	Treatment settings
	Gambacciani et al. (2015)[65]	Italy	Cohort	24 weeks, last	70	LASER = 60.9 ± 8.1. Estriol = 63 ± 4.5; Postmenopausal	6 J/cm^2

Note: General characteristics, findings, and adverse events in included studies. The table is sorted by (1) LASER type, (2) study design, (3) year of publication and (4) author name.

Abbreviations: AE, adverse event(s); APFQ, Australian Pelvic Floor Questionnaire; BC, breast cancer; B&A treatment, before & after treatment; CO_2, carbon dioxide LASER; DIVA, Day-to-day Impact of Vaginal Aging Questionnaire; Er:YAG, Erbium: Ytrium-Aluminum-Garnet LASER; FSDS-R, The Female Sexual Distress Scale-Revised Questionnaire; FSFI, Female Sexual Function Index; GSM, genitourinary syndrome of menopause; ICIQ-FLUTS, International Consultation on Incontinence Questionnaire - Female Lower Urinary Tract Symptoms; ICIQ-SF or ICIQ-UI SF, International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form; IQR, interquartile range; J, joule; KHQ, King's Health Questionnaire; mJ, millijoule; MV, maturation value; N/A, not available or not applicable; PGI-I, patient global impression of improvement; QoL, quality of life; SAE, serious adverse event(s); SF-12, 12-item short-form health survey; UDI, Urinary Distress Inventory; UDI-6, Urinary Distress Inventory, short form; UTI, urinary tract infection; VAS, Visual Analog Scale; VAS*, Vaginal Assessment Scale; VHI or VHIS, Vaginal Health Index or Vaginal Health Index Score; VMI, Vaginal Maturation Index; VuAS, Vulvar Assessment Scale; VVA, vulvovaginal atrophy; WBFS, Wong–Baker Faces Scale.

[a]Follow-up is reported as time from initial treatment session (first) or final treatment session (last).

[b]Age is reported in mean ± SD unless otherwise specified.

TABLE 4 Vulvovaginal atrophy

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age [years][b]; menopause status	Treatment settings
CO_2	Dutra et al. (2021)[29]	Brazil	RCT	4 months, first	25	55.3 ± 4.3; Postmenopausal	30 W, stack 2
	Ruanphoo et al. (2020)[30]	Thailand	RCT	12 weeks, last	88	60.78 ± 7.77; Postmenopausal	40 W, stack 1–3
	Cruz et al. (2018)[31]	Brazil	RCT	20 weeks, first	45	LASER: 55.9 ± 5.2, Estriol: 56.9 ± 6.0, L+E: 55.7 ± 4.4; Postmenopausal	30 W, stack 2
	Alexiades (2021)[66]	USA	Cohort	12 months, last	18	53 ± 7; Postmenopausal	50 mJ
	Gardner & Aschkenazi (2021)[67]	USA	Cohort	13 weeks, first	139	62 ± 10; N/A	30 W, stack 1–3
	Luvero et al. (2021)[68]	Italy	Cohort	3 months, last	44	34.5 ± 5.1; Premenopausal	Internal: 40 W, stack 1. External: 25 W, stack 1

No. treatments, interval	Comparison	Outcome	Conclusion	Adverse events
3 sessions, 30 days	Topical estriol ($n = 25$)	Primary: VAS and VHIS. Secondary: ICIQ-UI SF	Significant between-group difference in VAS and VHIS after 24 months, with biggest improvement in the LASER group	No SAE. Transient: burning sensation ($n = 1$), "bad experience" ($n = 2$)

No. treatments, interval	Comparison	Outcome	Conclusion	Adverse events
3 sessions, 1 months	Topical estrogen	Primary: Frost Index, Meisel index, SQ-F, histomorphometry of the vaginal mucosa and sexual function	Significant improvement in vaginal thickness and sexual function in both groups. No difference between the groups at baseline and after treatment	No SAE
4 sessions, 1 months	Sham LASER (1:1)	Primary: VHI. Secondary: VAS and ICIQ-VS	Significant improvement in VHI, VAS and ICIQ-VS in both groups. Significant difference between LASER group and sham group	No SAE
2 sessions, 1 months	Estriol vs LASER vs LASER+estriol (L+E)	Primary: VHI, VAS, FSFI, and MV	No significant between-group difference at follow-up. Significant improvement in VHI and FSFI for L+E and in dyspareunia, burning and dryness for LASER and L+E group. Significant improvement only in dryness for estriol group	No SAE
3 sessions, N/A	B&A treatment	Primary: VHI, VAS, and FSFI	Significant improvement in VHI and FSFI	No SAE. Transient: mild erythema at the introitus and vulva
3 sessions, 6 weeks	B&A treatment	Primary: FSFI, VSQ, and VAS	Significant improvement in FSFI, VSQ (18/21 questions) and VAS for intercourse and vulvar dryness	No SAE
3–4 sessions, 1 months	No treatment	Primary: VAS	Significant improvement in all symptoms compared with the control group	No SAE

(Continues)

TABLE 4 (Continued)

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age [years][b]; menopause status	Treatment settings
	Rosner-Tenerowicz et al. (2021)[69]	Poland	Cohort	12 months, last	205	58.45 ± 8.73; Perimenopausal	N/A
	Salvatore et al. (2021)[70]	Italy	Cohort	20 weeks, first	40	57.6 ± 7.2; N/A	30 W, stack 1–3
	Adabi et al. (2020)[71]	Iran	Cohort	3 months, last	140	56.8 ± 9.3; Postmenopausal	50 to 60 mJ.
	Angioli et al. (2020)[72]	Italy	Cohort	4 weeks, last	165	53 (31–73); N/A	40 W, N/A
	Di Donato et al. (2020)[73]	Italy	Cohort	3 months, last	53	57.8 ± 10.4; Postmenopausal	7.5–12.5 mJ
	Ghanbari et al. (2020)[74]	Iran	Cohort	3 months, first	47	57.2 ± 6.8; Postmenopausal	40 W, stack 1
	Hersant et al. (2020)[75]	France	Cohort	6 months, last	20	56.1 ± 8.8; Menopause ($n = 17$)	11.5 J/cm^2, stack 3
	Marin et al. (2020)[76]	France	Cohort	6 months, first	50	M: 44 (24–52). NM: 58 (52–73); Menopausal ($n = 25$), non-menopausal ($n = 25$)	18 W, N/A
	Mezzana (2020)[77]	Italy	Cohort	12 weeks, first	40	N/A, Menopausal	8 & 5 W
	Eder (2019)[78]	USA	Cohort	18 months, last	20	60.65 ± 6.34; Postmenopausal	7.5–12.5 mJ
	Pearson et al. (2019)[79]	Australia	Cohort	1 months, last	29	Median: 56 y; Postmenopausal	40W, stack 2
	Singh et al. (2019)[80]	Singapore	Cohort	6 months, last	45	59.7 ± 9.2; Premenopausal ($n = 4$), postmenopausal ($n = 41$)	40 W, stack 2
	Eder (2018)[81]	USA	Cohort	6 months, last	28	60.1 ± 5.55 Postmenopausal	7.5–15.5 mJ

No. treatments, interval	Comparison	Outcome	Conclusion	Adverse events
3 sessions, 4–6 weeks	B&A treatment	Primary: VAS, VHIS, and ICIQ-UI-SF	Significant improvement in VAS, VHIS and ICIQ-UI-SF	No SAE
5 sessions, 1 months	Past vs current use of endocrine therapies	Primary: Satisfaction. Secondary: VHI, VAS, QoL, SF-12, PCS-12, MCS-12, FSFI	Significant improvement in VAS and VHI with no difference between the two groups	No SAE
3 sessions, 1 months	B&A treatment	Primary: VHI, ICIQ, FSFI, and SF-12	Significant improvement in QoL, arousal and SS. Significant improvement in vaginal elasticity, fluid, epithelial integrity, wetness, urinary incontinence, enuresis, urgency and leaking	N/A
3–4 sessions, 1 months	B&A treatment	Primary: VAS	Improvement in VAS for VVA symptoms	No SAE
3 sessions, 1 months	B&A treatment	Primary: Pain related to probe insertion	Significant improvement in pain related to probe insertion and rotation. The pain did not significantly change. High satisfaction in 89.7%	No SAE. Transient: dizziness ($n = 1$), dysuria ($n = 2$)
3 sessions, 1 months	B&A treatment	Primary: VAS for VVA symptoms severity	Significant improvement in VAS for VVA symptoms	No SAE
2 sessions, N/A	B&A treatment	Primary: VHIS. Secondary: FSD and VAS	Significant improvement in VHIS for vaginal elasticity, fluid volume, epithelial integrity and moisture	No SAE. Transient: bleeding ($n = 2$)
2 sessions, 6 weeks	Menopausal (M) vs non-menopausal (NM)	Primary: FSFI. Secondary: QoL	Significant improvement in FSFI and QoL for both groups. No between-group comparison available	AE: worsening of symptoms ($n = 2$) and UTI ($n = 1$)
3 sessions, 1 months	B&A treatment	Primary: FSFI and SUI scale	Significant improvement in both FSFI and SUI in all outcomes	No SAE
N/A	B&A treatment	Primary: VHI, VAS, FSFI, satisfaction with treatment	Significant improvement in VHI, VAS and FSFI at 12, 15 and 18 months	No SAE. Transient: mild to moderate severity
3 sessions, 1 months	B&A treatment	Primary: VAS. Secondary: FSFI and QoL	Significant improvement in dryness, burning and dysuria	N/A
5 sessions, N/A	B&A treatment	Primary: Severity of symptoms, VHI, SF-2, FSFI, treatment satisfaction	General improvement: 90% of the patients improved in dryness, 89.5% of the patients improved in dyspareunia	No SAE
3 sessions, 1 months	B&A treatment	Primary: VHI. Secondary: VAS and FSFI	Significant improvement in VHI the 1st mo. following the 1st treatment. Significant improvement in VHI from baseline to 6-month follow-up	No SAE. Transient: vaginal bleeding ($n = 1$)

(Continues)

TABLE 4 (Continued)

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age [years][b]; menopause status	Treatment settings
	Samuels et al. (2018)[82]	USA	Cohort	12 months, last	40	56 ± 8; Postmenopausal	45–60 mJ
	Arroyo (2017)[83]	Spain	Cohort	24 weeks, last	21	45 ± 7; Perimenopausal	40–55 mJ
	Filippini et al. (2017)[84]	Italy	Cohort	2 months, last	386	Range: 48->70; Postmenopausal	Internal: 40 W, stack 2. External: 30 W, stack 1
	Pagano et al. (2017)[85]	Italy	Cohort	1 months, last	82	Median: 44 y; Postmenopausal (*n* = 10)	30 W, stack 1–3
	Pieralli et al. (2017)[86]	Italy	Cohort	24 months, last	184	56 y (range 38–72 y); Postmenopausal	30 W, stack 1
	Siliquini et al. (2017)[87]	Italy	Cohort	15 months, last	91	58.6 ± 6.9; Postmenopausal	40 W, stack 1–3
	Lekskulchai et al. (2016)[88]	Thailand	Cohort	3 months, last	112	61.0+7.0; Postmenopausal	30 W, stack 1–3
	Pagano et al. (2016)[89]	Italy	Cohort	1 months, last	26	Median: 42 y; Postmenopausal (*n* = 1)	30 W, stack 1–3
	Pieralli et al. (2016)[90]	Italy	Cohort	4 weeks, last	50	53.3 (range: 41–66); Postmenopausal	30 W, stack 2
	Perino et al. (2014)[91]	Italy	Cohort	1 months, last	48	Median (IQR): 56 (7.75); Postmenopausal	40W, stack 2
	Salvatore et al. (2014)[92]	Italy	Cohort	4 weeks, last	50	59.6 ± 5.8; Postmenopausal	30 W, stack 1–3
	Salvatore et al. (2014)[93]	Italy	Cohort	4 weeks, last	77	60.6 ± 6.2; Postmenopausal	Internal: 30 W, stack 1–3. External: 20 W
CO_2 & Er:YAG	Salcedo et al. (2020)[126]	Spain	Case Report	Case 1: N/A, Case 2: 24 weeks	2	61 and 63 y; Postmenopausal	Case 1: 40 W, case 2: 5.5 + 10 J/cm^2

No. treatments, interval	Comparison	Outcome	Conclusion	Adverse events
3 sessions, 1 months	B&A treatment	Primary: VHI. Secondary: VAS, FSFI, treatment satisfaction, histology, and ICIQ-UI-SF	Significant improvement in VHI after the 1st treatment. Improvement in VHI after 6 months. Significant improvement in all evaluations	No SAE. AE: mild itching ($n = 2$), mild itching and swelling ($n = 1$), moderate burning sensation with urination ($n = 2$), moderate soreness and spotting ($n = 1$), major itching ($n = 1$)
3 sessions, 3–4 weeks	B&A treatment	Primary: VHI at 12 weeks. Secondary: VHI at 24 weeks, sexual function, satisfaction and improvement	Significant improvement in VHI score 12 weeks after last treatment. The improvement was also significant at 24 weeks follow-up	No SAE. AE: Mild urinary infection ($n = 1$). Transient: Burning sensation, itching, bruising, swelling, twinging sensation, numbness, and purpura
3 sessions, N/A	B&A treatment	Primary: VAS (laxity, dryness, irritation/burning, and dyspareunia)	Patients reported improvement in symptoms 2 months after last treatment	No SAE. Transient: Discomfort during insertion, blood–serum secretions (1–2 days), mild burning (1–2 hours) after treatment
3 sessions, 30–40 days	B&A treatment	Primary: VAS for VVA symptoms	Significant reduction in VAS for all VVA related symptoms except vaginal laxity	No SAE
3 sessions, 1 months	N/A	Primary: Patient satisfaction	Patient satisfaction declined over time, from 92% being satisfied after 6 months, to 25% at 24 months	N/A
3 sessions, 1 months	B&A treatment	Primary: VAS (dryness and dyspareunia), DIVA, VHI, VVHI	Significant improvement in VAS, VHI and VVHI scores at 15-month follow-up	No SAE
3 sessions, 1 months	B&A treatment	Primary: VVA symptom-score, vaginal pH and VMI	Significant improvement in VVA symptom-score, pH and VMI	No SAE
3 sessions, 30–40 days	B&A treatment	Primary: VAS for VVA symptoms	Significant improvement in all VAS scores except for vaginal laxity among BC survivors	No SAE
3 sessions, 1 months	B&A treatment	Primary: VHI and VAS	Significant improvement in VHI and VAS scores among BC survivors	No SAE
3 sessions, 1 months	B&A treatment	Primary: VHI and VAS for VVA symptoms	Significant improvement in VHI and VAS scores	No SAE or AE
3 sessions, 1 months	B&A treatment	Primary: VHIS, VAS for VVA symptoms, SF-12	Significant improvement in VHIS, SF-12 and VVA scores, except for vaginal burning	No SAE or AE
3 sessions, 1 months	B&A treatment	Primary: FSFI. Secondary: SF-12, VAS (SS and VVA)	Significant improvement in FSFI and sexual activity	N/A
C1: 3+3 sessions, 4–6 weeks. C2: 3 sessions, 1 months	N/A	Case1: VAS, case 2: VAS, VHI	Combination of LASER and ospemifene showed improvement in VVA symptoms	N/A

(Continues)

TABLE 4 (Continued)

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age [years][b]; menopause status	Treatment settings
Er:YAG	Lee (2014)[32]	South Korea	RCT	2 months, last	30	41.7 (33–56); Premenopausal (*n* = 23), perimenopausal (*n* = 2), postmenopausal (*n* = 5)	Group A:1.7 J. Group B: 1.7 J and 3.7 J
	Arêas et al. (2019)[94]	Brazil	Cohort	1 months, last	24	53.67 ± 9.66; Postmenopausal	2.0 J/cm^2(360°) and 35 mJ/MTZ (90°)

Note: General characteristics, findings, and adverse events in included studies. The table is sorted by (1) LASER type, (2) study design, (3) year of publication and then (4) author name.

Abbreviations: AE, adverse event(s); B&A treatment, before and after treatment; CO_2, carbon dioxide LASER; DIVA, Day-to-day Impact of Vaginal Aging Questionnaire; Er:YAG, Erbium: Ytrium-Aluminum-Garnet LASER; FSD, The Female Sexual Distress Scale; FSFI, Female Sexual Function Index; ICIQ, International Consultation on Incontinence Questionnaire; ICIQ-SF or ICIQ-UI SF, International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form; ICIQ-VS, International Consultation on Incontinence Questionnaire – Vaginal Symptoms Module; IQR, inter quartile range; MCS-12, 12-item Short-Form Health Survey's Mental health Component Scale ; MV, maturation value; N/A, not available or not applicable; PCS-12, 12-item Short-Form Health Survey's Physical health Component Scale; QoL, quality of life; SAE, serious adverse event(s); SF-12, 12-item Short-Form Health Survey; SPEQ, Short Personal Experiences Questionnaire; SQ-F, female sexual quotient; SS, sexual satisfaction; SUI, stress urinary incontinence; UTI, urinary tract infection; VAS, Visual Analog Scale; VHI or VHIS, Vaginal Health Index or Vaginal Health Index Score; VMI, Vaginal Maturation Index; VSQ, Vulvovaginal Symptoms Questionnaire; VVA, vulvovaginal atrophy; W, watt.

[a]Follow-up is reported as time from initial treatment session (first) or final treatment session (last).

[b]Age is reported in mean ± SD unless otherwise specified.

TABLE 5 Urinary incontinence

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years);[b] menopause status	Treatment settings
CO_2	Aguiar et al. (2020)[33]	Brazil	RCT	2 weeks, last	72	57.28 ± 5.15; Postmenopausal	40 W, stack 2–3
	Alcalay et al. (2021)[95]	Israel	Cohort	12 months, first	42	49 (32–73); N/A	40–120 mJ
	Franić et al. (2021)[96]	Slovenia	Cohort	6 months, last	85	47(42–56); N/A	Menopause > 10 y: 60–70 mJ/px, <50 y old: 80–90 mJ/px. Thereafter + 10 mJ/px
	Nalewczynska et al. (2021)[97]	Poland	Cohort	12 months, last	59	51.0 ± 1.4; N/A	70–120 mJ/pixel
	Toplu et al. (2021)[98]	Turkey	Cohort	6 months, last	30	48.3 ± 7; Premenopausal (*n* = 3), perimenopause (*n* = 22), postmenopausal (*n* = 5)	30–45 mJ

No. treatments, interval	Comparison	Outcome	Conclusion	Adverse events
4 sessions, 1–2 weeks	Group A: 2x360° & 2x90°. Group B: 2x90°; 2x90°+360°	Punch biopsies, perineometer, partner's evaluation of vaginal tightening and patient's SS	Thicker and more cellular epithelium. More compact lamina propria with more connective tissue. Significant between group difference in maximum pressure and SS in group A compared to B	No SAE.
3 sessions, 1 months	B&A treatment	Primary: VHIS and SPEQ	Significant improvement in VHIS and SPEQ at follow-up	No SAE. AE: vaginal candidiasis ($n = 1$), acute cystitis ($n = 1$)

No. treatment, interval	Comparison	Outcome	Conclusion	Adverse events	UI type
3 sessions, 30–45 days	1) CO_2 LASER, 2) intravaginal promestriene, 3) vaginal lubricant (1:1)	Primary: ICIQ-UI SF and ICIQ-OAB. Secondary: Urinary symptoms related to GSM	No significant between-group difference in ICIQ-UI scores, but significant in-group change in the LASER arm only. Significant improvement in ICIQ-OAB between LASER vs lubricant, but not promestriene	No SAE	UI
3 sessions, 1 months	B&A treatment	Primary: 1-hour pad test, PFDI-20, PFIQ, PGI-I, and VHI	Significant improvement in 1-h pad test, PFDI and PFIQ. Improvement in PGI-I	No SAE. Transient: vaginal secretion and irritation, fever, and UTI	SUI
2 sessions, 1 months	B&A treatment	Primary: VAS, and ICIQ-UI SF	Significant improvement in ICIQ-UI-SF for women (BMI >30). No significant results in VAS	No SAE	SUI
3 sessions, 1 months	B&A treatment	Primary: Sandvik score, 1-h pad test, VHIS, FSFI, PGI-S, PGI-I, and PFIQ-7	Gradual improvement of symptoms and the best outcome was observed between 3 and 6 months	No SAE	SUI
1–3 sessions, 1 months	B&A treatment	Primary: Discomfort during and satisfaction with the procedure. Secondary: QUID, PISQ-12	A general high level of patient comfort and satisfaction related to the procedure was found	NO SAE	SUI

(Continues)

TABLE 5 (Continued)

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years);[b] menopause status	Treatment settings
	Zhang et al. (2021)[99]	China	Cohort	6 months, last	33	43.15 ± 6.49; Premenopausal	30 W, 60–100 mJ/ppxl.
	Dabaja et al. (2020)[100]	Israel	Cohort	6 months, last	33	43 (32–51); N/A	N/A
	Palacios et al. (2020)[101]	Spain	Cohort	6 weeks, last	25	54.4 ± 9.9; N/A	70 mJ, 396 J/cm^2
	Behnia-Willison et al. (2019)[102]	Australia	Cohort	12–24 months, last	58	57.4 ± 11.4; Postmenopausal ($n = 45$)	40 W, stack 3
	González Isaza et al. (2018)[103]	Colombia	Cohort	36 months, last	161	53 ± 5.1; Postmenopausal	N/A
	Perino et al. (2016)[104]	Italy	Cohort	1 months, last	30	56(8.5); Menopausal	40 W, stack 2
CO_2 & Er:YAG	Lin et al. (2018)[105]	Taiwan	Cohort	2 months, last	31	48.43 ± 12.75; Menopause (44.8%)	CO_2: Internal: 30 W, external: 20 W. Er:YAG: 3, 6 and 10 J/cm^2
CO_2+ other	Behnia-Willison et al. (2020)[106]	Australia	Cohort	24 months, last	62	55.98 ± 11.27; Postmenopausal ($n = 48$).	40 W, stack 3
Er:YAG	Blaganje et al. (2018)[34]	Slovenia	RCT	3 months, last	114	LASER: 39.95 ± 6.36. Sham: 41.84 ± 5.67; Premenopausal	2940 nm, 10 J/cm^2
	Okui et al. (2021)[107]	Japan	Cohort	12 months, last	327	TVT = 42.5 (35–48), VEL = 42.7 (37–49); Postmenopausal (TVT = 11.8%; VEL = 11.5%)	1st step: 6 J/cm^2, 2nd step: 3 J/cm^2 and 3rd step: 10 J/cm^2
	Erel et al. (2020b)[108]	Turkey	Cohort	Open (6–48 months)	82	53.72 (29–78); Premenopausal ($n = 28$), postmenopausal ($n = 54$)	2940 nm, 10.0 J/cm^2
	Erel et al. (2020a)[109]	Turkey, Croatia and Italy	Cohort	Open (6–24 months)	69	Hysterectomized 62 (53–66) and non-hysterectomized 50 (45–55)	2940 nm, 10.0 J/cm^2

No. treatment, interval	Comparison	Outcome	Conclusion	Adverse events	UI type
3 sessions, 1 months	B&A treatment	Primary: ICIQ-SF, and 1-h pad test	Significant improvement in ICIQ-SF. Improvement in 1-h pad test for all patients	No SAE	UI
3 sessions, 1 months	B&A treatment	Primary: UDI-6 and ICIQ-UI	Significant improvement in UDI-6 and ICIQ-UI at 3-month follow-up. Both returned to baseline at 6-month follow-up	No SAE. Transient: stinging sensation (70%), vulvar sensitivity (30%), untimely menstrual pain (10%)	SUI
3 sessions, 4–6 weeks	B&A treatment	Primary: ICIQ-UI, Sandvik Index, and FSFI	Significant improvement in ICIQ-UI and Sandvik Index after 2nd and 3rd treatment. Significant improvement after 1st treatment in UI severity	No SAE	SUI + MUI
3 sessions, 4–6 weeks	B&A treatment	Primary: APFQ	Improvement in 82% after treatment. Improvement in 71% at 12–24-month follow-up	No SAE. Transient: thrush ($n = 3$), UTI ($n = 2$) and genital herpes ($n = 1$)	SUI
4 sessions, 30–45 days	B&A treatment	Primary: ICIQ-UI SF, 1-h pad test, and punch biopsies	Significant improvement in ICIQ-UI-SF and 1-h pad test at 36-month follow-up	No SAE	SUI
3 sessions, 1 months	B&A treatment	Primary: VHI, VAS, and micturition diary	Significant improvement in VHI, micturition diary in number of urge episodes and VAS; dryness, burning, itching and dyspareunia	No SAE	OAB
N/A	CO_2 ($n = 10$) and Er:YAG ($n = 21$)	Primary: ICIQ- SF, 1-h pad test, and FSFI	Significant improvement in ICIQ-SF, but not in 1-h pad test or FSFI. No between-group analysis available.	No SAE. Transient: mild irritation	SUI
3 sessions, 4–6 weeks + platelet rich plasma	B&A treatment	Primary: APFQ	Significant improvement in bladder function at 12-month follow-up except pad use	No SAE	SUI
1 session	Sham LASER (1:1)	Primary: ICIQ-UI SF. Secondary: PISQ-12, FSFI, and perineometry	Significant superiority of the LASER vs sham group in ICIQ-SF	No SAE	SUI
3 sessions, 1 months	TVT	Primary: 1-h pad test. Secondary: ICIQ-SF, OABSS	No significant between-group differences in 1-h pad test, but significant within-group improvement in both groups.	N/A	SUI
1–4 sessions, N/A	B&A treatment	Primary: ICIQ-SF and KHQ	Significant improvement in ICIQ-SF and KHQ. Significant better results in the premenopausal group	No SAE	SUI + MUI
1–4 sessions, 1 months	Hysterectomized vs non-hysterectomized.	Primary: ICIQ-SF. Secondary: 'Maximum improvement time' and 'total improvement time'	Significant improvement in ICIQ-SF in both hysterectomized and non-hysterectomized patients	N/A	SUI

(Continues)

TABLE 5 (Continued)

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years);[b] menopause status	Treatment settings
	Kuszka et al. (2020)[110]	Germany	Cohort	2 years, last	59	49 ± 11, postmenopausal (*n* = 25)	2940 nm, 3 J/cm^2, 6 J/cm^2, and 10 J/cm^2
	Lin et al. (2019)[111]	Taiwan	Cohort	6 months, last	41	45.9 ± 7.2; menopausal (*n* = 33).	2940 nm, 10 J/cm^2
	Okui et al. (2019)[112]	Japan	Cohort	12 months, first	50	LASER: 63.8 ± 2.56, anticholinerg: 63.9 ± 2.76, and beta3: 65.32 ± 2.28; N/A	2940 nm
	Reisenauer et al. (2019)[113]	Germany	Cohort	5 months, last	33	51.9 ± 9.8; N/A	Phase 1: 25 J/cm^2 + 300 μs. Phase 2: 9 J/cm^2 + 1000 μs.
	Su et al. (2019)[114]	Taiwan	Cohort	3 months, last	20	SUI = 46.5 (36–59) MUI = 45.5 (34–54); N/A	10 J/cm^2
	Okui et al. (2018)[115]	Japan	Cohort	12 months, last	150	TVT = 48.7 ± 13.9; TOT = 47.8 ± 13.9; LASER = 50.3 ± 13.2; N/A	N/A
	Lin et al. (2017)[116]	Taiwan	Cohort	12 months, last	30	52.6 ± 8.8, N/A	2940 nm
	Fistonić et al. (2016)[117]	Croatia	Cohort	6 months, last	31	46.6 ± 9.1; N/A	3 and 10 J/cm^2
	Pardo et al. (2016)[118]	Chile	Cohort	3–6 months, first	42	Median (IQR): 46.5 y (42–57); N/A	1st step: 3 J/cm^2, 2nd step: 6 J/cm^2 and 3rd step: 10 J/cm^2
	Tien et al. (2016)[119]	Taiwan	Cohort	6 months, first	35	43.3 ± 7.2; Postmenopausal (*n* = 7)	N/A

No. treatment, interval	Comparison	Outcome	Conclusion	Adverse events	UI type
5 sessions, N/A	B&A treatment	Primary: 1-h pad test, ICIQ-UI SF, and PISQ-12	Significant improvement in mild and moderate UI after 2 treatments. Improvement sustained at 1-year follow-up. Minor effect on severe UI	No SAE. AE: vaginal discharge ($n = 1$). Transient: Pain ($n = 6$)	SUI
3 sessions, 1 months	B&A treatment	Primary: ICIQ-SF, UDI-6, IIQ-7, OABSS, and POPDI-6	Significant improvement in ICIQ-SF, UDI-6, IIQ-7, OABSS, and POPDI-6	No SAE. Transient: Burning sensation and vaginal bleeding	SUI
3 sessions, 1 months	Anticholinergic agent vs beta3-adrenoreceptor agonist vs LASER	Primary: OABSS and VHIS	Significant improvement for all groups in OABSS. Significant improvement for LASER group in VHIS. After LASER, negative correlation between urinary urgency and UI	No SAE	OAB
2 sessions, 1 months	B&A treatment	Primary: ICIQ-SF and QoL	Significant improvement in ICIQ-SF and QoL 5 months after treatment.	No SAE. Transient: Vaginal discharge, spotting and burning/irritation ($n = 10$)	SUI (70%) + MUI (30%)
2 sessions, 1 months	MUI and SUI	Primary: ICIQ-SF	No significant between-group difference in change in ICIQ-SF scores	No SAE or AE.	SUI (50%) + MUI (50%)
3 sessions, 1 months	TVT and TOT	Primary: 1-h pad test. Secondary: ICIQ-SF and OABSS	No significant between-group differences in 1-h pad test, but significant within-group improvement for 1-h pad test and ICIQ-SF in all groups	No SAE or AE in the LASER group	SUI
2 sessions, 1 months	B&A treatment	Primary: OABSS, ICIQ-SF, UDI-6, IIQ-7, POPDI-6, PISQ-12, 1-h pad test, urodynamic testing, and vaginal pressure	Significant improvement in OABSS, ICIQ-SF, UDI-6, IIQ-7, POPDI-6, PISQ-12, 1-h pad test, and vaginal pressure at 3-month follow-up. Significant improvement in POPDI-6 at 12-month follow-up	No SAE.	SUI
1 session	B&A treatment	Primary: ICIQ-UI-SF and mucosa surface temperatures. Secondary: Perineometry and residual urine volume	Significant improvement in ICIQ-UI-SF after all follow-ups	No SAE. Transient: vaginal discharge and slight vulvar edema	SUI
2 sessions, 3–4 weeks	B&A treatment	Primary: ICIQ-SF	Significant improvement in ICIQ-SF	No SAE. Transient: mild pain during treatment	SUI
1 session	B&A treatment	Primary: Pad test. Secondary; Urodynamic assessment, PPBC, USS, OABSS, UDI-6, IIQ-7, KHQ and FSFI.	Significant improvement in pad weights at follow-up.	NO SAE or AE.	SUI

(Continues)

TABLE 5 (Continued)

LASER	Author	Country	Design	Follow-up[a]	Sample size, *n*	Age (years);[b] menopause status	Treatment settings
	Fistonić et al. (2015)[120]	Croatia	Cohort	6 months, last	73	Median (IQR): 47 y (41–54); Premenopausal (*n* = 51), postmenopausal (*n* = 22)	Total: 2500–3000 J
	Ogrinc et al. (2015)[121]	Slovenia	Cohort	12 months, last	175	49.7 ± 10; N/A	10.0 J/cm^2
	Cañadas Molina & Baro (2021)[127]	Spain	Case Report	3months, last	1	48 y	N/A

Note: General characteristics, findings, and adverse events in included studies. The table is sorted by (1) LASER type, (2) treatment indication, (3) study design, (4) year of publication and (5) author name.

Abbreviations: AE, adverse event(s); APFQ, Australian Pelvic Floor Questionnaire; B&A treatment, before and after treatment; CO_2, carbon dioxide LASER; Er:YAG, Erbium: Ytrium-Aluminum-Garnet LASER; FSFI, Female Sexual Function Index; GSM, Genitourinary syndrome of menopause; ICIQ, International Consultation on Incontinence Questionnaire; ICIQ-OAB, International Consultation on Incontinence Questionnaire—Overactive Bladder Module; ICIQ-SF or ICIQ-UI SF, International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form; IIQ-7, Incontinence Impact Questionnaire; IQR, interquartile range; KHQ, King's Health Questionnaire; MUI, mixed urinary incontinence; N/A, not available or not applicable; OAB, overactive bladder; OABSS, Over-Active Bladder Symptom Score; PFDI-20, pelvic floor distress inventory 20; PFIQ, Pelvic Floor Impact Questionnaire; PFIQ-7, Pelvic Floor Impact Questionnaire—short form 7; PGI-I, Patient Global Impression of Improvement; PGI-S, patient global impression of severity; PISQ-12, The Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire with 12 questions; POPDI-6, pelvic organ prolapse distress inventory 6; PPBC, patient perception of bladder condition; QoL, quality of life; QUID, Questionnaire for Urinary Incontinence Diagnosis; SAE, serious adverse event(s); SUI, stress urinary incontinence; TOT, transoburator tape; TVT, tension-free vaginal tape; UDI-6, urinary distress inventory, short form; USS, Urgency Severity Scale questionnaire; UTI, urinary tract infection; VAS, Visual Analog Scale; VEL, vaginal Erbium:YAG LASER; VHI or VHIS, Vaginal Health Index or Vaginal Health Index Score.

[a]Follow-up is reported as time from initial treatment session (first) or final treatment session (last).

[b]Age is reported in mean ± SD unless otherwise specified.

clinical [31] difference in VVA symptoms was found between groups at respectively 4 and 5 months after the first session.

Ruanphoo et al. studied 88 women exposed to either CO_2 LASER or sham LASER and found significant improvement in Vaginal Health Index Score at 3 months post treatment in both groups, with a significantly higher improvement in the LASER group.[30] Two different treatment regimens for the Er:YAG LASER were examined in an RCT with 30 women. At a 2-month follow-up after the last session, they found a significant difference in improvement in sexual satisfaction and maximum pressure measured by a perineometer between the two treatment regimens of Er:YAG LASER favoring group A (sessions 1 and 2 with a 360° scope at 1.7 J/shot, and sessions 3 and 4 with a 90° scope at 1.7 J/shot).[32]

Across different subjective and objective outcome measurements, observational studies found a significant improvement in vaginal atrophic symptoms after application of CO_2 LASER.[66–85,87–93] Of women exposed to either CO_2 or Er:YAG in observational studies, 558 of 2274 women were followed for 12 months or more.[66,69,78,82,86,87]

3.3 | LASER application for GSM and VVA symptoms among cancer survivors

Twenty-four of the studies identified in this review provided information on including patients with a history of breast cancer or other gynecologic cancers,[24,26,39,40,42–44,48,50,54,61,63,67,70,72,75,79,80,85–87,89,90,94] two of which were RCT (Table 7).[24,40] All of the women studied had either GSM or VVA primary indication for LASER application. Across these studies, 959 women with current or previous breast cancer or gynecologic cancers were included. The review identified a single study with the aim of comparing the effect in women with and without breast cancer. In a controlled cohort of 45 women with breast cancer and 90 healthy women, Siliquini et al. found significant improvement in Vaginal Health Index Score and VAS for GSM symptoms in both groups 12 months after application of CO_2 LASER. The authors did not, however, report on the statistical or clinical significance of between-group differences.[42] All observational studies which either partly or solely included

No. treatment, interval	Comparison	Outcome	Conclusion	Adverse events	UI type
1 session	B&A treatment	Primary: ICIQ-UI SF. Secondary: PISQ-12	Significant improvement in ICIQ-SF scores at follow-up.	No SAE. Transient: irritation, vaginal discharge, slight vulvar edema, de novo urgency ($n = 1$).	SUI
3 sessions, 4–6 weeks	B&A treatment	Primary: ICIQ-SF and ISI	Significant improvement at follow-up and patients with SUI improved significantly more than MUI patients.	No SAE. Transient: mild discomfort.	SUI (66%) and MUI (34%)
2 sessions, N/A	N/A	AE	A case of complete transverse vaginal septum and shortening of vaginal length after two sessions of vaginal Er:YAG LASER treatment for SUI.	SAE	SUI

women with a history of breast cancer or gynecologic cancer found significant improvement at follow-up across outcomes.[39,40,42–44,48,50,54,61,63,67,70,72,75,79,80,85–87,89,90,94] Nevertheless, in a pilot randomized study among 18 women with gynecologic cancer, Quick et al. did not find any difference in VAS at follow-up for CO_2 compared with sham LASER.[26]

3.4 | Urinary incontinence

Thirty studies on the effect of vaginal LASER on UI were identified through this review (Table 5).[33,34,95–121,127] The studies include 2053 women with study sizes ranging from 1 to 327 women with a median (IQR) of 46 (31.5–72.75) women. Of these studies, 17 studies investigated the effect of Er:YAG,[34,107–121,127] and 11 studies the effect of CO_2 LASER.[33,95–104] We identified two RCTs including 186 women,[33,34] 27 cohort studies including 1866 women[95–121] and one case-report with one woman.[127]

One RCT of 72 women found no significant between-group differences between CO_2 laser and intravaginal promestriene measured by the International Consultation on Incontinence Questionnaire – Urinary Incontinence—Short Form (ICIQ-UI-SF) and International Consultation on Incontinence Questionnaire—Over-Active Bladder (ICIQ-OAB) 2 weeks after the last session; however, they found a significant within-group improvement at follow-up in the LASER group only.[33] One RCT of 114 women showed a significantly higher improvement in ICIQ-UI-SF in the Er:YAG LASER group compared with sham LASER 3 months after the last session.[34]

Four observational studies on CO_2 LASER with 320 women had a follow-up of 12 months or longer,[95,97,102,103] of whom 262 women did a 1-h pad test which showed a significant improvement of UI symptoms.[95,97,103] Thirteen observational studies with 1132 women investigated the ICIQ-SF for Er:YAG. The follow-up period was 3 months to 2 years after the last session, and the findings generally show an improvement in ICIQ-SF score at follow-up.[107–111,113–118,120,121] Of these 1132 women, 741 were followed for more than 12 months.[107,110,115,116,121]

TABLE 6 Lichen sclerosus

LASER	Author	Country	Design	Follow-up[a]	Sample size [n]	Age [years][b]; menopause status	Treatment settings
CO_2	Burkett et al. (2021)[35]	USA	RCT	6 months, first	52	64.5 ± 10.4; Postmenopausal (n = 52)	26 W (1st) and 30 W (2nd and 3rd)
	Mitchell et al. (2021)[36]	USA	RCT	8 weeks, last	40	Median (IQR): 59 (51–64); N/A	18–26 W, stack 1
	Stewart et al. (2021)[122]	USA	Cohort	12 months, last	12	57 ± 10; Postmenopausal (n = 11)	Deep: 50–65 mJ, Fusion: 50–70 mJ, Ring: 78.5–94.4 mJ
	Balchander & Nyirjesy (2020)[123]	USA	Cohort	6 months, last	40	59.3 ± 9; N/A	24 W, stack 1
	Pagano et al. (2020)[124]	Italy	Cohort	3 month, last	40	57.9 ± 11.1; Menopausal (n = 37)	External: 25 W, stack 1–3. Internal: 30 W, stack 1–3.
	Mendieta-Eckert et al. (2021)[128]	Spain	Case Report	4–16 weeks, last	4	53–62 years; N/A	15–17.5 mJ
	Lee et al. (2016)[129]	Australia	Case Report	6–48 months, N/A	5	56 (39–65); Postmenopausal (n = 3)	40 W and 140–170 mJ
	Kroft & Shier (2012)[130]	Canada	Case Report	11–120 months, last	20	47 ± 14; Postmenopausal (n = 9)	6 W and 200 mJ pr. pulse
	Kartamaa & Reitamo (1997)[131]	Finland	Case Report	1 and 6 y	2	47 and 56; N/A	20 W
Er:YAG	Hobson et al. (2019)[132]	USA	Case Report	>1 year, last	2	58 and 73; Postmenopausal	C1: Depth 750 μm. C2: Depth 550–750 μm
Nd:YAG	Bizjak Ogrinc et al. (2019)[37]	Slovenia	RCT	6 months, last	38	LASER: 59 ± 10. Corticosteroids: 57 ± 14; N/A	90 J/cm^2 + corticosteroid

Note: General characteristics, findings, and adverse events in included studies. The table is sorted by (1) LASER type, (2) study design, (3) year of publication and (4) author name.

Abbreviations: AE, adverse event(s); B&A treatment, before and after treatment; CO_2, carbon dioxide LASER; CSS, Clinical Scoring System for Vulvar Lichen Sclerosus; Er:YAG, Erbium: Ytrium-Aluminum-Garnet LASER; FSFI, Female Sexual Function Index; IQR, interquartile range; N/A, not available or not applicable; Nd:YAG, Neodymium-doped yttrium aluminum garnet; NRS, Numeric Rating Scale; PGI-I, Patient Global Impression of Improvement; PGI-S, Patient Global Impression of Severity; QoL, quality of life; SAE, serious adverse event(s); VAS, Visual Analog Scale; VLS, vulvar lichen sclerosus; VSQ, Vulvovaginal Symptoms Questionnaire.

[a]Follow-up is reported as time from initial treatment session (first) or final treatment session (last).

[b]Age is reported in mean ± SD unless otherwise specified.

3.5 | Lichen sclerosus

Eleven studies examining the effect of vulvar LASER on LS were identified (Table 6).[35–37,122–124,128–132] The studies include 263 women with study sizes ranging from two to 52 women with a median (IQR) of 20 (7.5–40) women. Among these studies, nine studies investigated the effect of CO_2 LASER,[35,36,122–124,128–131] counting two RCTs including 92 women[35,36] and three cohort studies including

No. treatments, interval	Comparison	Outcome	Conclusion	Adverse events
3 sessions, 4–6 weeks	Topical clobetasol propionate steroid (1:1)	Primary: mean Skindex-29. Secondary: VAS, VSQ, Skindex-29 sub-scores, PGI-S and PGI-I	Skindex-29 scores were significantly improved in the LASER group compared with the steroid group	No SAE. Transient: burning, irritation and poor healing ($n = 1$)
5 sessions, 1 months	Sham LASER (1:1)	Primary: histopathologic change on biopsy on a 0–6 point scale. Secondary: CSS	No significant difference in improvement in histopathologic changes between CO_2 and sham group	No SAE. Transient: mild discomfort
3–5 sessions, 1 months	B&A treatment	Primary: Investigator assessed severity, clinical signs. Secondary: VLS symptoms, QoL, sexual function, FSFI, biopsies ($n = 4$)	Significant improvement in severity of clinical signs and architectural changes at 12-month follow-up	No SAE. Transient: Severe erythema ($n = 1$) and mild pinpoint bleeding ($n = 1$)
≥2 sessions, 1 months	B&A treatment	Primary: NRS of symptoms. Secondary: Physical examination, reported events and patient self-assessment.	Significant improvement in all symptoms except from dryness	No SAE. Transient: mild or moderate pain ($n = 12$), burning pain lasting longer than 7 days ($n = 2$)
2 sessions, 30–40 days	B&A treatment	Primary: VAS for vulvar itching. Secondary: VAS for other lichen-related symptoms and treatment	Significant improvement in vulvar itching before and after treatment	No SAE
5–7, 1 months	N/A	N/A	General improvement.	No SAE. Transient: superficial ulcer ($n = 1$), allergic contact dermatitis ($n = 1$)
1–3, N/A	N/A	N/A	General improvement.	No SAE. Transient: discomfort posttreatment ($n = 2$)
1	N/A	N/A	General improvement.	No SAE. Transient: wound infection ($n = 1$)
1	N/A	N/A	General improvement.	No SAE
1 and 3, N/A	N/A	N/A	General improvement.	N/A
3 sessions, 2 weeks	Topical corticosteroids only (1:1)	Primary: VAS for symptoms. Secondary: sexual activity, treatment satisfaction, histologic and clinical evaluation	VAS scores were significantly lower in the LASER group at 1 and 3 months compared with the corticosteroids group	No SAE

92 women.[122-124] One study investigated the effect of Er:YAG[32] and one RCT with 38 women investigated the effect of Nd:YAG.[37]

One RCT of 40 women treated with either CO_2 or sham LASER showed no significant between-group difference in histopathologic change 8 weeks after the last session.[36] Two RCTs consisting of 90 women comparing respectively CO_2 and Nd:YAG with steroid treatment reported significant between-group and in-group improvement favoring the LASER groups.[35,37] Women

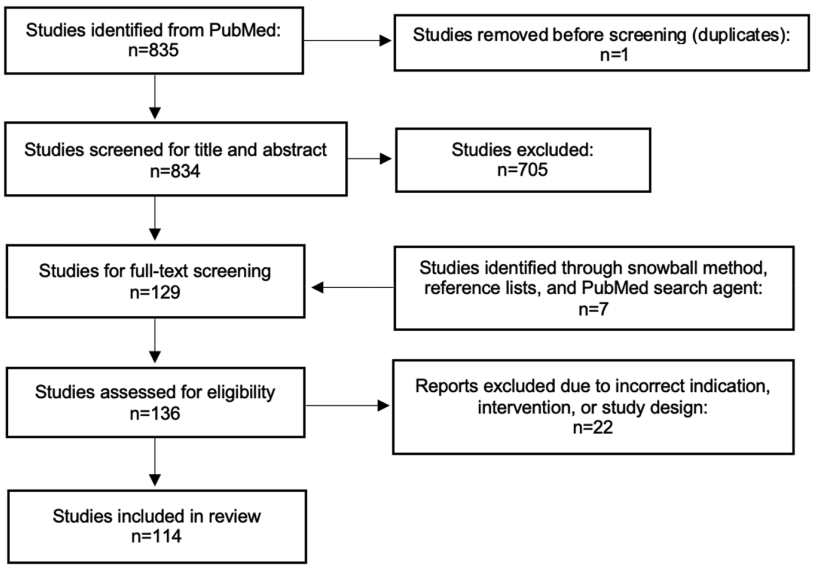

FIGURE 1 Flow diagram for the screening process for the review

in RCTs were followed for a maximum of 6 months after the last session.[35–37]

Across different outcome measures, observational studies including 92 women found a significant improvement in vulvar LS symptoms 3–12 months after application of CO_2 LASER.[122–124] The short follow-up meant that no follow-up concerning malignant transition was possible.

3.6 | Adverse events

In this review, 99 studies including 51 094 patients provided no information on severe adverse events (SAE) related to using LASER as a vaginal or vulvar treatment.[23–42,44,45,47–50,52–70,72–78,80–85,87–92,94–106,108,110–124,128–131,133,135] Eleven studies gave no information on SAE or AEs.[43,46,51,71,79,86,93,107,109,126,132] Two studies reported a total of five cases of SAE with fibrosis, scarring, agglutination, penetration injury, vaginal shortening, and complete transvaginal septum (Tables 3–6).[125,127] Of the 99 studies without SAEs, 47 studies reported mild to moderate AEs, eg pain and burning; most AEs were transient.[24–27,35,36,38,41,44,49,50,52–55,57,58,62,64–66,73,75,76,78,81–84,94,95,100,102,105,110,111,113,117,118,120–123,128–130,133] Three cross-sectional studies investigated the prevalence of AEs associated with vaginal LASER.[134–136] Ahluwalia et al. reported pain as the most common AE among 46 patients with AEs reported between October 2015 and January 2019. Of these patients, 33 reported chronicity of the AE. [134] In the review by Gambacciani et al., 188 practitioners reported that all observed AEs in 43 095 patients treated with vaginal erbium LASER were mild to moderate, transient and with a low prevalence.[135] Wallace et al. reported CO_2 LASER as the LASER with the highest prevalence of AE in the Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database. Two-thirds of AE in the MAUDE database were related to pain, and SAEs were rare.[136]

4 | DISCUSSION

In a best practice review from 2019, Preti et al. stated that vaginal laser could not be recommended as routine treatment for the indications VVA, UI, vulvodynia and LS unless high-quality clinical trials were done.[10] Since then, multiple papers have been published on the subject, including sham-controlled RCTs. As LASER technology is still a contentious topic in gynecology, this review provides an updated summary of the evidence within this field.

We identified 114 studies meeting our eligibility criteria. Across all indications, most observational studies show a significant improvement in urogenital symptoms after LASER application. The with-in group effects found in observational studies are reproducible in RCTs; however, the effect of neither CO_2 or Er:YAG LASER differs consistently from that of sham LASER or selected steroid treatments. To our knowledge, an RCT on vaginal histology in humans to prove the effect of LASER have not been conducted, signifying that LASER technology to this day remains controversial.

Studies on GSM suggest that 137 women in sham-controlled RCTs show a similar improvement 4 weeks after the last session, and 6 and 12 months after the first session when treated with either sham or CO_2 LASER. However, one RCT from Salvatore et al. with 58 women randomized to either CO_2 LASER or sham LASER showed a difference in improvement 1 month after the last session, favoring the LASER group.[25] In RCTs comparing CO_2 LASER and hormonal treatment, findings are likewise heterogeneous; one study found bigger improvement in the LASER group 14 weeks after the last session,[28] and another study found that vaginal estrogen and CO_2 had a similar effect on VAS score 6 months after the last session.[27] Both RCTs and observational studies are characterized by a short follow-up period. In observational studies on GSM, only 940 of 3880 women were followed for more than a year.

Studies with VVA as indication are also characterized by a short follow-up; in two RCTs, 70 women showed similar improvement in

TABLE 7 General characteristics, findings and adverse events in included studies that provide information of inclusion of patients with breast cancer (BC) or other gynecologic cancers

LASER	Author (year)	Design	Sample size [n]	Cancer (*n* or %)	Indication	Conclusion	Adverse events
CO_2	Li et al. (2021)[24]	RCT	85	BC (50%)	GSM	No significant between-group difference in change in overall VAS, VAS for most severe symptom or VSQ score for LASER vs sham, but scores improved in both groups at follow-up	No SAE. AE: LASER (*n* = 16) vs sham (*n* = 17); vaginal pain/discomfort (44% vs 68%), spotting (30% vs 5%), fewer UTI symptoms or confirmed UTI (15% vs 5%), and vaginal discharge (11% vs 11%). Upper UTI in LASER group (*n* = 1)
	Quick et al. (2021)[26]	RCT	18	Gynecologic cancer (*n* = 18)	GSM	No significant difference in overall VAS* from baseline to follow-up between active vs sham group	No SAE. AE: Vaginal discharge (*n* = 3), vaginal dryness (*n* = 3), vaginal pain (*n* = 1), vaginal inflammation (*n* = 2), flank pain (*n* = 1) (unrelated)
	Li et al. (2021)[39]	Cohort	162	BC (*n* = 3), gynecologic (*n* = 3), other (*n* = 2)	GSM	No significant difference was found for VAS and VHIS between CO_2 and topical estriol. VHIS was significantly better at 12 months than at baseline for both groups	No SAE
	Quick et al. (2021)[40]	Cohort	67	BC (*n* = 67)	GSM	Significant improvement in FSFI and FSDS-R scores was found at 12 months, but FSFI still indicated sexual problems	No SAE
	Siliquini et al. (2021)[42]	Cohort	135	BC (*n* = 45)	GSM	Significant improvement in VHI and VAS in both groups	No SAE
	Sindou-Faurie et al. (2021)[43]	Cohort	46	BC (*n* = 13) and gynecologic (*n* = 5)	GSM	Significant improvement in dryness and SUI	N/A
	Veron et al. (2021)[44]	Cohort	46	BC (*n* = 46)	GSM	Significant improvement in FSFI. Improvement in Ditrovie	No SAE. Transient: vaginal bleeding (*n* = 3)
	Gittens et al. (2019)[48]	Cohort	25	BC (*n* = N/A)	GSM	Significant improvement in every domain of FSFI, WBFS and FSDS-R	No SAE
	Quick et al. (2019)[50]	Cohort	64	BC (*n* = 64)	GSM	Improvement in VAS, FSFI and UDI	No SAE. Transient: vaginal discharge (*n* = 69) and vaginal dryness (*n* = 30)

(Continues)

TABLE 7 (Continued)

LASER	Author (year)	Design	Sample size [n]	Cancer (*n* or %)	Indication	Conclusion	Adverse events
	Lang et al. (2017)[54]	Cohort	368	BC (10%)	GSM	Significant improvement in vaginal dryness. 86% satisfied with the treatment	No SAE. AE: UTI symptoms (*n* = 5), vaginal pain/burning (*n* = 2), vaginal itching (*n* = 1) and dyspareunia (*n* = 1)
	Gardner & Aschkenazi (2021)[67]	Cohort	139	BC (*n* = 38)	VVA	Significant improvement in FSFI, VSQ (18/21 questions) and VAS for intercourse and vulvar dryness. BC cohort had same improvement as general cohort	No SAE
	Salvatore et al. (2021)[70]	Cohort	40	BC (*n* = 40)	VVA	Significant improvement in VAS and VHI, but no difference between patients with past vs current use of endocrine therapies	No SAE
	Angioli et al. (2020)[72]	Cohort	165	BC and gynecologic (*n* = 165)	VVA	Improvement in VAS for VVA symptoms	No SAE
	Hersant et al. (2020)[75]	Cohort	20	BC (*n* = 20)	VVA	Significant improvement in VHIS for vaginal elasticity, fluid volume, epithelial integrity and moisture	No SAE. Transient: bleeding (*n* = 2)
	Pearson et al. (2019)[79]	Cohort	29	BC (*n* = 29)	VVA	Significant improvement in dryness, burning and dysuria	N/A
	Singh et al. (2019)[80]	Cohort	45	BC (*n* = 8) and gynecologic (*n* = 5)	VVA	General improvement: 90% of the patients improved in dryness,. 89.5% of the patients improved in dyspareunia	No SAE
	Pagano et al. (2017)[85]	Cohort	82	BC (*n* = 82)	VVA	Significant reduction in VAS for all VVA-related symptoms except vaginal laxity	No SAE
	Pieralli et al. (2017)[86]	Cohort	184	BC (*n* = 56)	VVA	Patient satisfaction declined over time, from 92% being satisfied after 6 month(s), to 25% at 24 months	N/A
	Siliquini et al. (2017)[87]	Cohort	91	BC (*n* = 13)	VVA	Significant improvement in VAS, VHI and VVHI scores at 15-month follow-up	No SAE
	Pagano et al. (2016)[89]	Cohort	26	BC (*n* = 26)	VVA	Significant improvement in all VAS scores except for vaginal laxity among BC survivors	No SAE
	Pieralli et al. (2016)[90]	Cohort	50	BC (*n* = 50)	VVA	Significant improvement in VHI and VAS scores among BC survivors	No SAE

TABLE 7 (Continued)

LASER	Author (year)	Design	Sample size [n]	Cancer (*n* or %)	Indication	Conclusion	Adverse events
Er:YAG	Mothes et al. (2018)[63]	Cohort	16	BC (*n* = 16)	GSM	Significant improvement in VHI, but not in pH; 94% of patients were satisfied	No SAE
	Gambacciani & Levancini (2017)[61]	Cohort	43	BC (*n* = 43)	GSM	Significant improvement in VAS and VHIS up to 1 -month follow-up, but not after 1 month	No SAE or AE
	Arêas et al. (2019)[94]	Cohort	24	BC (*n* = 24)	VVA	Significant improvement in VHIS and SPEQ at follow-up	No SAE. AE: Vaginal candidiasis (*n* = 1), acute cystitis (*n* = 1)

Note: The table is sorted by (1) LASER type, (2) treatment indication, (3) study design, (4) year of publication and (5) author name.

Abbreviations: AE, adverse event(s); CO_2, carbon dioxide LASER; Er:YAG, Erbium: Ytrium-Aluminum-Garnet LASER; FSDS-R, The Female Sexual Distress Scale-Revised Questionnaire; FSFI, Female Sexual Function Index; GSM, genitourinary syndrome of menopause; N/A, not available or not applicable; SAE, serious adverse event(s); SPEQ, Short Personal Experiences Questionnaire; SUI, stress urinary incontinence; UDI, urinary distress inventory; UTI, urinary tract infection; VAS, Visual Analog Scale; VAS*, Vaginal Assessment Scale; VHI or VHIS, Vaginal Health Index or Vaginal Health Index Score; VSQ, Vulvovaginal Symptoms Questionnaire; VVA, vulvovaginal atrophy; WBFS, Wong–Baker Faces Scale.

CO_2 and estrogen groups at 4 and 5 months of follow-up;[29,31] however, Ruanphoo et al. found a significant improvement with CO_2 LASER compared with sham LASER at a 3-month follow-up.[30] In observational studies on VVA, only 558 of 2274 women were followed for more than a year. Adelman et al. released an editorial in 2021 that discussed the optimistic short-term studies, thereby highlighting the need for long-term evidence to illuminate the durability of LASER, since women can suffer from urogenital symptoms for several years.[2]

There is less high-quality evidence of the effect of vaginal LASER on UI symptoms compared with GSM and VVA, as we could only identify two RCTs on this topic.[33,34] The most recent RCT shows similar improvement at a 2-week follow-up for CO_2 and intravaginal promestriene[33] and an RCT from 2018 find more explicit improvement in the Er:YAG group than in the sham group among 114 women at a 3-month follow-up.[34] However, the heterogeneity of the trials complicates further comparisons. In accordance with the current literature, the identified cohort studies in the current review suggest improvement in stress UI and mixed UI symptoms after LASER application. Wang et al. conducted a meta-analysis on clinical studies on Er:YAG and CO_2 LASER and found a positive impact for stress UI patients measured by ICIQ-SF score and 1-h pad test. However, those authors highlight the same limitations as found in this review, namely, a lack of randomized controlled trials, small sample sizes and short-term follow-up.[139]

Vulvar LASER for LS patients is less documented than for the above-mentioned indications, as only 222 patients were distributed across six clinical studies investigating LS.[35–37,122–124] Data from RCTs on 90 women showed greater improvement in LASER groups than in topical steroid groups. One RCT did find similar improvement after CO_2 compared with sham LASER,[36] but the women were only followed for a maximum of 6 months in the RCTs, which is not long enough to illuminate the cancer-preventive effect. Tasker et al. investigated the use of CO_2 LASER for LS in a systematic review; a meta-analysis could not be done, as the studies were too heterogenous. They rated all included RCTS as 'high risk of bias', including two RCTs from the present review.[36,37,140]

Vaginal LASER therapy is often highlighted as a potential treatment alternative for women with hormone-sensitive diseases in the literature on vaginal LASER.[6] All observational studies on CO_2 and Er.YAG LASER, which include women with BC or gynecologic cancer, show significant improvement in GSM and VVA symptom severity. However, evidence from RCTs including women with BC or gynecologic cancer does not show a significant effect on primary outcomes after CO_2 LASER compared with sham LASER. In a pilot study, Quick et al. (2020) randomized 18 women (all with gynecologic cancer) to LASER (*n* = 10) or sham treatment (*n* = 8); they concluded that vaginal LASER was safe for cancer patients suffering from GSM. [26] However, we did not identify any large RCT studies comparing the effect and safety in women with a history of cancer.

This review illustrates how the evidence in the field of vaginal and vulvar LASER has developed over time. Although the most studied

LASER systems have been allowed for medical use on soft tissue since 2014 (DEKA SmartXide2 Laser System) and 2010 (Fotona LightWalker Laser System Family), 75% of studies, identified in current review, were published in the last 5 years.[141,142] They demonstrate substantial marketing prior to a surge in studies investigating the effect and safety of vaginal and vulvar LASER. The initial evidence that has led to a widespread clinical use is based primarily on short-term observational or uncontrolled studies showing promising improvement in GSM, VVA, UI and LS symptom severity. The limited use of control groups in current vaginal and vulvar LASER literature is problematic, considering potential treatment biases and the rapid uptake of the treatment among practitioners.[2] However, in recent years there has been an increase in RCTs, possibly as a result of the U.S. Food and Drug Administration alert on SAEs in 2018 yielding high-quality evidence in the area of LASER technology.[9] Most recently, Li et al. published the largest and longest term double-blinded randomized sham-controlled trial of whether CO_2 LASER reduces GSM symptoms. Even though VAS and Vaginal Health Index scores were improved 12 months after treatment, there was no statistically significant difference between the active and sham groups.[24] The study has been highlighted by editors as financially independent of the industry and as overcoming methodologic limitations in previous studies.[2] One limitation, however, is that it appears the study was powered to detect a with-in group improvement of 50% in the LASER group, and it is unclear whether it was powered to detect a statistical difference between groups.[24]

In accordance with previous reviews on the field, we identified several weaknesses in the current literature.[10,143–145] The relative shortness of follow-up is a challenge, as the majority of studies do not follow their participants more than 6 months post treatment, and in only one high-quality study a follow-up of 1 year after the first treatment.[24] A longer follow-up period after treatment is needed to establish the long-term effect of vaginal LASER. Comparison of the studies is made difficult by heterogeneity in reporting practices related to LASER settings and intensity. To heighten the comparability between studies, reporting practices need to be standardized, eg energy setting, total number of shots emitted, and stack used. If the total amount of energy delivered per session is not reported systematically, it is difficult to establish when and whether vaginal LASERs are safe and effective.

Current literature lacks reporting of adherence to the international guidelines of good clinical practice. Good clinical practice is important to secure standardization, improve data, and eliminate bias within the trials. Li et al. carried out a review using the QUADAS-2 tool and Cochrane REVIEW MANAGER version 5.4 to assess the risk of bias; they found that most of the studies on women with postmenopausal genital symptomswere at high risk of bias. The types of bias included reporting bias and industry involvement, as some of the studies are industry-financed, and some of the authors are consultants for the LASER firms.[145] A cost-effective analysis estimated an out-of-pocket cost at US$2733 for three sessions of LASER.[146] The ethics of increased uptake and high out-of-pocket spending should be carefully considered, as RCTs and histologic studies cast doubt on the evidence of the effect and durability related to LASER in gynecology.[2] The U.S. Food and Drug Administration and several studies have flagged up the problem that some manufacturers marketing "vaginal rejuvenation" devices, profit from women suffering from vaginal symptoms, without sufficient evidence of treatment effect. The possibility that LASER is driven by a commercial interest rather than well-founded evidence should be considered.[9]

This review covers the quantity and variety of evidence, providing an overview of the field to highlight gaps in the current literature. As a result of the broad scope we did not estimate the quality and risk of bias for all included studies according to PRISMA best practice. A limitation to this study is that the search string specifically includes search terms for CO_2 LASER but not for other LASERs, favoring this type of LASER in the search, as we hypnotized that CO_2 LASERs were the most commonly used LASER for female urogenital diseases. Broad terms such as "vaginal LASER" and "energy-based device" were used to allow studies on other LASER types to be included. PubMed was the only database used for this state-of-the-art review, which could result in the authors missing relevant articles. However, after the initial database-search, the authors screened references in systematic reviews on vaginal LASER in order to confirm that all relevant studies were included.

5 | CONCLUSION

Observational studies identified in this review found a positive amendment in GSM, VVA, UI and LS symptoms over time; however, this association is not as noticed in RCTs, as the effect of LASER does not deviate considerably from steroid treatment and sham LASER. Hence LASER technology continues to be highly controversial, as there is no consistency in the existing evidence. Reporting practices for gynecologic LASER need standardization in the treatment protocols and homogeneity within the literature. The current literature is dominated by short-term cohort studies; larger long-term and high-quality RCTs are needed within this field before LASER can be considered a routine treatment for GSM, VVA, UI and LS.

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CONFLICT OF INTEREST

All authors state that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

EL contributed to the idea. OEM, SEC and EL conceptualized and designed the review. OEM and SEC carried out the screening process and data extraction. OEM, OE and SEC drafted the initial manuscript. All authors reviewed and approved the final manuscript as submitted.

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