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REVIEW

Practical Guidance on the Use of Vaginal Laser Therapy: Focus on Genitourinary Syndrome and Other Symptoms

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Abstract: Genitourinary syndrome of the menopause (GSM) is a chronic, often progressive condition, characterised by symptoms relating to oestrogen deficiency including; vaginal dryness, burning, itching, dyspareunia, dysuria, urinary urgency and recurrent urinary tract infections. GSM affects up to 70% of breast cancer survivors with a tendency to particularly severe symptoms, owing to the effects of iatrogenic menopause and endocrine therapy. Patients and clinicians can be reluctant to replace oestrogen vaginally due to fear of cancer recurrence. Vaginal laser is a novel therapy, which may become a valuable nonhormonal alternative in GSM treatment. There are currently 6 published studies regarding Erbium:YAG laser treatment for GSM, 41 studies regarding CO2 laser treatment for GSM and 28 studies regarding vaginal laser treatment for GSM in breast cancer survivors. Number of participants ranges from 12 to 645. The majority of studies describe a course of 3 treatments, but some report outcomes after 5. Significant improvements were reported in vaginal dryness, burning, dyspareunia, itch, Vaginal Health Index Scores (VHIS), Quality of Life, and FSFI (Female Sexual Function Index). Most studies reported outcomes at short-term follow-up from 30 days to 12 months post-treatment. Few studies report longer-term outcomes with conflicting results. Whilst some studies suggest improvements are sustained up to 24 months, others report a drop-off in symptom improvement at 12–18 months. Patient satisfaction ranged from 52% to 90% and deteriorated with increasing time post-procedure in one study. The findings in this review must be validated in robust randomised sham-controlled trials of adequate power. There remain a number of unanswered questions in terms of which laser medium to use, optimal device settings, ideal interval between treatments, pre-treatment vaginal preparation, as well as safety and efficacy of repeated treatments long term. These issues could be addressed most efficiently with a mandatory registry of vaginal laser procedures.

Keywords: vaginal laser, breast cancer, genitourinary syndrome of the menopause, GSM, CO2, Erbium:YAG, vulvovaginal atrophy

Background

Genitourinary syndrome of menopause (GSM) is the term used to describe symptoms of oestrogen deficiency related to changes in the vulva, vagina and lower urinary tract.[1,2] Prior to the introduction of this consensus terminology in 2014, these changes were commonly referred to as vulvovaginal atrophy.[2]

GSM is characterised by a number of clinical symptoms including: genital symptoms of dryness (up to 100%), burning (57%), itching (57%), and irritation (77%); sexual symptoms of lack of lubrication and dyspareunia (78%); and urinary symptoms of dysuria (6%), urgency and recurrent urinary tract infections.[2–4] Although women may present with one or multiple symptoms, the most common symptom of GSM is vaginal dryness.[5–8]

A high concentration of oestrogen receptors exist in the vagina, vestibule, and trigone of the bladder. The decline of circulating oestrogen leads to a reduced collagen content, decreased elastin, thinning of the epithelium, altered function of smooth muscle cells and fewer blood vessels. This results in anatomical changes including regression and thinning of the labia minora, retraction of the introitus with reduced elasticity (often leading to entry dyspareunia), prominence of the urethral meatus (making it vulnerable to physical irritation and trauma), reduction in vaginal blood flow and diminished

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lubrication. Increased friability may predispose to epithelial damage with vaginal penetration, leading to vaginal pain, fissuring and bleeding after sex.[2]

In the pre-menopausal state, the stratified squamous vaginal epithelium is thick with rugae.[9] As epithelial cells exfoliate and die, they release glycogen, which is subsequently transformed to lactic acid by the action of a normal vaginal commensal organism, lactobacillus. At menopause, the epithelium becomes thinner, leading to a reduction in the shedding of glycogenated cells and subsequent loss of lactobacilli, resulting in an increased pH and change to the microbiome.[2] This leads to an increased growth of pathogenic bacteria such as streptococci, staphylococci, and coliforms, which in turn, can cause vaginal inflammation and urogenital infections.[10]

GSM is a chronic and often progressive condition, impacting the quality of life of up to 50% of postmenopausal women.[2,11] The average age of menopause is 51–52 years; with increasing life expectancy, many women will live 40% of their lives after menopause, potentially suffering with these symptoms.[12]

Treatment of GSM includes vaginal moisturisers (for use at any time) and lubricants (for symptomatic relief during sex). However, these have limited efficacy as they do not restore the local physiology. The gold standard treatment is vaginal oestrogen replacement.[13] It is well recognised that local oestrogen therapy restores vaginal pH, thickens the epithelium, induces collagen synthesis and increases vaginal secretions.[14–16] However, local oestrogen treatment is associated with a high recurrence rate of symptoms, once treatment is discontinued.[17] Alternatives including prasterone and ospemifene (selective oestrogen receptor modulator) are licensed in the treatment of GSM but have not been tested against vaginal oestrogen.[18,19]

GSM can affect up to 70% of postmenopausal breast cancer patients and symptoms appear to be more severe, especially for those requiring pharmacological cancer treatment.[20–25] Aromatase inhibitors (AIs) are frequently prescribed to those with endocrine sensitive tumours as they reduce peripheral conversion of androgen to oestrogen, thus resulting in vulvovaginal atrophy.[10,20] Up to 93% of women on AI therapy report sexual dysfunction and 28% report the intention to discontinue treatment due to side effects.[26,27] Chemotherapy may also lead to iatrogenic premature ovarian failure.[23,28]

Improved treatment and screening for female breast cancer in developed countries has resulted in higher survival rates, with current five-year survival rates around 90%. As a result, there are many millions of breast cancer survivors living in Western countries, many of whom are suffering with symptoms of GSM.[23]

In these patients, treatment options for GSM are limited. Vaginal moisturisers and lubricants are safe and indicated but are less effective than hormonal therapies and perhaps due to poor efficacy are associated with low compliance.[29] Vaginal oestrogen is generally not advised, particularly for oestrogen receptor positive tumours, as it can be absorbed into the bloodstream in small amounts and potentially stimulate occult breast cancer cells. Current data do not show an increase in cancer recurrence with local oestrogen therapy; however, some studies do demonstrate elevated serum oestradiol levels with certain preparations, which may reverse the effects of AIs.[30–32] Current recommendations suggest an individual risk:benefit assessment via the oncology team, but there is often both clinician and patient reluctance to use topical oestrogen due to fear of cancer recurrence.[33,34] The safety of intravaginal dehydroepiandrosterone and oral ospemiphene after breast cancer have not been established.[23]

In recent years, it has been suggested that laser therapy may offer a nonhormonal alternative to the management of GSM.[35–38]

What is Laser?

The word LASER (amplification of light by stimulated emission of radiation) was created in 1959, when the first publications appeared in the literature.[39] Since then, medical applications have multiplied and laser is now widely used in dermatology, dentistry and aesthetic surgery.[1,40–42]

Laser light has three unique properties. First, it travels in one direction with very little divergence, unlike natural light that spreads and loses its intensity/power. Second, laser light is monochromatic: consisting of a narrow wavelength/colour range, allowing it to have very specific effects on the tissues. Third, laser light is coherent: all the light waves move in phase, allowing laser energy to be delivered accurately.[1]

Lasers are named according to the medium that is activated eg CO2, Erbium:YAG. Each medium produces light waves of a specific wavelength, giving it a characteristic colour.[43]

Three parameters determine the amount of energy delivered to the tissue; wattage, duration of application and the spot size of the beam. The duration of application can be altered by selecting an intermittent timed pulse mode, while spot size is altered by moving closer to the target. The combination of watts and spot size determines the rate of tissue treatment, known as power density and expressed as watts/cm.[2,43]

The mechanism of action of laser therapy is essentially to heat tissue, which in turn stimulates angiogenesis, collagen synthesis, formation of dermal papillae and epithelial thickening.[1,40,43]

Types of Laser

There are three types of energy device currently in use for vaginal therapy, although there are a number of different manufacturers within each category.[44] Two of these are laser in nature (CO2 and Erbium:YAG), whilst the third is radiofrequency based. Radiofrequency devices, in contrast to laser, emit focused electromagnetic waves that generate heat upon meeting tissue impedance.[43]

Laser sources can be ablative or non-ablative. Ablative sources vaporise tissue layers and are more destructive, whereas non-ablative lasers leave the epithelial surface intact. In terms of vaginal lasers; CO2 is ablative in nature, whereas Erbium:YAG is non-ablative.[43]

In vaginal treatment, fractionated energy devices are used. Non-fractionated energy devices act on the entire projected surface of the skin, whereas fractionated devices target an equally distributed portion of the projected area in a pixelated fashion. This produces small columns of thermal injury, involving both the epidermis and dermis in ablative lasers, or just the dermis in non-ablative lasers.[43]

The technique for performing vaginal laser therapy involves use of a specially designed vaginal speculum. Once this has been introduced, the laser probe can be inserted inside the speculum. The treatment is delivered, retracting the probe by 5mm each time, until the introitus is reached. The treatment is repeated three times, rotating the speculum by 45 degrees each time, to ensure 360-degree treatment. After the vaginal treatment is complete, some centres also offer a vestibule treatment with a different shaped probe. In total, the procedure lasts around 10 minutes.[35]

For both CO2 and Erbium:YAG laser, a typical course of treatment involves three sessions at 4–6 week intervals.[35]

The treatment is outpatient office-based. Most patients report only mild procedural discomfort and the majority do not require topical anaesthesia or analgesia. The majority of women report post-procedural erythema, oedema or discomfort, which resolves within 24–48 hours. No recovery time is usually required, with most patients able to resume regular activities later the same day. Sexual activity should be avoided for 1 week following the procedure.[35]

Histological changes following vaginal laser treatment have been described in a number of studies relating to CO2 laser including: increase in fibroblast activity, increased collagen and elastin, neoangiogenesis, thickening of the vaginal epithelium, increased glycogen storage, increased epithelial exfoliation, and formation of new dermal papillae.[22,44–49] A return in normal flora following vaginal laser treatment from 30% to 79% lactobacilli and resultant reduction in vaginal PH has also been observed, as may be expected from the epithelial changes.[50] One study has compared histological samples following vaginal oestrogen treatment vs Erbium:YAG laser.[17] This demonstrated epithelial improvements in both arms but observed angiogenesis in the laser group only.

Evidence to Date for the Use of Lasers in GSM

A number of indications for vaginal laser treatment have been described, including "rejuvenation", stress urinary incontinence, overactive bladder, vaginal laxity and GSM. The remit of this review is to examine the use of laser in GSM, hence the evidence for other indications will not be discussed further.

Erbium:YAG Laser

The evidence relating to the use of Erbium:YAG laser in GSM treatment, largely originates from a series of publications by Gambacciani with additional studies led by Gaspar, Guerette and Barber.[17,52–56] See Table 1 for a summary of the evidence. Evidence regarding the utility of Erbium:Yag in breast cancer survivors is cited separately in Table 2.

Table 1 Summary of Evidence for Erbium:YAG Laser in GSM Treatment

Study	Study Type	No. of Patients	No. of Treatments	Interval Between Treatments	Delivery of Treatment	Maximum Follow-Up Duration	Subjective Outcome	Objective Outcome	Adverse Events
Gambacciani 2015[54]	Observational	45 laser group 25 estriol group	Three	30 days	2940nm Spot size 7mm Pulsed 'SMOOTH' mode Frequency 1.6Hz Fluence 6J/cm^2 Vestibule treated	24 weeks	Both groups showed a significant improvement in vaginal dryness and dyspareunia but after 24 weeks the improvement had diminished in the estriol group following cessation of treatment	Significant increase in VHIS $p<0.01$, but improvement diminished in estriol group following cessation of treatment	<3% patients discontinued treatment due to adverse events.
Barber 2016[56]	Observational	40 8 (GSM)	Two	30 days	2940nm	4 months	80% reported improvement in vaginal dryness 90% of patients were satisfied		10% described procedure as painful (90% did not) 10% reported post-procedure discomfort
Guerette 2017[55]	Observational	24	Three	4 weeks		4 weeks after final treatment	Significant improvement in dyspareunia and dryness $p\leq0.05$	Significant improvement in atrophy and in all domains of FSFI* $p<0.05$	
Gaspar 2017[17]	Observational	25 estriol 25 estriol + laser	Three	3 weeks	2940nm Pulsed 'SMOOTH' mode Vestibule also treated	18 months	Statistically significant $p<0.05$ reduction in dyspareunia, dryness, irritation, and leukorrhea VAS in the laser group up to 18 months, estriol group only up to 6 months post treatment. The improvement in all endpoints was more pronounced and longer lasting in the laser group.	Histological lamina propria restructuring seen in both groups. Neoangiogenesis also seen in laser group. Significant improvement in maturation value and a decrease of pH in both groups up to 12 months, more prominent in laser group.	Side effects were minimal and transient in both groups, affecting 4% of laser group and 12% estriol group.

Gambacciani 2018[52]	Observational	205	Three	30 days	2940nm Spot size 7mm Pulsed 'SMOOTH' mode Frequency 1.6Hz Fluence 6J/cm^2 Vestibule treated	24 months	Significant decrease in VAS** for dryness and dyspareunia p<0.01 up to 12 months. Values returned to baseline by 18 and 24 months. VAS scores for dryness and dyspareunia were significantly better than a 'topical treatment' group (oestrogen or moisturiser) at 6 months post cessation of treatment p<0.05	Significant increase in VHIS*** p < 0.01 up to 12 months.	Less than 3% of patients discontinued treatment due to adverse events
Gambacciani 2020[53]	Observational	113,174 (9% GSM)	Not reported	Not reported	Not reported	Not reported			Discharge 4% Oedema 3.45% Painful treatment 1.44% Post-op irritation 0.44% Burns 0.16% Post-op pain 0.1% Infection 0.01%

Notes: *FSFI Female sexual function index, **VAS Visual analogue scores, ***VHIS Vaginal health index score.

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Table 2 Summary of Evidence for Laser Treatment of GSM in Breast Cancer Survivors

Study	Study Type	No. of Patients	No. of Treatments	Interval Between Treatments	Delivery of Treatments	Maximum Follow-Up Duration	Subjective Outcome	Objective Outcome	Adverse Events
ERBIUM:YAG									
Bojanini 2014[57]	Observational	40 (20 previous breast cancer, 20 no cancer history)	Two	3 weeks	2940nm	3 months post treatment	At 3 months in both groups, 70% of patients reported resolution of dryness; 90% of patients reported resolution of dyspareunia.	At 3 months in both groups, 90% reported reduced sex avoidance.	Minority of patients with transient mild burning, pain and itching.
Bojanini 2016[58]	Observational (same cohort as above with longer FU)	40 (20 previous breast cancer, 20 no previous cancer)	Two	3 weeks (cancer patients had PRP*, non-cancer patients had either PRP or oestrogen pre-laser)	2940nm 5.5Jcm^2, 1.6HZ, 7mm spot size, vulva: 10Jcm^2	12 months post treatment	Significant reduction in dryness and dyspareunia in all three groups up to 12 months.	Significant reduction in intercourse avoidance in all 3 groups up to 12 months.	Few transient mild burning, pain and itching.
Gambacciani 2017[59]	Observational	43	Three	30 days	2940nm, Spot size 7mm, pulsed 'SMOOTH' mode, frequency 1.6Hz	18 months	Significant improvement in VAS** score for dryness and dyspareunia up to 12 months $p<0.01$, this was not significant by 18 months.	Significant improvement in VHIS*** score up to 12 months $p<0.01$, this was not significant by 18 months.	None
Mothes 2018[60]	Observational	16	One	NA	2940nm Fluence varied according to operator	Mean 8.3 weeks	94% patients were satisfied with the treatment.	Significant improvement in VHIS score, $p=0.01$	None
Arêas 2019[61]	Observational	24	Three	30 days	2940nm 2.0 Jcm^2, frequency 0.5 hz, pulsed smooth-mode	1 month after treatment		Significant improvement in VHIS, $p<0.001$, total sexual function score ($p=0.04$) and dyspareunia domain score ($p=0.01$).	One case candidiasis, one case cystitis.
Okui 2023[62]	Observational	256 (102 erbium, 102 erbium + nd:YAG)	Three for all, additional for erbium+nd:YAG group			2 years	Significant improvement in VAS vulvodynia score in both groups sustained at 2 years, $p<0.001$.	Significant improvement in FSFI in erbium + nd:YAG group, sustained at 2 years. Improvement in VHIS was not significant.	

Fidecicchi 2023[63]	Randomised	68 (34 vagina treated, 34 vagina and vestibule treated)	Three	30 days	2940nm	3 months after last treatment	Significant improvement in VAS score for superficial dyspareunia in both groups, p<0.001. Improvement was greater in the group which also received vestibular treatment, p<0.001.		
Gold 2023[64]	RCT	43 (22 laser, 21 hyaluronic acid)	Two	One month	Fluence 20Jcm^2	3 months after initial treatment	Significant improvements in subjective bother of urogenital atrophy, quality of life and sexual health in both groups with no difference between the groups.	Significant improvement in VHIS in both groups with no difference between the groups.	
CO2 laser									
Filippini 2014[65]	Observational	46	One	NA	40w, dwell time 1000 μs, dot space 1000 μm, pulse mode	Approx 2 months	Burning reduced by 85%, dyspareunia reduced by 81%, dryness reduced by 79%, pain reduced by 76% and itching reduced by 73%.		
Pagano 2016[66]	Observational	26	Three	30–40 days	30w, dwell time 1000 μs, dot space 1000 μm	30 days after final treatment	Significant regression in GSM symptoms and procedure-related discomfort versus baseline (p<0.001 in almost all cases).		None
Pieralli 2016[67]	Observational	50	Three	30 days	30w, dwell time 1000 μs, dot space 1000 μm	11 months (mean)	Significant improvement in dyspareunia at 30 days after last treatment. 76% of patients satisfied with treatment at 30 days after last treatment, dropping to 52% at 11 months.	Significant improvement in VHIS, p<0.001 at 30 days after last treatment.	24% reported pain on probe insertion

(*Continued*)

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Table 2 (Continued).

Study	Study Type	No. of Patients	No. of Treatments	Interval Between Treatments	Delivery of Treatments	Maximum Follow-Up Duration	Subjective Outcome	Objective Outcome	Adverse Events
Pieralli 2017[68]	Observational	184 (128 spontaneous menopause, 56 oncological menopause)	Three	30 days	30w, dwell time 1000 μs, dot space 1000 μm	24 months	Satisfaction declined with time post-procedure from 95.4% at 4 weeks, to 92% at 6 months, 72% at 12 months, 63% at 18 months, and 25% at 24 months. Satisfaction dropped off less substantially in the oncological menopause group.		
Scibilia 2017[69]	Observational	40 (20 breast cancer, 20 gynaecological cancer)	Three	One month	Not reported	3 months following last treatment	Significant improvement in dryness, burning and dyspareunia sustained to 3 months. 90% were satisfied and reported improved quality of life.	Significant improvement in VHIS sustained to 3 months, $p<0.01$.	None
Becorpi 2018[44]	Observational	20	Two	Not reported	30w, dwell time 1000 μs, dot space 1000 μm	30 days after second treatment	Significant improvement in symptoms of dryness, burning, dyspareunia and itching, but not in dysuria.	Significant improvements in VHIS and FSFI**** but not in female sexual distress scale. Change in vaginal cytokine population. No significant change in microbiome.	
Pagano 2018[70]	Observational	82	Three	30–40 days	30w, dwell time 1000 μs, dot space 1000 μm	30 days after final treatment	Significant improvements in VAS scores for dryness, itching/ stinging, dyspareunia and dysuria ($p< 0.001$ for all), bleeding ($p=0.001$), probe insertion ($p=0.001$), and movement-related pain ($p=0.011$).		
Gittens 2019[71]	Observational	25 (12 previous breast cancer, 13 no previous cancer)	Three	Not reported	Not reported	6 weeks after final treatment		Significant improvement in both groups in every domain of FSFI, Wong-Baker Faces scale, and female sexual distress scale, $p<0.05$ for all.	

Pearson 2019[72]	Observational	26	Three	4 weeks	40w, dwell time 1000 μs, dot space 1000 μm	12 weeks post baseline	Significant improvement in VAS scores for all symptoms: dryness p<0.001, itch p<0.001, burning p=0.003, dysuria p<0.001 and dyspareunia p<0.001. 73% patients felt their symptoms had improved, 65% felt quality of life had improved and 50% felt sexual function had improved.	Significant improvement in FSFI p<0.001.	
Quick 2019[73]	Observational	64	Three	30–45 days	30w, dwell time 1000 μs, dot space 1000 μm, vulva: 26w, dwell time 800 μs, dot space 800 μm	1 month after final treatment	Significant improvement in VAS symptom scores for dryness, soreness, irritation and dyspareunia, p<0.001.	Significant improvement in FSFI and urogenital distress inventory-6 score, both p<0.001. Improvements in vaginal pH and signs of GSM on physical examination.	Minor vaginal discharge and dryness
Hersant 2020[74]	Observational	20	Two	1 month	11.5Jcm^2, pulsed	6 months		Significant improvement in VHIS and female sexual distress sustained at 6 months, p<0.0001 and p<0.001 respectively.	Two patients had procedure related bleeding
Siliquini 2021[75]	Observational	135 (45 with breast cancer, 90 no previous breast cancer)	Three or four	30 days	40w, Vulva: 20–35w	12 months	Significant improvement in both groups in VAS score for dryness and dyspareunia, as well as a procedure-related pain questionnaire, up to 12 months. Improvement was slower in the breast cancer group.	Significant improvement in VHIS, up to 12 months. Improvement was slower in the breast cancer group.	None
Quick 2021[76]	Observational	67	Three	30–45 days	Not reported	12 months		Significant improvement in total FSFI score and in all domains and in female sexual distress scale up to 12 months, p<0.001 for all.	None

(*Continued*)

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Table 2 (Continued).

Study	Study Type	No. of Patients	No. of Treatments	Interval Between Treatments	Delivery of Treatments	Maximum Follow-Up Duration	Subjective Outcome	Objective Outcome	Adverse Events
Veron 2021[77]	Observational	46	Three	1 month	26–40w, dwell time 1000 μs, dot space 1000 μm,	18 months		Significant decrease in vaginal pH up to 18 months, p=0.02. Significant improvement in FSFI at 6 months p<0.0001 and at 18 months p=0.01. Urinary quality of life (Ditrovie score) improved at 6 months p=0.01, but returned to baseline by 18 months. Epithelial maturation on pap smear did not change.	Mild discomfort and minor bleeding on day of treatment
Salvatore 2021[78]	Observational	40	Five	4 weeks	30w, dwell time 1000 μs, dot space 1000 μm, introitus: 25w	4 weeks after last treatment	77.5% of patients were satisfied. Significant improvement in GSM symptoms (burning, itching, dryness, dyspareunia, dysuria), p<0.05. No difference between those on endocrine therapy and those not.	Significant improvement in VHIS, FSFI (every domain) and quality of life, p<0.05 for all. No difference between those on endocrine therapy and those not.	None
Quick 2022[51]	Observational	67	Three	30–45 days	30w, dwell time 1000 μs, dot space 1000 μm, vulva: 26w, dwell time 800 μs, dot space 800 μm	2 years	Significant improvement in VAS scores, sustained at 24 months.	Significant improvement in FSFI and female sexual distress score, sustained at 24 months. Urogenital distress index scores returned to baseline by 24 months.	None
Angioli 2020[79]	Observational	165	Three	30 days	40w, dwell time 1000 μs, dot space 1000 μm	4 weeks after last treatment	Dryness improved by 66%, dyspareunia improved by 59%, burning improved by 66%, pain at introitus improved by 54%, and itching improved by 54%.	Level of pH (48 women) improved by 11% (pre-treatment pH 7.08, post-treatment pH 6.19)	None
Fernandes 2023[80]	RCT	70	Three	Monthly		30 days after last treatment	Significant improvement in VAS symptom scores in all groups (laser, radiofrequency and oestrogen) with no difference between the groups. High levels of satisfaction in all groups.	Four pre-treatment biopsies showed vulval atrophy. Post-intervention, all histological parameters normalised.	

Mension 2023[81]	RCT	72 (35 laser, 37 sham)	Five	Monthly	40w, dwell time 1000 μs, dot space 1000 μm	6 months	No significant difference in dyspareunia, body image or quality of life between the groups.	No significant difference in VHIS, FSFI, pH, VMV, epithelial thickness and elasticity between the groups.	
Solid-state vaginal laser									
Lubian-Lopez 2023[82]	Observational	27	Four	15–20 days	1470nm 15–20Jcm^2, vulva treated separately	6 months	Significant improvement in dyspareunia at 10 weeks and 6 months, p<0.001.	Significant improvement in VHIS, vulval health index, VMV and pH at 10 weeks and 6 months, all p<0.001. There was no significant difference in FSFI and quality of life at 10 weeks but these became significant at 6 months, all p<0.001.	Vaginal pain and bleeding related to the procedure, decreased significantly with more treatments.

Notes: *PRP Platelet-rich plasma, **VAS Visual analogue scale, ***VHIS Vaginal health index score, ****FSFI Female sexual function index.

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There are six studies in total. All studies are observational, with the number of participants ranging from 24 to 205. The earliest published study was in 2015. Studies reported administering two or three laser treatments, 3–4 weeks apart. Maximum follow-up duration was 24 months. All studies reported a significant improvement in symptoms of GSM including dryness and dyspareunia. Significant improvements in VHIS (vaginal health index), FSFI (female sexual function index) and histology were also reported. Mild and transient adverse effects were reported in up to 4% of 113,174 patients who underwent Erbium:YAG vaginal laser treatment. Studies with 18- and 24-month follow-up duration report a drop-off in benefits after 12 months, suggesting repeat treatments may be required.

Two reviews examining the use of vaginal Erbium:YAG and its indications have been written by Elia and Gambacciani.[1,83] These concluded that Erbium:YAG technology offers a safe and unique treatment, acting by thermal effect and not by tissue ablation. The authors called for randomised studies to compare Erbium:YAG with other laser therapies, as well as to evaluate the duration of therapeutic effects and the safety of repeated applications.[1,83]

Fractional Ablative CO2 Laser

Evidence for the use of fractional ablative CO2 laser in GSM treatment is more extensive and encompasses 41 publications.[45–50,64,84–117] See Table 3 for summary of evidence. Sample sizes range from 12[114] to 645[96] patients. However, evidence is largely observational data with only 8 RCTs, most of which are underpowered (18 to 170 participants) and have limited follow-up data (maximum 6 months).[100,102–104,106,107,109,117] Number of treatments vary from one to five. Intervals between treatments vary from 2 to 6 weeks. Follow-up duration varies from 1 month to 24 months. There are 2 systematic reviews regarding fractional CO2 laser but the meta-analyses are limited by the quality of data included.[105,118]

The pioneer of CO2 vaginal laser treatment was Gaspar, who, in 2011, published a study of 40 women with GSM who underwent 3 sessions of fractionated CO2 laser, 2 weeks apart. Significant improvements were observed in dyspareunia and histological analysis in the laser group compared with controls.[45]

Of the 41 publications regarding CO2 laser in GSM treatment, 39 reported significant improvements in subjective symptoms and/or objective signs of GSM.

Interestingly, the sham-controlled RCTs have reported conflicting results. A sham-controlled RCT of 88 patients by Ruanphoo reported significant differences in VAS, VHIS and ICIQ-VS in the laser group compared with sham.[100] Similar findings were reported by Salvatore et al in an RCT of 58 patients, in which there were significant improvements in VAS and FSFI in the laser group compared with sham.[103] This is in contrast to a sham-controlled RCT of 30 patients by Cruff et al, which reported significant improvement in VAS, VHIS and FSFI in both groups with no difference between the treatment group and the sham group, potentially demonstrating a placebo effect.[104] Similar findings were reported in an RCT of 18 patients by Quick et al. This showed no significant difference in VAS scores between the two groups, however there was a significant improvement in FSFI in the laser group compared with sham.[102]

Duration of treatment effect is also unclear. Sokol, Samuels, Li, Alexiades, Athanasiou and Siliquini report that treatment effects (according to VAS, VHIS and FSFI) maintain significance at 12 and 15 months.[46,89,92,101,108,111] Beyond this time-frame, there is some evidence that treatment benefits decline. Pieralli et al reported a drop-off in patient satisfaction to 25% at 24 months from 95% at 6 weeks, presumably reflecting a recurrence of symptoms.[90] Eder et al reported that 15/20 patients required an additional treatment between 12 and 15 months, in order to maintain improvements in symptoms, VHIS and FSFI.[95] In contrast, Behnia-Wilson et al reported that treatment effects were maintained at 24 months.[91] Arroyo et al reported improvements in "vaginal rejuvenation" and satisfaction remained high at 24 months but sexual symptoms had recurred.[114]

Patient reported satisfaction with CO2 laser treatment for GSM varies from 67.6% (vestibular application)[86] to 96%,[88] figures which are largely reflective of short-term evaluation. Satisfaction levels are likely to be dependent on follow-up duration, as they are likely to decrease with increased time post-procedure as benefits subside.

In 2020, Alexiades reported restoration of normal VHI in more patients who were recently postmenopausal (1–3 years) compared with patients who were postmenopausal for >3 years following CO2 laser, suggesting that early intervention is correlated with improved outcomes.[101]

Table 3 Summary of Evidence for CO2 Laser in GSM Treatment (Non-Cancer Population)

Study	Study Type	No. of Patients	No. of Treatments	Interval Between Treatments	Delivery of Treatment	Maximum Follow-Up Duration	Subjective Outcome	Objective Outcome	Adverse Events
Gaspar 2011[45]	Observational	40 laser group 52 control group (PRP* +PFE**)	Three	2 weeks	20–25w D-pulse	30 days after last treatment	Significant improvement in dryness, dyspareunia and irritation in the laser group compared with controls.	Significant improvement in histological analysis (increased fibroblasts, glycogenic load, epithelial thickening, neoangiogenesis) in laser group compared with controls.	Mild procedural discomfort was reported by 30% of the laser group.
Salvatore 2014[85]	Observational	50	Three	4 weeks	30w, dwell time 1000 μs, dot space 1000 μm, introitus 20w	4 weeks after final treatment	Significant improvement ($p = 0.001$) in symptoms (vaginal dryness, itching, burning, dyspareunia, dysuria) and quality of life ($p = 0.001$). 84% patients were satisfied.	Significant improvement in VHIS*** ($p = 0.001$)	None
Salvatore 2014[115]	Observational	15	Three	4 weeks	30w, dwell time 1000 μs, dot space 1000 μm, introitus 20w	4 weeks after final treatment	The intensity of dyspareunia significantly decreased from baseline (8.7 ± 1.0) to 12-week follow-up (2.2 ± 1.0; $p<0.001$). Other GSM symptoms also resolved, $p<0.05$.	Significant improvements in VHIS, FSFI and quality of life (all $p<0.001$).	None
Zerbinati 2014[47]	Observational	50 (5 selected for histology)	Not reported	Not reported	Operator dependent	60 days	Significant improvement in dryness, itching, dysuria, burning, dyspareunia, $p<0.001$.	Significant improvement in VHIS $p<0.001$. Histology showed epithelial thickening, increased glycogen and shedding, increased fibroblast and collagen, new papillae.	
Salvatore 2015[48]	Observational	5 (5 x treated biopsies, 5 x control biopsies)	Not reported	Not reported	30w, dwell time 1000 μs, dot space 1000–2000 μm	Not reported		The most pronounced histological effects were evident in smart stack 3 mode.	
Salvatore 2015[116]	Observational	77	Three	4 weeks	30w, dwell time 1000 μs, dot space 1000 μm, introitus 20w.	12 weeks	Overall satisfaction with sexual life significantly improved according to VAS ($p<0.001$). Significant improvement in all GSM symptoms ($p<0.001$) and in quality-of-life.	Significant improvement in FSFI total score and all domain scores at 12-weeks compared to baseline ($p<0.001$).	

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Table 3 (Continued).

Study	Study Type	No. of Patients	No. of Treatments	Interval Between Treatments	Delivery of Treatment	Maximum Follow-Up Duration	Subjective Outcome	Objective Outcome	Adverse Events
Perino 2015[84]	Observational	48	Three	30 days	40w, dwell time 1000 μs, dot space 1000 μm, pulsed mode, introitus 20/30w.	30 days after last treatment	Significant improvement in symptoms (vaginal dryness, itching, burning and dyspareunia) ($p < 0.0001$). 92% of patients were satisfied	VHIS were significantly higher $p<0.0001$	None
Murina 2016[86]	Observational	70 (33 GSM, 37 vulvodynia)	Three	Three treatments spaced over 30 days	30w, dwell time 1000 μs, dot space 700 μm, pulsed mode,	4 months after final treatment	Statistically significant ($p < 0.05$) improvement was noted in dyspareunia and pain scores, sustained at 4 months. No difference between two groups.	Vestibular health index score improved significantly. No difference between two groups.	3 patients reported a transient burning sensation
Pitsouni 2016[87]	Observational	53	Three	4 weeks	30w, dwell time 1000 μs, dot space 1000 μm, introitus 20w	4 weeks after final treatment	VAS**** scores for dyspareunia, dryness, burning, itching and dysuria decreased significantly.	VMV*****, VHIS and FSFI increased significantly	
Athanasiou 2016[50]	Observational	53	Three	4 weeks	40W, 1000 μs dwell time, 1000 μm spacing. Introitus: 24w, 400μs dwell time, 1000μm spacing.	4 weeks after final treatment		Laser therapy increased Lactobacillus from 30% to 79% ($p<0.001$) and normal flora ($p<0.001$), and decreased vaginal pH from a mean of 5.5 ± 0.8 to 4.7 ± 0.5 ($p < 0.001$).	Transient mild irritation of introitus
Sokol 2016[88]	Observational	30	Three	6 weeks	30w, dwell time 1000 μs, dot space 1000 μm	3 months after final treatment	Improvements in VAS scores for dyspareunia, dryness, burning, itching, pain and dysuria.	Significant improvements in VHIS and FSFI******, $p<0.001$.	Two patients had post-procedure pain for 2–3 days. One patient had transient post-procedure minor bleeding.

Sokol 2017[89]	Observational	30 (same cohort as above but longer FU)	Three	6 weeks	30w, dwell time 1000 μs, dot space 1000 μm	12 months after final treatment	Improvements in VAS scores for dyspareunia, dryness, burning, itching and pain sustained at 12 months, with the exception of dysuria.	Significant improvement in VHIS and FSFI p<0.001, sustained at 12 months.	
Cruz 2017[117]	RCT	45 14 Estriol (E) 13 laser (L) 15 laser + estriol (LE)	Two	4 weeks	300w, dwell time 1000 μs, dot space 1000 μm	20 weeks	L and LE groups showed a significant improvement of dyspareunia, burning, and dryness, and the E arm only of dryness ($p < 0.001$).	LE group showed a significant improvement in FSFI, $p< 0.02$. No difference in VMV between groups.	
Behnia-Wilson 2017[91]	Observational	102	Three	6 or more weeks	30w, dwell time 1000 μs, dot space 1000 μm, pulsed, vestibule probe 20w	24 months after the initial treatment	Significant improvement in GSM symptoms and sexual function sustained at 24 months post-procedure (using Australian pelvic floor questionnaire).		3 patients had infection, 3 patients had transient pelvic pain, 1 patient had herpes recurrence, 2 patients had bleeding.
Pieralli 2017[90]	Observational	184	Three	4 weeks	30w, dwell time 1000 μs, dot space 1000 μm	24 months	Drop-off in patient satisfaction to 25% at 24 months from 95% at 6 weeks. Drop-off more prominent in spontaneous menopause group compared to iatrogenic menopause.		
Lang 2017[64]	Observational	122	Three	Not reported	Not reported	Mean 31 weeks	Patient reported vaginal dryness significantly improved following treatment ($p < 0.05$). The frequency of intercourse increased from "once a month" to "few times a month" ($p < 0.001$). 86% of patients reported being satisfied.		Five patients (4%) reporting urinary symptoms, two patients (1.6%) reporting vaginal pain/burning, one patient (0.1%) reporting vaginal itching, and one patient (0.1%) reporting dyspareunia.
Siliquini 2017[92]	Observational	87	Three	4 weeks	40w, introitus 15–30w	15 months after final treatment	Improvement in VAS scores for dyspareunia and dryness, maintained at 15 months ($p < 0.001$).	Significant improvement in VHIS p<0.001	Pain encountered during the laser applications progressively improved with the number of treatments

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Table 3 (Continued).

Study	Study Type	No. of Patients	No. of Treatments	Interval Between Treatments	Delivery of Treatment	Maximum Follow-Up Duration	Subjective Outcome	Objective Outcome	Adverse Events
Athanasiou 2017[110]	Observational	55 (55 had 3 sessions, 53 had 4 sessions, 22 had 5 sessions)	Three, four or five	4 weeks	Not reported	4 weeks after final treatment	Following the third, fourth and fifth laser sessions, respectively: dyspareunia completely regressed in 15/55 (27%), 32/55 (58%) and 38/47 (81%); dryness completely regressed in 20/55 (36%), 36/55 (66%) and 44/51 (86%); normal sexual function resumed in 23/55 (41%), 37/54 (69%) and 41/49 (84%).	Following the third, fourth and fifth laser sessions, respectively: VMV regained non-atrophic values in 29/55 (53%), 38/55 (69%) and 42/50 (84%); and VHIS regained non-atrophic values in 44/55 (80%), 53/55 (96%) and 55/55 (100%).	Some patients reported mild irritation at the introitus during the procedure and immediately afterwards, which resolved spontaneously.
Pitsouni 2017[119]	Observational	50 (25 had 30w, 25 had 40w)	Three	4 weeks	30 or 40w, dwell time 1000 μs, dot space 1000 μm, pulsed.	1 month after final treatment	Significant improvement in dryness, dyspareunia and itching in both groups. No difference between the 30w and 40w groups.	Significant improvement in VHIS, VMV and FSFI in both groups. No difference between the 30w and 40w groups.	Mild transient introital irritation
Arroyo 2017[114]	Observational	12	Three	3–4 weeks	40–55mJ Pulsed mode	24 weeks post final treatment	100% reported satisfaction with treatment. At 24 weeks subjective improvement in vaginal rejuvenation and overall satisfaction remained high at 88%, while sexual gratification decreased to findings similar to those at the 6-week follow-up.	VHIS improvement remained significant at 6–8 months after treatments ($P<0.01$).	97% reported no to mild discomfort with treatment. Responses were mild and transient following treatment, with itching being the most commonly reported (20%).
Salvatore 2018[49]	Observational	63	One	NA	30w, dwell time 1000 μs, dot space 1000 μm	Histology examined 1 hour after laser		1 hour post laser, biopsy shows thicker epithelium with desquamation and new papillae, compared with pre-treatment biopsies.	

Samuels 2018[46]	Observational	40	Three	4 weeks	50–60mJ, Pulsed, vestibular probe also used.	12 months after final treatment	Symptoms of dryness, itching, and dyspareunia improved significantly ($p < 0.05$) at all evaluations.	VHIS improved significantly after first treatment and this was maintained at 12 months $p<0.001$. Significant improvement in FSFI maintained at 12 months $p<0.001$. Histological findings showed increased collagen and elastin, and thicker epithelium.	4 cases of itching, 1 case of dysuria, 1 case of spotting.
Singh 2018[93]	Observational	45	Five	0, 1, 2, 3, and 6 months	40w, dwell time 1000 μs, dot space 1000 μm, pulsed.	6 months after final treatment	Reduction in patient reported dryness and dyspareunia.	Significant improvement in VHIS scores, $p<0.05$.	A few patients reported discomfort on probe insertion and soreness.
Eder 2018[94]	Observational	28	Three	4 weeks	7.5–12.5mJ	6 months after final treatment	GSM symptoms significantly improved after first treatment, and improved further at 3 and 6 months. 89% patients satisfied at 6 months.	VHIS and FSFI improved significantly after first treatment, and improved further at 3 and 6 months, $p<0.05$.	One case of bleeding.
Eder 2019[95]	Observational	20 (same cohort as above with 18 month FU)	Three	4 weeks	7.5–12.5mJ	18 months after final treatment		15/20 patients required an additional treatment between 12–15 months, but this maintained improvements in symptoms, VHIS and FSFI	
Athanasiou 2019[111]	Observational	94 (35 had 3 sessions, 35 had 4 sessions, 24 had 5 sessions)	Three, four or five	30 days	30–40w, dwell time 1000 μs, dot space 1000 μm, pulsed, introitus 24w.	12 months	All GSM symptoms according to VAS score improved significantly up to 12 months in all groups. Significant difference between 3 and 4 sessions for dryness and dyspareunia, and between 3 and 5 sessions for dryness. No difference between four or five sessions.	FSFI and frequency of intercourse improved significantly $p<0.001$ up to 12 months in all groups. Significant difference between 3 and 4 sessions for total FSFI score. No difference between four or five sessions.	None
Paraiso 2019[106]	RCT	62 (30 Laser 32 oestrogen)	Three	6 weeks	30w, dwell time 1000 μs, dot space 1000 μm, vulva 26w.	6 months	No significant difference in patient satisfaction between groups.	VMI higher in oestrogen group, $p=0.02$. No difference in FSFI between groups.	57% reported procedure was moderately uncomfortable

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Table 3 (Continued).

Study	Study Type	No. of Patients	No. of Treatments	Interval Between Treatments	Delivery of Treatment	Maximum Follow-Up Duration	Subjective Outcome	Objective Outcome	Adverse Events
Filippini 2019[96]	Observational	645	Three or four	Treatment course spread over a mean of 6.5 months.	40 W, dwell time 1000ms, spacing 1000mm. Vulva: 25w, dwell time 500ms, spacing 500mm	One month after final treatment.	Significant improvements were found in all VAS scores for dryness, burning, itching, dyspareunia, vaginal orifice pain p<0.0001.	Significant reduction in pH p<0.0001. Improvements in VAS scores, all significantly more pronounced in the group who had four treatments compared with three.	None
Politano 2019[107]	RCT	72 (24 laser, 24 oestrogen, 24 lubricants)	Three	30 days	40W, dwell time 1000ms, spacing 1000mm.	14 weeks		VHI score higher in laser group (mean score 18.68) than in the oestrogen (15.11) and lubricant (10.44) groups (p<0.001). VMV improvement most pronounced in laser group, p<0.001. No differences in total FSFI score among the three groups.	
Tovar-Huamani 2019[97]	Observational	60	Three	30 days	40W, dwell time 1000ms, spacing 1000mm.	1 month after final treatment	Significant improvement in symptoms including dryness, itching, burning, dyspareunia, dysuria, urinary urgency, p<0.001.	Significant improvement in VHIS, Frost index, and FSFI, p<0.001.	One patient dysuria and urinary frequency.
Marin 2019[98]	Observational	50	Two	6 weeks	18W, On time: 320 ms, Off time 1200 ms.	6 months		Significant improvement in FSFI and quality of life, p<0.05.	Common: vaginal itching, leukorrhoea and mild oedema. Rare: UTI.
Takacs 2020[99]	Observational	52	Three	4 weeks	30W, 1000 µs dwell time, 1000 µm spacing, pulsed.	4–6 weeks after final treatment.	Significant improvement in VAS score for dryness.	No significant improvement in VMV.	
Gardner 2020[119]	Observational	139	Three	6 weeks	Not reported	12 weeks	Significant improvement in VAS scores for dryness p<0.001 and dyspareunia p<0.001 and in Vulvovaginal symptoms questionnaire, p<0.05.	Significant improvement in FSFI p<0.001.	None

Ruanphoo 2020[100]	RCT	88 (44 laser, 44 sham)	Three	4 weeks	4 W, dwell time 1000 ms, spacing 1000mm, pulsed.	12 weeks	Significant difference in ICIQ-VS and VAS score for dryness between sham and laser group, p=0.03.	Significant difference in VHIS score between sham and laser group, p<0.001.	Pain after procedure 1%. Bleeding, discharge, vaginitis <1%.
Li 2020[108]	Observational	162 (Laser 108, Oestrogen 54)	Two or three	4 ± 1 week	35–40W, 800–1000 µs dwell time, 800–1000 µm spacing,	12 months	Both laser and oestrogen groups showed a significant improvement in VAS scores for burning, dryness, and dyspareunia (p>0.05). No difference between the groups.	VHIS improved significantly in both laser and oestrogen groups up to 6 months FU, but the improvement was sustained at 12 months in the laser group only.	None
Di Donato 2020[113]	Observational	53	Three	4 weeks	7.5–12.5mJ	3 months after last treatment	Mean procedure-related pain score decreased significantly from first treatment to third treatment, p<0.001. 84% patients would recommend the treatment, 94% would repeat the treatment if needed.		One patient reported procedure-related pain, bleeding and dizziness. One patient reported discharge, one infection and two cases of dysuria post procedure. No severe complications reported.
Alexiades 2020[101]	Observational	18	Three	Monthly	50mJ, fractional density 5%, fluence 283 J/cm^2, vulval probe also used.	12 months	94% patients satisfied at 12 months.	Significant improvement in VHIS p<0.003 and FSFI p<0.03. Improvement more marked at 6 months than at 12 months.	No-to-slight discomfort in the majority of subjects, and transient erythema and oedema.
Quick 2021[102]	RCT	18 (10 laser, 8 sham)	Three	30 days	30W, 1000 µs dwell time, 1000 µm spacing. Vulva: 26w, 800µs dwell time, 800µm spacing.	4 weeks after final treatment	No difference in VAS scores between groups.	Significant improvement in FSFI in the laser group compared with sham p = 0.02.	Discharge, dryness, pain or inflammation n=1-5.

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Table 3 (Continued).

Study	Study Type	No. of Patients	No. of Treatments	Interval Between Treatments	Delivery of Treatment	Maximum Follow-Up Duration	Subjective Outcome	Objective Outcome	Adverse Events
Salvatore 2021[103]	RCT	58 (28 laser, 30 sham)	Three	4 weeks	30W, 1000 µs dwell time, 1000 µm spacing. Vulva: 24w, 400µs dwell time, 1000µm spacing.	1 month after final treatment	Significant improvement in VAS scores for dryness, dyspareunia, itching and burning in laser group. VAS dryness score also significantly improved in sham group but was significantly lower than the laser group $p<0.005$.	Significant improvement in FSFI in laser group compared to sham.	Mild vulva irritation for 30 mins post procedure 100% laser group.
Cruff 2021[104]	RCT	30 (14 laser, 16 sham)	Three	6 weeks	30W, 1000 µs dwell time, 1000 µm spacing. Vulva: 26w, 800µs dwell time, 800µm spacing.	6 months	Significant improvement in VAS in both groups with no difference between the groups.	Significant improvement in VHIS and FSFI in both groups with no difference between the groups.	None
Dutra 2021[109]	RCT	25 (13 laser group, 12 oestrogen group)	Three	30 days	30W, 1000 µs dwell time, 1000 µm spacing.	30 days after last treatment	Subjective evaluation through physical examination showed a significant improvement in atrophy in both groups.	Histology showed a significant increase in epithelial thickness in both groups with no difference between the groups. Sexual function scores increased significantly in both groups with no difference between the groups.	

Notes: *PRP Platelet-rich plasma, **PFE Pelvic floor exercises, ***VHIS Vaginal health index score, ****VAS Visual analogue scale, *****VMV Vaginal maturation value, ******FSFI Female sexual function index.

The first multicentre and largest study to-date was published by Filippini in 2019, involving 645 women with GSM. Significant improvements were found in all parameters (dryness/atrophy, burning, itching, dyspareunia, vaginal orifice pain, pH) at 1 month post 3 or 4 CO2 laser treatments.[96]

In 2022, Filippini also published a systematic review of 25 studies investigating CO2 laser treatment for GSM. This involved 1152 patients. The pooled mean differences for the symptoms were: dryness −5.15 ($p < 0.001$), dyspareunia −5.27 ($p < 0.001$), itching −2.75 ($p < 0.001$), burning −2.66 ($p < 0.001$) and dysuria −2.14 ($p < 0.001$). FSFI, VHIS and VMV scores also improved significantly and no major adverse events were reported.[105]

Systematic Reviews and Meta-Analysis

There are a number of systematic reviews that incorporate evidence for both CO2 and Erbium:YAG lasers in treatment of GSM.

In 2017, reviews were published by Arunkalaivanan, Tadir, Pitsouni and Gambacciani involving 4–20 studies. These yielded promising results for vaginal laser treatment of GSM and called for an urgent need for large, long-term, randomised, placebo-controlled and drug-controlled studies to further evaluate safety and efficacy.[35,83,120,121]

In 2018 and 2019, further reviews were published by Rabley, Song, Bhide and Franic, again acknowledging promising early data but conclusions remained limited by the weak observational data, small sample sizes and short follow-up duration.[122–125]

Focus on: Comparison of Laser with Oestrogen

A number of studies have compared the effect of vaginal laser and vaginal oestrogen on GSM,[17,54,106–109,117] 5 of which relate to CO2 laser[106–109,117] and 2 of which relate to Erbium:YAG laser.[17,54]

The first comparison of laser and topical oestrogen for GSM was reported by Gambacciani in 2015. This study compared 3 × monthly Erbium:YAG laser treatments ($n = 45$) vs 3 months vaginal oestrogen twice weekly ($n = 25$). Both groups showed a significant improvement in vaginal dryness and dyspareunia but after 24 weeks the improvement had diminished in the oestrogen group following cessation of treatment.[1,54]

Gaspar 2017 reported a study comparing the treatment of 25 women receiving estriol for 8 weeks with 25 women receiving 2 weeks of estriol followed by 3 sessions of Erbium:YAG laser. There was a statistically significant reduction in all symptoms in both groups up to the 6-month follow-up ($p < 0.05$); however, the relief of symptoms was more pronounced in the laser group. Furthermore, the effect of the laser treatment remained statistically significant at 12 and 18-months, while the effect of estriol diminished. Side effects were minimal and of transient nature in both groups, affecting 4% of patients in the laser group and 12% of patients in the estriol group.[1,17]

Also, in 2017, a double-blinded RCT was published by Cruz comparing CO2 laser vs topical oestrogen vs combination treatment with 15 women in each arm. The VHIS was significantly higher in all groups, but the greatest improvement was seen in the combined treatment group ($p = 0.01$). Laser and combination therapy groups showed a significant improvement in vaginal dryness, burning and dyspareunia, whereas the oestrogen arm demonstrated improvement in the symptom of dryness only ($p < 0.001$). Only the combination therapy group showed an improvement in FSFI scores, overall suggesting that combination therapy may be superior if oestrogen is not contraindicated, though this was underpowered for some of the outcomes.[117]

In 2019, the multicentre "VeLVET" RCT was published comparing CO2 laser with topical oestrogen for GSM. There was no significant difference between the groups in terms of symptom improvement, FSFI scores and adverse events at 6-month follow-up, although vaginal maturation index (VMI) remained higher in the oestrogen group.[106] Similarly, in 2020, a multicentre cohort study comparing CO2 laser with 3 months of topical oestrogen was published. This showed that at 6 months there was symptomatic improvement in both groups with no significant difference between the two groups.[108] These findings were supported by an RCT by Dutra in 2021, which compared CO2 laser with topical oestrogen. Histological analysis at 30 days reported a significant increase in vaginal epithelium thickness in both groups, with a tendency for a higher maturation index in the oestrogen group. The authors also reported a significant improvement in sexual function in both groups.[109]

However, in 2019, an RCT by Politano comparing CO2 laser vs topical oestrogen vs vaginal lubricant reported that at 14-week follow-up, the VHIS was higher in the CO2 laser group (mean score 18.68) than in the oestrogen (15.11) and lubricant (10.44) groups ($p < 0.001$).[107]

A systematic review was published by Li in 2021 including data from 3 RCTs, 16 prospective, and 7 retrospective observational studies, representing 2678 participants overall. Pooled data failed to demonstrate a difference in terms of vaginal or sexual symptoms between vaginal laser and vaginal oestrogen treatments.[126]

The jury is still out on whether laser or oestrogen is the superior treatment for GSM. Current evidence suggests their effects are comparable. Symptom recurrence may be quicker following cessation of oestrogen treatment then after a course of laser; however, most evidence suggests that symptoms do eventually recur following laser treatment also, in the region of 12–24 months later. With little between the apparent treatment effects, the primary utility of vaginal laser may be for breast cancer survivors, as topical oestrogen use is controversial in this patient group.

Evidence for Vaginal Laser Treatment of GSM in Breast Cancer Survivors

There are currently 28 studies published regarding the use of vaginal laser treatment for GSM in breast cancer survivors, of which 19 relate to CO2 laser[44,51,65–81], 8 relate to Erbium:YAG laser[57–64] and one relates to solid-state vaginal laser.[82] See Table 2 for a summary of the evidence.

Three studies are RCTs and the remainder are observational studies. Number of participants vary from 16 to 256. Number of laser treatments vary from one to five. Follow-up duration varies from 30 days to 2 years. All studies report a significant improvement in objective signs and/or subjective symptoms of GSM except one, the only sham-controlled RCT by Mension et al. In contrast to all other studies, this reported that after five treatments there was no significant difference in VHIS, VMV, FSFI, pH, dyspareunia, body image or quality of life compared with the sham group at follow-up up to 6 months.[81]

Studies with a duration follow-up of 2 years reported conflicting results in terms of long-term treatment effect. Gambacciani et al reported a significant improvement in VAS scores for dryness, dyspareunia and VHIS for up to 12 months, following 3 treatments with Erbium:YAG laser. However, by 18 months, these improvements were no longer significant.[59] Whereas Quick et al reported significant improvements in VAS, VHIS and FSFI following three CO2 laser treatments, which were maintained at 24 months, with a drop off in urinary symptom relief only (urogenital distress index).[51] Similar findings were reported by Veron et al, with significant improvements in FSFI and pH maintained at 18 months, but the significant improvement seen in urinary quality of life (Ditrovie score) at 6 months had returned to baseline at 18 months.[77] Pieralli et al reported a step-wise decline in patient satisfaction with time post-procedure from 95.4% at 4 weeks, to 92% at 6 months, 72% at 12 months, 63% at 18 months, and 25% at 24 months, suggesting repeat treatments are likely to be required and perhaps with a shorter time interval than in non-oncological patients.[68]

Last year, Lopez et al published a study, which utilised a different medium for vaginal laser treatment in breast cancer survivors, solid-state vaginal laser (SSVL). They reported on 27 patients who received three laser treatments, 15–20 days apart. At 6 months, there was significant improvement in dyspareunia, VHIS, vulval health index, VMV, FSFI and quality of life.[82]

Six systematic reviews evaluating vaginal laser for GSM treatment in breast cancer patients have been produced.[22,127–131] Four were published in 2019, although conclusions were limited by the small observational studies included. About 6–10 studies were pooled and significant improvements were demonstrated in GSM symptoms (VAS), FSFI scores and VHIS. Whilst the authors acknowledged the promising results, they called for further research to establish long-term follow-up data and clarify the optimum medium for laser therapy, device settings, how many treatments are required and how often treatment needs to be repeated.[22,129–131] Two further systematic reviews were published in 2023, which analysed 12 and 20 studies, respectively, including over 700 breast cancer survivors though only two randomised trials. Both made similar conclusions to the earlier reviews; further studies are required to establish long-term efficacy and safety.[127,128]

Whilst conclusive evidence and powered multicentre RCTs are still awaited, findings thus far suggest vaginal laser may be an efficacious treatment for GSM in the breast cancer population but improvements may not be as marked, more treatments may be required to alleviate symptoms, and results may not be as long-lasting as the natural menopause

population. Despite those caveats, this patient group are set to gain the most if vaginal laser is to be deemed safe and efficacious, due to the lack of hormonal alternatives available.

Number of Sessions

The majority of studies reviewed utilise 3 treatments at intervals of 4 weeks (range 2–6 weeks). Few studies report outcomes following 1 or 2 treatments. One study in breast cancer survivors reported outcomes following 5 treatments, based on the presumption that GSM is more severe in this population.[78]

Only one study by Athanasiou compares alternative regimes of 3, 4 or 5 CO2 treatments (monthly intervals).[110] In this study, 55 women received three sessions, 53 received 4 sessions and 22 received 5 sessions. Following the third, fourth and fifth laser sessions, vaginal dryness resolved in 36%, 66% and 86%, respectively; dyspareunia resolved in 27%, 58%, and 81%, respectively; sexual function improved in 41%, 69% and 84%, respectively; and VHIS improved in 80%, 96%, and 100% of participants. The authors concluded that CO2-laser therapy appears to treat signs and symptoms of GSM in a dose-responsive manner and an additional fourth or fifth session may add value in terms of further reduction in symptoms.[110] This paper was followed by the publication of 12-month outcomes for this same cohort a year later. The positive laser effect was sustained at 12-months in all groups regardless of the number of laser sessions, but there was a significant difference between 3 and 5 sessions, in favour of the 5-session group. No differences were detected between 4 and 5 session groups.[111]

Energy Power Setting

The majority of studies referenced in this review reported power settings of 20–40w. Only one study by Pitsouni has compared 30 vs 40w CO2 laser treatment of GSM, with 25 women in each group. This demonstrated no significant difference between the 30w and the 40w groups.[112]

Preparation of Vaginal Mucosa

The majority of studies in this review did not utilise preparatory topical vaginal treatments prior to vaginal laser treatment. Bojanini reported two studies that compared pre-treatment topical oestrogen 3 × per week for 2 weeks vs platelet-rich plasma (PRP) intravaginal injection 2 weeks prior to Erbium:YAG laser. The authors hypothesised that efficacy of laser treatment would be improved if mucosa is hydrated as this will potentiate the warming effects. The aim of platelet-rich plasma (PRP) is bio-stimulation, involving an increase in growth factors and the secretion of proteins that are able to maximize the healing of the tissue, as well as being a safe alternative for breast cancer survivors. There was significant improvement in GSM symptoms in both groups, with no significant difference between the groups. Unfortunately, these studies did not have a control group with patients who had not had vaginal preparation prior to laser treatment.[57,58]

The majority of studies included in this review did not routinely offer topical local anaesthetic prior to vaginal laser treatment.

Safety

A number of small observational studies have reported on adverse outcomes following vaginal laser treatment, with reassuring results that these are infrequent, transient and mild in nature.

In 2015, Gambacciani reported a review of the Italian vaginal Erbium:YAG laser Academy results, evaluating 622 procedures performed in a number of centres. 20 patients reported the treatment was a "bad experience", one patient described it an "unacceptable experience", 36 patients felt the treatment was "acceptable" and the remaining 565 patients reported the treatment was a "good to excellent experience".[40]

However, the FDA issued a statement in July 2018 declaring "the safety and effectiveness of vaginal energy-based devices has not yet been established", that they "can lead to serious side effects, including burns, vaginal discharge, scarring, pain during intercourse and recurrent/chronic pain" and calling for "high vigilance and robust data to validate claims they are both safe and effective".[11,132]

This was followed by a publication by Gambacciani in 2020 focussing on the safety of Erbium:YAG laser. This study involved responses from 188 clinicians, who provided information regarding adverse outcomes for 62,727 patients. The collated data revealed a mean frequency of the following transient effects; vaginal discharge 6.5%, oedema 3.7%, pain during procedure 1.9%, post-operative pain 0.5%, burns 0.1%, irritation 0.5%, itch 0.06%, infection 0.03%, abnormal bleeding 0.04%, and dyspareunia 0.004%. All adverse outcomes were classified as mild or moderate and no permanent complications were reported.[53] This is in contrast to a study by Samuels, who reported erythema in 54% and oedema in 55% with CO2 laser treatment, although this did involve vestibular treatment as well as vaginal.[46] Similarly, a study by Marin reported itch in 95%, and leukorrhoea in 70% post CO2 laser, as well as intra-operative symptoms of "warmth" in 70% and irritation in 18%.[98]

A case series of adverse events following vaginal laser treatment was published by Gordon in 2019. The first case was a 65-year-old lady with vaginal stenosis who suffered vaginal lacerations related to intercourse. Two cases were of persistent dyspareunia post laser, and the final case was the formation of vaginal adhesion resulting in dyspareunia.[133]

A study investigating the safety of vaginal CO2 laser for 53 GSM patients was published in 2020 by Di Donato. One patient reported post-procedure transient dizziness, one patient reported a minor bleed related to probe introduction, and two patients reported transient post-procedure dysuria. In one case, the laser treatment was abandoned due to discomfort; however, this patient later completed the treatment 2 weeks later. The mean pain score at first treatment was 3.57 ± 1.50. This significantly decreased between the first and third treatment. There were no severe complications reported within the 6-month follow-up period, leading the authors to conclude that vaginal CO2 laser seems a safe therapeutic option for GSM.[113]

There is a high degree of variability regarding the prevalence of post-procedure side effects reported in the literature yet, with the exception of the FDA warning and case series by Gordon, no serious complications have been reported. However, evaluation of the safety of repeated applications is certainly lacking in the literature to date.[1]

Currently, this is not a standardised or centralised mechanism for reporting complications associated with vaginal laser treatment. If we are to learn from the mistakes of the vaginal mesh scandal, we must surely establish a national/international registry for reporting outcomes for this relatively novel medical device in order to allow early recognition of any emerging patterns of complications and prompt intervention in an effort to reduce incidence.

Limitations of Evidence

Despite a wealth of observational data, there are a number of limitations regarding the evidence-base for vaginal laser treatment of GSM. There is a paucity of adequately powered RCTs and existing systematic reviews are limited by the quality of data included.

To date, there is no evidence regarding safety or efficacy of vaginal laser treatment beyond 24 months.

The majority of studies report VAS and VHI scores. VHI is assessed and graded by a clinician and is subject to interobserver variation and bias.[22] Quality of life outcomes are only reported in a handful of studies, and there is a lack of studies utilising validated patient reported outcome measures (PROMs).[66,69,78,85,98,116] The DIVA (Day-to-Day Impact of Vaginal Aging) questionnaire, is a recently developed multidimensional self-reported tool for the assessment of GSM, validated to measure the impact of vaginal symptoms including dryness, irritation, soreness, itching, and dyspareunia on quality of life.[134]

There remain a number of unanswered questions with regard to laser machine settings (dwell time, spacing, depth, mode), number of sessions, interval between sessions, energy power settings and pre-treatment vaginal preparation, all of which warrant more rigorous investigation.[22]

There are no studies directly comparing CO2 with Erbium:YAG in the context of GSM treatment, although a protocol for a large multicentre RCT to investigate the effectiveness of CO2 vs Erbium:YAG in GSM treatment has been published.[11]

Recommendations of Official Bodies

The UK National Institute for Health and Care Excellence (NICE) published interventional procedure guidance for "Transvaginal laser therapy for urogenital atrophy" in 2021. This advised laser treatment be restricted to research settings

until robust data are available.[135] This was echoed in the RCOG Scientific Impact Paper "Laser Treatment for Genito-urinary syndrome of the menopause" in July 2022.[134]

This stance is also consistent with the International Urogynaecological Association (IUGA) committee opinion on vaginal laser devices published in 2018, which stated;

> The therapeutic advantages of nonsurgical laser-based devices in urogynaecology can only be recommended after robust clinical trials have demonstrated their long-term complication profile, safety and efficacy.[136]

Similar statements have also been issued by the American College of Obstetricians and Gynaecologists, the North American Menopause Society, the International Society for the Study of Vulvovaginal Disease (ISSVD), and the International Continence Society (ICS); all recommending against use of vaginal laser therapy pending the availability of rigorous evidence to verify long-term effectiveness and safety.[127–140]

Future Research

There is an urgent need for adequately powered randomised sham-controlled trials with long-term follow-up to validate findings seen in observational data before widespread implementation of vaginal laser. Evidence to date suggests that effects diminish with time and repeat treatments are likely to be necessary. As such, the efficacy and safety of repeated treatments must also be established.

Further comparison trials with vaginal oestrogen (in patients not affected by breast cancer) and CO2 vs Erbium:YAG would also be of value. By virtue of its ablative nature, CO2 laser may theoretically be associated with more transient symptoms or complications than Erbium:YAG but results may potentially be more dramatic – these are questions worthy of further investigation.

A cost–benefit analysis comparing vaginal oestrogen with vaginal laser for GSM in non-breast cancer patients, as well as a study of patient views and preferences regarding the two options, would be essential before laser treatment in this patient group could be considered.

Further clarification is required regarding the necessity of vaginal preparation as well as optimum machine settings.

Conclusion

While evidence remains in its infancy and national/international bodies cannot currently recommend it outside of a research context, this review suggests that vaginal laser is likely to be a safe and effective treatment for GSM, with breast cancer patients set to benefit most. However, these findings must be validated in robust randomised sham-controlled trials of adequate power. There remain a number of unanswered questions in terms of which laser medium to opt for, optimal device settings, ideal interval between treatments, vaginal preparation prior to treatment, as well as efficacy and safety of repeated treatments in the long-term. These issues could be addressed most efficiently with a mandatory registry of all vaginal laser procedures. The development of registries is paramount for the safety monitoring and governance of any new medical device, and surely a lesson we must heed from the vaginal mesh scandal.

Disclosure

The authors report no conflicts of interest in this work.

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