NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transvaginal laser therapy for urogenital atrophy

Urogenital atrophy is thinning, drying and inflammation of the tissues around the vaginal area. It most often happens after the menopause and can cause itching, burning and painful sexual intercourse. In this procedure, a device containing a laser is inserted into the vagina (transvaginal). The laser heats the tissue of the vaginal wall, causing changes that are thought to increase the strength and elasticity of the vagina. The aim is to improve the symptoms of urogenital atrophy.

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Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2020.

Procedure name

- Transvaginal laser therapy for urogenital atrophy.

Professional societies

- British Society of Urogynaecology
- British Association of Urological Surgeons
- British Menopause Society
- Royal College of Obstetrics and Gynaecology.

Description of the procedure

Indications and current treatment

Urogenital atrophy most often happens during or after the menopause when the lack of the hormone oestrogen affects the vagina, urethra and bladder trigone. The lack of oestrogen leads to a thinning of the tissues around the vaginal area and a reduction in the number of the mucus producing glands. The most common symptoms affecting the vulva and vagina include dryness, pain on sexual intercourse, vaginal itching and vaginal discharge. There is increased vulnerability to inflammation, trauma and infection. Urogenital atrophy can also result in urinary symptoms, such as urgency to urinate and urinary tract infections.

NICE's guideline on diagnosis and management of menopause describes the management of menopausal symptoms. The main treatments for urogenital atrophy are vaginal oestrogen, and non-hormonal lubricants and moisturisers.

What the procedure involves

Transvaginal laser therapy for urogenital atrophy is done as an outpatient procedure and can be done without anaesthetic. A laser-probe device is inserted into the vagina to apply laser energy to the vaginal wall. The laser causes controlled thermal injury, which is claimed to make the tissue remodel and stimulate the production of new collagen. Treatment typically consists of 3 sessions at 4 to 6 weeks apart. The aim is to reduce the symptoms associated with urogenital atrophy.

There are different types of lasers used for this procedure, including CO_2 and erbium-doped yttrium aluminium garnet (Er:YAG) lasers. The type of laser and the energy level used have different tissue penetration and can cause different types of thermal injury.

Outcome measures

Vaginal Health Index

The Vaginal Health Index assesses 5 components on a scale of 1 to 5: elasticity, fluid volume, pH, epithelial integrity and moisture. The minimum total score of 5 points indicates severe vulvovaginal atrophy and the maximum total score of 25 points indicates no clinical signs of vulvovaginal atrophy.

Female Sexual Function Index

The Female Sexual Function Index (FSFI) is a multidimensional measure of female sexual functioning with 19 items that are scored from 0 (or 1) to 5. There are 6 domains: desire, arousal, lubrication, orgasm, satisfaction and pain. The scoring algorithm sums items on each domain and then scales the sums so that the maximum score is 6, with higher scores indicating better functioning. The FSFI total score is the sum of the 6 domain scores and has a maximum score of 36. A total score of 26 or less has been validated as a cutoff score for diagnosing female sexual dysfunction.

Efficacy summary

Dryness or atrophy

In a systematic review of 542 patients (14 studies), there was a statistically significant improvement in the dryness visual analogue scale (VAS) score at

1-month follow up (pooled mean difference -5.5, 95% confidence interval [CI] - 6.7 to -4.4, 7 studies, I^2=0%, n=298).[1] In a systematic review of 522 women with a history of breast cancer treatment (10 studies), there was a statistically significant improvement in the dryness VAS score after laser therapy (mean difference 2.7, 95% CI 2.5 to 2.9, 5 studies, I^2=97%, n=208).[2]

In a randomised controlled trial (RCT) of 88 patients, the median score for vaginal dryness (measured on the International Consultation on Incontinence Modular Questionnaire, Vaginal Symptoms) reduced from 5.00 at baseline to 3.24 at 12-week follow up (p=0.02) in the laser group and from 4.00 to 2.00 (p=0.07) in the sham treatment group. The difference between the groups was not statistically significant. The vaginal atrophy symptom score reduced from 2.27 at baseline to 1.83 at 12-week follow up (p<0.001) in the laser group and increased from 2.02 to 2.06 (p=0.59) in the sham group. The difference between the groups was statistically significant 12 weeks after treatment (p=0.03).[3]

In an RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant reduction in the VAS score for dryness in all 3 groups from baseline to week 20 (from 8.0 to 1.4 in the laser group, from 5.6 to 0.5 in the oestrogen cream group and from 7.9 to 0.3 in the group who had both, p<0.001 for all 3 groups). There was no statistically significant difference between the groups.[4] In an RCT of 69 patients who had laser therapy or vaginal oestrogen cream, there were similar reductions in dryness between the groups at 6-month follow up (mean difference in VAS score -5.48 and -5.76 respectively, p=0.67).[5] In an RCT of 72 patients who had laser therapy, vaginal oestrogen cream or vaginal lubricant, there was a statistically significant increase in moisture from baseline to week 14 in the laser and oestrogen groups (moisture domain of Vaginal Health Index score increased from 2.17 to 3.98 and from 1.83 to 3.11 respectively, p<0.05 for both). The mean difference in scores between baseline and week 14 were 1.45, 1.16 and -0.06 for laser, oestrogen and lubricant respectively (p<0.001 between groups).[6]

In a non-randomised comparative study of 254 patients who had laser therapy or local treatment (hormonal or non-hormonal topical treatments), the VAS score for atrophy improved from 8.3 and 8.0 at baseline to 3.5 (p<0.01) and 6.0 (not statistically significant) respectively at 6-month follow up (p<0.05 between groups). At 12, 18 and 24-month follow up, the scores in the laser group were 5.6 (p<0.01), 6.2 (not statistically significant) and 7.0 (not statistically significant).[7]

In a case series of 645 patients, the VAS score for dryness or atrophy reduced from 8.30 before treatment to 2.97 at 1-month follow up (p<0.0001).[8]

Dyspareunia

In the systematic review of 542 patients there was a statistically significant improvement in the dyspareunia visual analogue scale (VAS) score at 1-month follow up (pooled mean difference -5.6, 95% CI -6.8 to -4.5, 7 studies, I^2=0%, n=270).[1] In the systematic review of 522 women with a history of breast cancer treatment, there was a statistically significant improvement in the dyspareunia VAS score after laser therapy (mean difference 2.2, 95% CI 2.0 to 2.5, 4 studies, I^2=96%, n=183).[2]

In the RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant reduction in the VAS score for dyspareunia in the laser therapy and combined-treatment groups from baseline to week 20 (from 4.9 to 0.7 in the laser group [p=0.01], from 3.2 to 0.2 in the oestrogen cream group [p=0.058] and from 6.5 to 0.9 in the group who had both [p=0.009]). There was no statistically significant difference between the groups.[4]

In the non-randomised comparative study of 254 patients who had laser therapy or local treatment (hormonal or non-hormonal topical treatments), the VAS score for dyspareunia improved from 8.5 and 8.0 at baseline to 4.2 (p<0.01) and 7.7 (not statistically significant) respectively at 6-month follow up (p<0.05 between groups). At 12, 18 and 24-month follow up, the scores in the laser group were 5.3 (p<0.01), 7.5 (not statistically significant) and 8.2 (not statistically significant).[7]

In the case series of 645 patients, the VAS score for dyspareunia reduced from 8.70 before treatment to 3.51 at 1-month follow up (p<0.0001).[8]

Itching or burning

In the systematic review of 542 patients there was a statistically significant improvement in the VAS score for itching and for burning at 1-month follow up (pooled mean difference -4.0, 95% CI -5.7 to -2.2, 6 studies, I^2=79%, n=272 and - 3.9, 95% CI -5.9 to -2.0, 6 studies, I^2=87%, n=281).[1]

In the RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant reduction in the VAS score for burning in the laser therapy and combined-treatment groups from baseline to week 20 (from 3.9 to 0.5 in the laser group [p=0.02], from 0.9 to 0.1 in the oestrogen cream group [p=0.51] and from 4.9 to 0.4 in the group who had both [p=0.002]). This symptom was statistically significantly milder at baseline in the oestrogen cream group compared with the other 2 groups (p=0.017), but there were no statistically significant differences between the groups at follow up.[4] In the RCT of 69 patients who had laser therapy or vaginal oestrogen cream, there were similar

reductions in itching between the groups at 6-month follow-up (mean difference in VAS score -1.84 and -1.24 respectively, p=0.45).[5]

In the case series of 645 patients the VAS score for itching reduced from 6.09 to 1.32 and the VAS score for burning reduced from 6.12 to 1.78 at 1-month follow up (p<0.0001 for both).[8]

Female Sexual Function Index

In the systematic review of 542 patients there was a statistically significant improvement in the Female Sexual Function Index (FSFI) at 1-month follow up (pooled mean difference 13.2, 95% CI 9.1 to 17.3, 3 studies, I^2=0%, n=143).[1]

In the RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant improvement in total FSFI score only in the combined-treatment group (from 18.7 at baseline to 23.6 at week 20 [p=0.02]). The score decreased in the laser group, from 18.6 to 14.4 (p=0.26) and increased in the oestrogen cream group from 23.6 to 25.4 (p=0.56).[4] In the RCT of 69 patients who had laser therapy or vaginal oestrogen cream, there were no statistically significant differences between the groups at 6-month follow up (mean difference in FSFI 1.7 and 4.9 respectively, p=0.1).[5] In the RCT of 72 patients who had laser therapy, vaginal oestrogen cream or vaginal lubricant, there was no statistically significant difference in FSFI score improvements between the groups at 14 weeks (score differences were 2.95, 1.99 and 3.05 respectively, p=0.577).[6]

Vaginal Health Index

In the systematic review of 542 patients there was a statistically significant improvement in the Vaginal Health Index (VHI) score at 1-month follow up (pooled mean difference 10.7, 95% CI 8.7 to 12.7, 7 studies, I^2=0%, n=274).[1] In the systematic review of 522 women with a history of breast cancer treatment the mean difference in the VHI score after laser therapy was -11.4, 95% CI -11.8 to - 10.9, 5 studies, I^2=98%, n=130).[2]

In the RCT of 88 patients the VHI score improved from 14.18 at baseline to 17.45 at 12 weeks (p<0.001) in the laser group and from 14.66 to 16.08 in the sham group (p=0.06). The difference in the 2 groups at 12 weeks after treatment was statistically significant (p<0.001).[3]

In the RCT of 45 patients who had laser therapy, vaginal oestrogen cream or both, there was a statistically significant improvement in mean VHI score in all 3 treatment groups from baseline to week 20 (from 11.7 to 18.5 in the laser group [p<0.01], from 12.6 to 22.0 in the oestrogen cream group [p<0.01] and from 12.6 to 23.0 in the group who had both [p<0.01]). The difference between the groups

was statistically significant ($p<0.05$).[4] In the RCT of 69 patients who had laser therapy or vaginal oestrogen cream, there were similar differences in the VHI score after treatment between the groups at 6-month follow up (mean difference 0.9 and 1.2 respectively, $p=0.07$).[5] In the RCT of 72 patients who had laser therapy, vaginal oestrogen cream or vaginal lubricant, there was a statistically significant increase in total VHI score from baseline to week 14 in the laser and oestrogen cream groups (from 9.50 to 18.68 and from 9.00 to 15.11 respectively, $p<0.001$ for both). The mean difference in scores between baseline and week 14 were 9.36, 5.89 and 0.06 for laser, oestrogen cream and lubricant respectively ($p<0.001$ between groups).[6]

In the non-randomised comparative study of 254 patients who had laser therapy or local treatment (hormonal or non-hormonal topical treatments), the VHI score improved from 10.6 and 10.8 at baseline to 18.7 ($p<0.01$) and 12.0 ($p<0.01$) respectively at 6-month follow up. At 12, 18 and 24-month follow-up the scores in the laser group were 16.5 ($p<0.01$), 15.3 ($p<0.01$) and 12.7 (not statistically significant).[7]

Patient satisfaction

In the systematic review of 522 women with a history of breast cancer treatment the proportion of patients with improvement in symptoms or satisfaction after laser treatment ranged from 59% to 96% (mean 84%, 6 studies).[2]

In the RCT of 88 patients who had laser therapy or sham treatment, the proportion of patients who were satisfied or very satisfied was 79.5% (31/39) and 44.7% (17/38) respectively ($p=0.002$).[3]

In the RCT of 69 patients who had laser therapy or vaginal oestrogen cream, the proportion of patients who were satisfied or very satisfied was 76% in both groups.[5]

In the non-randomised comparative study of 254 patients who had laser therapy or local treatment (hormonal or non-hormonal topical treatments), 4% (8/205) of patients who had laser therapy stated it was not effective in reducing symptoms. Laser therapy was defined as effective up to 3 months by 23 patients (11%), up to 6 months by 18 patients (9%) and 74% (151/205) of patients stated it was effective for 12 to 18 months. Only 5 patients (2%) were still satisfied 24 months after the last laser treatment session.[7]

In a case series of 184 patients, patient satisfaction was 92% (170/184), 72% (118/162), 63% (60/94) and 25% (4/16) at 6, 12, 18 and 24-month follow up respectively.[9]

Safety summary

Persistent and worsening dyspareunia

Persistent painful intercourse was reported by 3 patients in a case series of 4 patients who had complications after laser therapy for genitourinary syndrome of menopause. The first patient had mild dyspareunia before the laser treatment but the pain became progressively worse afterwards. On examination 10 months after finishing 3 courses of laser therapy this patient had moderate vaginal dryness, a vaginal pH of 6.5, a positive Q-tip test with vestibular inflammation, and pelvic floor hypertonus with spasm of both levator and vaginal muscles. Treatment involved vaginal rehabilitation with topical hormones to the vestibule, intravaginal Valium and intravaginal sex steroid for moderate to severe dyspareunia.

The second patient had persistent and worsening painful intercourse after completing 3 courses of laser treatment. She had severe vaginal dryness, with burning and itching and associated coital pain. On examination, there was a crescent shaped fibrous band mid vagina, which impinged on the diameter of the vaginal canal, creating a partial obstruction and vaginal canal stricture. The vaginal pH was 6.5 and there was decreased rugae, pale, frail and inelastic tissues. Treatment involved vaginal rehabilitation with nightly intravaginal local prasterone, vaginal moisturisers and a home vaginal dilator programme. At 1-month follow up she reported improvement in vaginal dryness but was concerned about resuming intercourse.

The third patient also had persistent and progressively worsening painful intercourse after 3 laser treatments. She had a history of hysterectomy with a bladder sling, mesh erosion surgery with removal and fascial sling placement and a third operation to loosen the sling because of overtightening. Before the laser procedure, she had vaginal dryness and mild to moderate dyspareunia. After the laser treatments, sexual intercourse was severely painful, with increased pain on penile insertion. On examination, she had a moderate amount of pelvic floor hypertonus, and a moderate amount of levator ani spasms with minimal anterior and lateral wall scarring. Treatment involved vaginal moisturiser and nightly off-label use of intravaginal Valium, and self-dilation exercises.[10]

Vaginal lacerations after resumption of intercourse

Vaginal lacerations were reported in 1 patient after resumption of intercourse a few weeks after laser therapy. These were repaired but the patient presented several months later with severe vaginal pain, dryness and inability to engage in penetrative intercourse. On examination, she had a foreshortened vaginal canal

(about 2.5 cm in length) and fibrotic tissue was noted at the apex and within the canal of the vagina. She was offered intravaginal dehydroepiandrosterone, genitopelvic physical therapy and a vaginal dilator programme. At 3-month follow up she reported being able to engage in intercourse using alternative sexual positions, copious amounts of silicone-based lubricant and use of dilators before coitus.[10]

Discomfort during treatment

Discomfort or a burning sensation that made it necessary to discontinue treatment was reported in less than 1% of patients (2/542) in the systematic review of 542 patients and 4% (3/82) of patients in 1 study included in the systematic review of 522 patients.[1,2]

Pain

Pain after the procedure was reported in 1% (3/41) of patients who had laser therapy and 1% (4/38) of patients who had sham treatment in the RCT of 88 patients.[3] Vaginal pain was reported in 1 patient who had laser therapy in the RCT of 69 patients.[5]

Bleeding

Vaginal bleeding was reported in 7% (2/30) of patients who had laser therapy and 6% (2/32) of patients who had oestrogen cream in the RCT of 69 patients.[5]

Infection

Vaginitis was reported in 1 patient who had laser therapy in the RCT of 88 patients.[3] Urinary tract infection was reported in 1 patient who had laser therapy in the RCT of 69 patients.[5]

Vaginal discharge

Vaginal discharge was reported in 1% (3/41) of patients who had laser therapy and less than 1% (1/38) of patients who had sham treatment in the RCT of 88 patients.[3] Vaginal discharge was reported in 1 patient who had laser therapy in the RCT of 69 patients.[5]

Adverse events reported to the US Food and Drug Administration

Adverse events relating to laser and energy-based devices for vaginal rejuvenation were reported on the Food and Drug Administration MAUDE

database for 45 patients (including 9 procedures to treat vaginal atrophy): pain (n=19), burning or numbness (n=11), scarring or burns (n=7), dyspareunia (n=6), increased urinary frequency or incontinence (n=4), redness or irritation (n=3), infection (n=2), bladder or urethral pain (n=2), discomfort (n=2), miscellaneous (n=3).[11]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts did not describe any additional anecdotal or theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transvaginal laser therapy for urogenital atrophy. The following databases were searched, covering the period from their start to 20 July 2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with urogenital atrophy.
Intervention/test	Transvaginal laser therapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 2,500 patients from 2 systematic reviews, 4 randomised controlled trials, 1 non-randomised comparative study and 4 case series.[1 to 11] Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on transvaginal laser therapy for urogenital atrophy

Study 1 Pitsouni E (2017)

Details

Study type	**Systematic review**
Country	Not reported for individual studies
Recruitment period	Search date: October 2016
Study population and number	**n=542 (14 studies)** Postmenopausal women with symptoms and clinical signs of genitourinary syndrome of menopause, with or without urinary incontinence
Age	Mean age range 53 to 63 years
Patient selection criteria	The search strategy included the following combinations of keywords: 'laser genitourinary syndrome of menopause' or 'laser vulvovaginal atrophy' or 'laser vaginal atrophy' or 'laser women incontinence'. No limits were used. Articles were full-text, peer-reviewed and English language.
Technique	10 studies used CO_2 laser (SmartXide^{2}V^{2}LR, Monalisa Touch, DEKA, Italy) and 4 studies used Er:YAG laser (Fotona Smooth XS, Fotona, Slovenia). In all studies, the treatment protocol involved 3 laser sessions.
Follow-up	**Range 1 to 25 months (8 studies had 1-month follow-up)**
Conflict of interest/source of funding	One author has had financial relations (expert testimonies and lectures) with DEKA laser. No funding was received for the review.

Analysis

Study design issues: All authors independently evaluated the studies design for quality of reporting, risk of bias and quality of evidence. Quality of reporting was assessed using Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist. Risk of bias assessment was done using the methodological index for non-randomised studies (MINORS) checklist. A study with score 50% or less of maximum score was considered to be at 'high risk of bias'; none of the studies were in this category. Quality of the body of evidence was assessed by the GRADE system of rating for the outcomes that could be meta-analysed; it was described as 'low' or 'very low'.

Of the 14 studies, 12 were prospective uncontrolled before- and after-studies and 2 were prospective controlled before- and after-studies, using estriol as a control group. The 2 controlled studies were not included in the meta-analysis.

Dyspareunia and dryness were measured on a visual analogue scale (VAS) from 0 to 10 (2 studies that used a different scale were excluded from the meta-analysis). Itching, burning, and dysuria were also assessed by VAS 0 to 10.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **542** All genitourinary syndrome of menopause symptoms (dryness, dyspareunia, itching, burning, dysuria, urgency, frequency) and urinary incontinence decreased significantly and consistently in all available publications. **Primary outcomes - pooled mean differences at 1-month follow-up:** • Dryness=-5.5 (95% CI -6.7 to -4.4; 7 studies; I^2=0%, n=298) • Dyspareunia=-5.6 (95% CI -6.8 to -4.5; 7 studies; I^2=0%, n=270) • Itching=-4.0 (95% CI -5.7 to -2.2; 6 studies; I^2=79%, n=272) • Burning=-3.9 (95% CI -5.9 to -2.0; 6 studies; I^2=87%, n=281) • Dysuria=-2.9 (95% CI -5.1 to -0.7; 4 studies; I^2=90%, n=185) • Urinary incontinence=-4.9% (95% CI -6.4 to -3.4; 2 studies; I^2=0%, n=54) Subgroup analysis – pooled mean differences in CO_2 laser group (6 studies) • Dryness=-5.5 (95% CI -6.6 to -4.4, p<0.00001, I^2=0%, n=255) • Dyspareunia=-5.5 (95% -6.6 to -4.4, p<0.00001, I^2=0%, n=229) **Secondary outcomes - pooled mean differences at 1-month follow-up:** • Female Sexual Function Index=13.2 (95% CI 9.1 to 17.3; 3 studies; I^2=0%, n=143) • Mental Component Summary-12=4.5 (95% CI 1.9 to 7.0; 3 studies; I^2=59%, n=139) • Physical Component Summary-12=6.2 (95% CI 0.8 to 11.5; 3 studies; I^2=91%, n=139) • Vaginal Health Index Score (above 15 is considered the threshold of non-atrophic values)=10.7 (95% CI 8.7 to 12.7; 7 studies; I^2=0%, n=274) • Vaginal Maturation Value=20.6 (95% CI 1.4 to 39.9; 2 studies; I^2=76%, n=78)	6 studies (n=230) reported that there were no adverse events. In other studies, adverse events included: • Pain during probe insertion • Discomfort related to first application • Mild irritation of the introitus that started immediately after laser therapy and resolved spontaneously in about 2 hours • Mild or moderate pain lasting 2 to 3 days • Minor bleeding or spotting • Sensation of warmth and slight oedema 0.4% (2/542) of patients discontinued therapy because of discomfort related to the first application or a burning sensation that started 36 hours after laser treatment and lasted for 2 days. Both women had Er:YAG laser therapy.
Abbreviations used: CI, confidence interval	

Study 2 Jha S (2019)

Details

Study type	**Systematic review**
Country	Italy, US, Belgium, Germany, Australia
Recruitment period	2014 to 2017
Study population and number	**n=522 (10 studies)** Women with genitourinary syndrome of menopause after breast cancer treatment
Age	Mean age range 44 to 71 years
Patient selection criteria	The study population included women with breast cancer who had completed preliminary treatment for their cancer and subsequently had genitourinary syndrome of menopause. Conference abstracts were included if data could be extracted. Unpublished work was excluded. No language restrictions were applied.
Technique	7 studies used a CO_2 laser and 3 used an Erbium YAG laser. The treatment protocol varied in the different studies, ranging from 3 to 5 treatment sessions in the CO_2 laser studies and 1 to 3 in the Erbium YAG laser studies.
Follow-up	**4 weeks to 24 months (1 study reported 24-month outcomes)**
Conflict of interest/source of funding	The authors of the review stated that they have no conflicts of interest.

Analysis

Study design issues: The review followed the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines for the reporting of meta-analysis of observational studies. When data were incomplete, the authors were contacted by email, and if no response was received after 2 weeks, a further email was sent. The risk of bias assessment based on the quality of the studies was done using the Modified Newcastle Ottawa Scale. Meta-analysis was done if more than 3 studies reported data.

All included studies were observational cohort studies reporting on the effects of laser treatment before and after completion of treatment on the same cohort of patients. There were no randomised controlled trials.

There was significant heterogeneity of the studies with respect to women having the laser treatment. The time elapsed since the completion of active treatment for breast cancer varied, as did the age of patients and time elapsed since menopause. Most studies did not comment on the type of endocrine therapies the patients were on.

Of the 10 studies, 5 were conference abstracts with limited data available. None of the studies reported a formal sample size calculation.

Study population issues: Most women in the studies were on some form of antioestrogen therapy, either tamoxifen or an aromatase inhibitor.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **522** **Vaginal Health Index** Mean difference=-11.4 (95% CI -11.8 to -10.9; 5 studies, I^2=98%; n=130) 2 further studies reported a statistically significant improvement (p<0.01) but were not included in the meta-analysis because individual scores before and after treatment were not reported. **Dyspareunia (VAS)** Mean difference=2.2 (95% CI 2.0 to 2.5; 4 studies, I^2=96%, n=183) **Dryness (VAS)** Mean difference=2.7 (95% CI 2.5 to 2.9; 5 studies, I^2=97%, n=208) **Sexual Function (measured using Female Sexual Function Index)** 3 studies reported this outcome and all 3 showed an improvement in sexual function (no further details given) **Improvement or satisfaction after treatment** The percentage of patients with improvement in symptoms or satisfaction after laser treatment ranged from 58.9% to 96.1% (mean 83.5%; 6 studies).	**Adverse events** 9 studies reported no adverse effects from treatment. In 1 study, 3.7% (3/82) of patients discontinued treatment after 2 cycles because of discomfort.
Abbreviations used: CI, confidence interval; VAS, visual analogue scale	

Study 3 Ruanphoo P (2020)

Details

Study type	**Randomised controlled trial**
Country	Thailand
Recruitment period	2016 to 2017
Study population and number	**n=88 (44 laser therapy, 44 sham)** Postmenopausal women with any vaginal atrophy symptom of moderate to severe intensity
Age	Mean 61 years
Patient selection criteria	Inclusion criteria: postmenopausal women (aged at least 50 years and had their last menstruation at least 1 year ago) with any vaginal atrophy symptom (burning, dryness or dyspareunia) of moderate to severe intensity. Exclusion criteria: history of hormonal therapy within the last 6 months, vaginal moisturiser or lubricant applications within the past 30 days, acute or recurrent urinary tract infection, active genital infection, genital hiatus diameter of less than 2 cm or pelvic organ prolapse stage 2 or higher according to pelvic organ prolapse quantification system classification.
Technique	Laser therapy: Laser treatment was done with a CO_2 laser (SmartXide^2, V^{2}LR, DEKA, Italy). In the lithotomy position, the vaginal laser probe was inserted into the total length of the vagina and subsequently withdrawn 0.5 cm following each laser beam application until the distal end of the vaginal probe reached the introitus. Sham: the vaginal probe was inserted and withdrawn in the same manner as the laser treatment but without using the laser. Treatment was done on an outpatient basis without local anaesthesia. There were 3 treatment sessions, 4 weeks apart. All patients were advised to avoid sexual intercourse or intravaginal devices for at least 3 days after the procedure.
Follow-up	**12 weeks**
Conflict of interest/source of funding	No funding or support was reported. A laser machine was supported by Lasermed Co. Ltd without involvement in the study protocol, data collection or manuscript development.

Analysis

Follow-up issues: 10% (9/88) of patients were lost to follow-up (3 in the laser treatment group and 6 in the sham group). All patients were scheduled for 4 visits with a 4-week interval. One patient in the laser group withdrew from the study because she could not tolerate the pain when the vaginal probe was inserted into the vagina. The remaining 8 patients withdrew because it was inconvenient for them to attend the clinic.

Study design issues: Prospective randomised controlled trial. Simple randomisation was generated by a computer and allocation concealment was done using opaque, sealed envelopes. The envelopes were opened by a research assistant at the first visit before starting treatment. Signs of vaginal atrophy were evaluated by an investigator who was blinded to the treatment allocation. Treatment was done by an investigator who did not know the clinical outcomes of the treatment. The primary outcome was vaginal health index (VHI) score. Secondary outcomes were vaginal atrophy symptoms score, score for vaginal dryness from the International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms (ICIQ-VS) questionnaire, patient satisfaction, and adverse events. Intention-to-treat analysis was used for the primary outcome. The sample size calculation was based on the primary efficacy variable, a 5% level of significance (2-sided) and a power of 80%. A sample size of 44 women per group was needed, assuming a 20% dropout rate.

Study population issues: In the laser group, 23% (10/44) of women were sexually active compared with 55% (24/44) in the sham group. At baseline, the VHI score, vaginal atrophy symptoms score and ICIQ-VS score for vaginal dryness were comparable between the groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: 88 (44 laser, 44 sham)

Vaginal signs and symptoms at baseline and 12 weeks after treatment

Outcome measure	Baseline	12 week follow-up	p value
VHI score (mean±SD)			
Laser group	14.18±3.39	17.45±2.61	<0.001
Sham group	14.66±2.91	16.08±3.27	0.06
p value	0.48	<0.001	
Vaginal atrophy symptoms score (mean±SD)			
Laser group	2.27±0.42	1.83±0.51	<0.001
Sham group	2.02±0.40	2.06±0.49	0.59
p value	0.06	0.03	
ICIQ-VS vaginal dryness (median [IQR])			
Laser group	5.00 (2.00 to 6.00)	3.24 (0 to 4.00)	0.02
Sham group	4.00 (2.00 to 6.00)	2.00 (0.26 to 4.00)	0.07
p value	0.09	0.56	

The results of the per protocol analysis were similar to the intention-to-treat analysis.

Patient satisfaction, n (%)

Level of satisfaction	Laser group (n=39)	Sham group (n=38)	p value
Very satisfied or satisfied	31 (79.5%)	17 (44.7%)	0.002
Neither satisfied or dissatisfied or lower	8 (20.5%)	21 (55.3%)	

Safety

Complications, n (%)

Complication	Laser group (n=41)	Sham group (n=38)	p value
Vaginal bleeding	0 (0)	1 (0.26)	0.30
Vaginal discharge	3 (0.73)	1 (0.26)	0.34
Vaginitis	1 (0.24)	0 (0)	0.33
Pain after procedure	3 (0.73)	4 (1.05)	0.34
De novo dyspareunia	0 (0)	0 (0)	-

Abbreviations used: ICIQ-VS, International Consultation on Incontinence Modular Questionnaire-Vaginal Symptoms; IQR, interquartile range; SD, standard deviation; VHI, vaginal health index

Study 4 Cruz V (2018)

Details

Study type	**Randomised controlled trial**
Country	Brazil
Recruitment period	2015
Study population and number	**n=45 (15 laser therapy, 15 estriol, 15 laser plus estriol)** Postmenopausal women with vulvovaginal atrophy
Age	Mean 56 years (laser therapy and laser plus estriol), 57 years (estriol)
Patient selection criteria	Women aged between 45 and 70 years who presented with amenorrhoea for 24 months or longer and at least 1 moderate symptom (score of 4 or more on visual analogue scale from 0 to 10) of vulvovaginal atrophy (dyspareunia, dryness or burning). Exclusion criteria: Body mass index 35 kg/m^2 or above, chronic kidney or liver disease, drug-induced menopause, history of any form of cancer, previous vaginal radiotherapy, pap smear consistent with atypical squamous cells of undetermined significance, low-grade intraepithelial lesion or high-grade intraepithelial lesion in the previous 12 months, current use of vaginal lubricants or moisturisers, use of anabolic steroids, ospemifene or systemic oestrogen therapy in the past 6 months or diagnosis of vulvovaginitis within previous 30 days.
Technique	Laser treatment was done using a fractional microablative CO_2 laser (Monalisa Touch, DEKA laser, Italy). Patients had 2 sessions, 4 weeks apart. Estriol therapy consisted of 1 mg vaginal estriol therapy 3 times a week for 20 consecutive weeks. Patients in the laser therapy group also had placebo vaginal cream treatment (similar in appearance, odour, consistency and packaging to the estriol cream) and patients in the estriol group also had sham laser treatment (power adjusted to 0 W).
Follow-up	**16 weeks**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Of the 45 randomised patients, 3 (7%) were lost to follow-up (2 in the laser group and 1 in the estriol group).

Study design issues: Randomised, double-blind, placebo-controlled clinical trial. Patients were block randomised into the 3 treatment groups using a computer-generated randomisation list. An unblinded nurse programmed the laser parameters before the doctor and patient entered the room. Once programmed, a cover was placed over the screen to maintain blinding. The same nurse was responsible for selecting the appropriate topical cream of either placebo or estriol for each patient. The same physician conducted all appointments and laser sessions. The main outcomes included improvement in Vaginal Health Index (VHI) and in vulvovaginal symptoms using a visual analogue scale from 0 to 10. Secondary outcome measures included analysis of vaginal smear samples and the assessment of sexual function using the validated Portuguese version of the Female Sexual Function Index (FSFI). The sample size of 45 was calculated to detect a 3-point difference in the VHI with $p<0.05$ and power ≥0.8, allowing for a potential loss of 20% of patients throughout the study. Intention-to-treat analysis and per-protocol analysis were used for the main outcomes.

Study population issues: There were no statistically significant differences in demographic characteristics between the groups at baseline. Clinical characteristics were similar except for burning, which was statistically significantly milder in the estriol group.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **45 (15 laser, 15 estriol, 15 laser plus estriol)**

Vaginal Health Index mean score (per protocol analysis)

Timepoint	Laser	estriol	Laser plus estriol	p
Baseline	11.7	12.6	12.6	0.76
8 weeks*	19.0^	21.0^	20.0^	-
20 weeks*	18.5**	22.0**	23.0**	<0.05#

* estimated from chart; ^p<0.05, **p<0.01 compared with baseline; # laser compared with other study arms

Mean differences between groups at week 20

- Laser and estriol groups=-2.87 (95% CI -5.99 to 0.26)
- Laser and laser plus estriol=4.73 (95% CI 2.42 to 7.07)
- Estriol and laser plus estriol=1.87 (95% CI -0.59 to 4.31)

Visual analogue scale symptom scores (intention-to-treat analysis), mean±sd

	Laser (n=15)	Estriol (n=15)	Laser plus estriol (n=15)	p
Dyspareunia				
Baseline	4.9±3.7	3.2±3.4	6.5±3.9	0.09
Week 8	2.9±2.9	0.6±1.7	2.5±3.8	0.16
Week 20	0.7±1.5	0.2±0.6	0.9±1.8	0.95
p	0.01	0.058	0.009	
Dryness				
Baseline	8.0±2.6	5.6±2.9	7.9±3.0	0.07
Week 8	3.6±2.6	2.4±2.0	3.3±2.9	0.57
Week 20	1.4±2.0	0.5±1.4	0.3±0.7	0.35
p	<0.001	<0.001	<0.001	
Burning				
Baseline	3.9±4.5	0.9±1.6	4.9±3.8	0.017
Week 8	1.0±2.0	0.1±0.5	1.2±2.7	0.33
Week 20	0.5±1.5	0.1±0.3	0.4±1.1	0.95
p	0.02	0.51	0.002	

Total FSFI score, median (interquartile range); higher scores better

Timepoint	Laser	estriol	Laser plus estriol	p
Baseline	18.6 (16.4, 24.6)	23.6 (17.5, 29.8)	18.7 (7.2, 22.6)	0.21
8 weeks	18.0 (11.4, 20.7)	22.9 (8.4, 29.7)	22.6 (11.3, 26.3)	0.39
20 weeks	14.4 (7.8, 22.4)	25.4 (16.8, 29.3)	23.6 (14.9, 28.6)	0.10
p (week 20 vs baseline)	0.26	0.56	0.02	

Pain domain of FSFI score, median (interquartile range)

Timepoint	Laser	estriol	Laser plus estriol	p
Baseline	4.4 (1.6, 5.6)	4.8 (2.2, 5.7)	2.4 (1.2, 3.6)	0.04
8 weeks	2.0 (0.0, 4.4)	5.2 (0.0, 6.0)	3.6 (1.2, 4.8)	0.39
20 weeks	2.0 (0.0, 3.6)	6.0 (3.9, 6.0)	2.8 (1.6, 5.6)	0.006
p (week 20 vs baseline)	0.04	0.16	0.02	

No statistically significant difference was observed in vaginal smear samples between the groups.

Safety

No adverse effects of laser treatment or pain during laser application were observed during the study.

Abbreviations used: CI, confidence interval; FSFI, female sexual function index; sd, standard deviation

Study 5 Paraiso MFR (2020)

Details

Study type	**Randomised controlled trial (VeLVET trial)**
Country	US (6 centres)
Recruitment period	2016 to 2017
Study population and number	**n=69 (34 laser treatment, 35 vaginal oestrogen cream)** Women with vulvovaginal atrophy/genitourinary syndrome of menopause
Age	Mean 61 years
Patient selection criteria	Inclusion criteria: menopausal women with absence of menstruation for 12 months and bothersome vaginal dryness of 7 cm or more on visual analogue scale (VAS). Exclusion criteria: contraindication to vaginal oestrogen therapy, history of vulvovaginal condyloma, vaginal intraepithelial neoplasia, vaginal carcinoma, lichen sclerosus, lichen planus, history of vaginal radiation, history of cervical cancer, other gynaecological cancer or pelvic radiation, acute or recurrent urinary tract infection, or genital infection. Women were also excluded if they had a personal history of thrombophlebitis, heart failure or myocardial infarction within 12 months, scleroderma, or any chronic condition that could interfere with study compliance. They were also excluded if they had pelvic organ prolapse higher than stage 2, if they had had pelvic surgery within 6 months or if they previously had reconstructive pelvic surgery with transvaginal mesh kits. Previous midurethral sling and sacrocolpopexy with synthetic mesh for prolapse were not excluded. Patients were excluded if they had used vaginal oestrogen cream, ring or tablet within 1 month before entering the study, or vaginal moisturisers, lubricants, or homeopathic preparations within 2 weeks of therapy.
Technique	Laser group: laser treatment was done using a fractional microablative CO_2 laser (Monalisa Touch, DEKA laser, Italy). Patients had 3 sessions, at least 6 weeks apart. The laser beam was applied using a 90° vaginal probe gently inserted up to the top of the vaginal canal and subsequently withdrawn at centimetre intervals while rotated to 6 positions in an alternating clockwise and counter clockwise fashion to provide complete circumferential treatment of the vagina. At the investigator's discretion, a flat probe was used to treat the introital area and vestibule. EMLA cream was applied to the introitus for 10 minutes beforehand, if desired. Patients were advised to avoid coital sexual activity for at least 3 days after each laser application and topical lidocaine 5% ointment was prescribed for vulvar pain after the procedure for those patients who wanted it. Vaginal oestrogen cream group: conjugated oestrogen cream 0.5 g intravaginally daily was prescribed for 14 days followed by 0.5 g twice weekly for 24 weeks.
Follow-up	**6 months**
Conflict of interest/source of funding	The study was supported by an unrestricted research grant from the Foundation of Female Health Awareness. 6 authors declared research support from companies including NICHD, Coloplast, Caldera, Acell, FFHA, NIH, Solace, Pelvalon, Boston Scientific, Pelvalon, National Vulvodynia Association, International Society for the Study of Women's Sexual Health. 3 authors are consultants for companies including Pelvalon, Eximis, Boston Scientific, Hologic, Coloplast.

Analysis

Follow-up issues: Of the 69 randomised patients, 4 withdrew before they had treatment (2 in each group) and 3 were lost to follow-up (2 in the laser group and 1 in the vaginal oestrogen group).

Study design issues: Multicentre randomised controlled trial comparing laser treatment with vaginal oestrogen cream. Patients were not blinded to their treatment allocation. A computer-generated randomisation schedule with random block sizes was used. All follow-up questionnaires and examinations were done by study personnel blinded to treatment allocation. The primary outcome of the study was to compare subjective improvement of vaginal dryness using a VAS 6 months after treatment between groups. Secondary outcomes included comparisons between groups of the vaginal health index and vaginal maturation index scores, the effect of genitourinary syndrome of menopause on quality of life, the effect of treatment on sexual function, the effect of treatment on urinary symptoms, and comparison of patient satisfaction.

IP overview: transvaginal laser therapy for urogenital atrophy

A sample size of 85 patients in each group was calculated to provide 90% power to reject the null hypothesis that the true difference in vaginal dryness VAS score is less than or equal to 1.0 in favour of the alternative hypothesis that the true difference is greater than 1.0 using a 1-sided 2-sample t test. A 15% loss to follow-up or dropout rate was accounted for. The study was closed early because of a request from the US Federal Drug Administration to obtain an Investigational Device Exemption, so the planned sample size was not reached. The study therefore lacked power. An intention-to-treat analysis was done, but it showed no changes from the per protocol analysis and the results were not included in the paper.

Study population issues: The 2 treatment groups were similar with regard to baseline characteristics. According to the body of the text in the paper, patients in the laser group were less parous than those in the oestrogen group (0 [0 to 4] compared with 2 [0 to 6], p=0.04), but the table in the paper shows similar parity between the groups.

Most patients (80%) had previously taken exogenous hormones and 78% had previously used vaginal oestrogen.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **62 (30 laser, 32 oestrogen cream)**

Outcome measures at 6-month follow-up

Outcome	Laser, n=30	Oestrogen cream, n=32	p
Mean difference VAS score - dryness	-5.48±2.68	-5.76±2.48	0.67
Mean difference VAS score - itching	-1.84±3.01	-1.24±2.96	0.45
Mean difference VAS score - irritation	-3.29±3.73	-3.49±3.19	0.87
Mean difference VAS score - dysuria	-1.4±2.89	-2.11±2.85	0.36
Mean difference VHI	0.9±0.7	1.2±0.9	0.07
Mean difference DIVA	-3.3±3.2	-4.4±3.1	0.18
Mean difference VMI*	3.9±30.6	25±22.6	0.04^
Mean difference FSFI	1.7±6.7	4.9±8.3	0.1
Mean difference UDI	-9.4±15.7	-6.2±12	0.37
% sexually active	45.5 (15)	48.3 (14)	0.82

* remained statistically significant after controlling for confounding factors

^ baseline and follow-up data were only available for 55% of patients

FSFI subgroup outcomes at 6 months (mean differences)

Subgroup	Laser	Oestrogen cream	p
Desire*	0.32±1.3	1.02±1.4	0.05
Arousal*	0.62±1.6	1.63±1.9	0.03
Lubrication	0.11±1.2	0.35±1.4	0.50
Orgasm	0.37±1.3	0.9±1.6	0.17
Satisfaction	0.88±2.1	1.7±1.7	0.50
Pain	-0.59±2.8	-0.04±3.3	0.81

* No longer statistically significant after controlling for confounding factors

Proportion of patients who rated improvement as 'better or much better'

- Laser=71.9%
- Oestrogen cream=82.8%, p=not significant

Proportion of patients who were 'satisfied or very satisfied'

- Laser=75.8%
- Oestrogen cream=75.9%, p=not significant

Safety

Adverse events, n (%)

	Laser, n=30	Oestrogen cream, n=32
Vaginal bleeding	2 (6.7)	2 (6.3)
Vaginal pain	1 (3.3)	0 (0)
Vaginal discharge	1 (3.3)	0 (0)
Urinary tract infection	1 (3.3)	0 (0)
Breast tenderness	0 (0)	1 (3.1)
Migraine	0 (0)	1 (3.1)
Abdominal cramping	0 (0)	1 (3.1)

Abbreviations used: DIVA, day-to-day impact of vaginal ageing; FSFI, female sexual function index; UDI, urogenital distress inventory; VAS, visual analogue scale; VHI, vaginal health index; VMI, vaginal maturation index

Study 6 Politano CA (2019)

Details

Study type	**Randomised controlled trial**
Country	Brazil
Recruitment period	2017 to 2018
Study population and number	**n=72 (24 laser treatment, 24 vaginal oestrogen cream, 24 vaginal lubricant)** Postmenopausal women with genitourinary syndrome of menopause
Age	• Laser treatment group: mean age 58 years • Vaginal oestrogen group: mean age 57 years • Vaginal lubricant group: mean age 57 years
Patient selection criteria	Inclusion criteria: women aged 50 to 70 years; physiological amenorrhoea for at least 12 months; symptoms of vaginal dryness with or without dyspareunia, vaginal burning or pruritis; no use of hormonal medications to treat vaginal symptoms in the previous 6 months. Exclusion criteria: previous bilateral oophorectomy; body mass index less than 18.5 or greater than 30 kg/m^2; contraindications to local oestrogen use, including recent myocardial infarction, severe hypertension, diabetes mellitus, thromboembolic disorders, previous breast or endometrial cancer, or abnormal postmenopausal bleeding. Women having behavioural treatment for depression or taking antidepressant medications, those with any other psychiatric disorders, HIV-positive women on antiretroviral therapy, women with a history of previous radiation therapy, and women with previous surgery for stress urinary incontinence were also excluded.
Technique	Laser treatment was done with a fractional CO_2 laser (SmartXide^2, V^{2}LR, Monalisa Touch, DEKA laser, Italy). Three sessions were done at 30-day intervals. A 360° cylindrical probe was introduced into the vaginal and rotated and slowly withdrawn, with continuous use of the pedal according to precalibrated marks on the probe. Patients were advised to abstain from sexual activity for 10 days before treatment. Vaginal oestrogen cream treatment consisted of 1 vaginal applicator containing 1 g of cream and 10 mg of promestriene administered 3 times a week. Vaginal lubricant treatment consisted of water-based lubricant applied with sexual activity.
Follow-up	**14 weeks**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Of the 72 randomised patients, 15 (21%) were lost to follow-up (2 in the laser group, 5 in the oestrogen group and 8 in the lubricant group). One patient in the lubricant group discontinued treatment because of allergic vaginitis.

Study design issues: Single centre randomised controlled trial. Randomisation was done using a computer-generated list that was prepared by a statistician. The primary outcome was improvement in vaginal atrophy, measured by the Vaginal Health Index (VHI) and vaginal maturation. The Frost index was used to determine the degree of atrophy. This index evaluates the differential count of each cell group (parabasal, intermediate and superficial) expressed as a percentage. A deep cell percentage between 30% and 49% indicated moderate hypoestrogenism and a more than 50% deep cell percentage indicated hypoestrogenism. The secondary outcome was sexual function, measured using the FSFI. A cut-off score of 26.55 was used to differentiate the presence or absence of sexual dysfunction. A sample size of 20 for each group was calculated based on a standard deviation of 2.5, a difference of 2 points in the VHI, a significance level of 5% and a power of 80%.

Study population issues: The 3 treatment groups were similar with regard to age, years since menopause and menopause age. There was a statistically significantly higher proportion of patients in the laser group (96%) who declared themselves to be white compared with those in the oestrogen group (67%) and the lubricant group (71%), p=0.032.

Other issues: A total of 267 women were recruited to take part in the study, but only 27% (72) met the inclusion criteria.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **72 (24 laser, 24 vaginal oestrogen, 24 vaginal lubricant)**

VHI score at baseline and 14 weeks according to treatment group, mean (SD)

VHI domain	Laser	Oestrogen	Lubricant	p
Elasticity at baseline	2.04 (0.55)	1.96 (0.55)	2.08 (0.65)	0.817
Elasticity at week 14	3.41 (0.91)	2.58 (0.81)	2.19 (0.54)	**<0.001**
p	**0.006**	**0.025**	0.970	
Difference	1.36 (0.79)	0.58 (0.69)	0.00 (0.63)	**<0.001**
Fluid volume at baseline	1.92 (0.58)	1.79 (0.66)	1.92 (0.72)	0.736
Fluid volume at week 14	3.41 (0.73)	2.79 (0.99)	2.00 (0.63)	**<0.001**
p	**0.029**	**0.03**	0.572	
Difference	1.50 (0.91)	1.05 (0.85)	-0.13 (0.62)	**<0.001**
pH at baseline	6.33 (0.64)	6.21 (0.66)	6.17 (0.70)	0.799
pH at week 14	3.98 (0.59)	4.89 (0.94)	5.75 (0.58)	**<0.001**
p	**0.001**	**0.043**	0.262	
difference	-2.38 (0.93)	-1.32 (1.34)	-0.31 (0.87)	**<0.001**
Moisture at baseline	2.17 (0.92)	1.83 (0.70)	2.04 (0.75)	0.799
Moisture at week 14	3.98 (0.59)	3.11 (0.88)	2.13 (0.89)	**<0.001**
p	**0.036**	**0.03**	0.392	
Difference	1.45 (1.26)	1.16 (0.76)	-0.06 (0.57)	**<0.001**
Epithelial integrity at baseline	2.00 (0.66)	1.92 (0.50)	2.00 (0.66)	0.868
Epithelial integrity at week 14	3.68 (0.99)	3.00 (0.88)	2.13 (0.72)	**<0.001**
p	**<0.001**	**<0.001**	1.00	
Difference	1.73 (1.03)	1.05 (0.78)	0.19 (0.40)	**<0.001**
Total at baseline	9.50 (2.59)	9.00 (2.52)	9.79 (3.09)	0.836
Total at week 14	18.68 (3.20)	15.11 (3.98)	10.44 (2.78)	**<0.001**
p	**<0.001**	**<0.001**	1.00	
Difference	9.36 (3.40)	5.89 (3.68)	0.06 (1.65)	**<0.001**

Frost index at baseline and 14 weeks according to treatment group, mean (SD)

Cells	Laser	Oestrogen	Lubricant	p
Basal at baseline	27.23 (17.20)	27.84 (22.62)	37.00 (21.69)	**0.044**
Basal at week 14	5.82 (4.23)	20.84 (23.39)	40.19 (18.10)	**<0.001**
p	**<0.001**	0.080	0.537	
Difference	-21.41 (16.50)	-7.00 (10.36)	3.19 (23.26)	**<0.001**
Intermediary at baseline	73.45 (16.72)	71.89 (22.67)	61.50 (24.15)	**0.027**
Intermediary at week 14	88.73 (5.81)	77.68 (22.66)	58.88 (18.24)	**<0.001**

Safety

One woman assigned to the lubricant group discontinued the study because she developed allergic vaginitis in week 4. No other adverse effects were reported in any of the treatment groups.

p	**<0.001**	**0.042**	0.715	
Difference	15.27 (14.98)	5.79 (10.86)	-2.63 (26.75)	**<0.001**
Superficial at baseline	0.50 (1.74)	0.26 (1.15)	0.25 (0.77)	0.877
Superficial at week 14	5.00 (3.83)	2.00 (2.62)	0.31 (1.25)	**<0.001**
p	**<0.001**	**0.004**	1.00	
difference	4.50 (4.27)	1.74 (2.56)	0.06 (1.53)	**<0.001**

FSFI score at baseline and 14 weeks according to treatment group, mean (SD)

FSFI domain	Laser	Oestrogen	Lubricant	p
Desire at baseline	2.80 (1.20)	2.83 (1.24)	2.98 (1.45)	0.643
Desire at 14 weeks	3.16 (1.19)	2.97 (0.93)	2.89 (1.09)	
p	**0.047**	0.910	0.406	
Difference	0.41 (0.86)	-0.03 (1.07)	0.28 (0.93)	0.071
Arousal at baseline	2.95 (1.80)	2.64 (1.87)	2.63 (1.77)	0.628
Arousal at 14 weeks	3.22 (1.61)	2.87 (1.83)	2.93 (1.52)	
p	0.533	0.417	0.399	
Difference	0.23 (1.60)	0.19 (1.54)	0.42 (1.54)	0.0823
Lubrication at baseline	2.46 (1.74)	2.00 (1.46)	2.44 (1.65)	0.234
Lubrication at 14 weeks	3.59 (1.94)	2.75 (2.02)	2.86 (1.44)	
p	**0.011**	0.139	0.051	
difference	1.02 (1.94)	0.69 (1.82)	0.58 (1.09)	0.295
Orgasm at baseline	2.93 (1.96)	2.85 (1.89)	2.67 (1.93)	0.404
Orgasm at 14 weeks	3.64 (1.96)	2.86 (2.14)	3.39 (1.74)	
p	0.061	0.808	**0.014**	
Difference	0.62 (2.14)	-0.13 (1.88)	0.89 (1.31)	0.175
Satisfaction at baseline	3.58 (1.55)	3.30 (1.62)	3.13 (1.48)	0.918
Satisfaction at 14 weeks	3.76 (1.53)	3.96 (1.58)	4.00 (1.37)	
p	0.351	0.098	**0.038**	
Difference	0.20 (2.06)	0.67 (1.50)	0.92 (1.52)	0.562
Pain at baseline	2.55 (1.85)	1.73 (1.50)	2.00 (1.80)	0.202
Pain at 14 weeks	3.18 (2.39)	2.63 (2.09)	1.72 (1.07)	
p	0.456	0.188	0.969	
Difference	0.47 (2.36)	0.59 (1.95)	-0.05 (1.16)	0.978
Total at baseline	17.28 (8.46)	15.35 (7.57)	15.84 (7.66)	0.396
Total at 14 weeks	20.55 (8.68)	18.04 (9.46)	17.79 (7.13)	
p	0.134	0.182	**0.038**	
Difference	2.95 (8.92)	1.99 (7.74)	3.05 (5.59)	0.577

Abbreviations used: FSFI, female sexual function index; VHI, vaginal health index

Study 7 Gambacciani M (2018)

Details

Study type	**Non-randomised comparative study**
Country	Italy
Recruitment period	Not reported
Study population and number	**n=254 (205 laser treatment, 49 local treatment)** Postmenopausal women with genitourinary syndrome of menopause
Age	Mean 61 years (laser group); 62 years (local treatment group)
Patient selection criteria	Inclusion criteria: presence of genitourinary syndrome of menopause in women with plasma levels of gonadotropin and oestradiol in the postmenopausal range and negative Pap smear. Exclusion criteria: use of lubricants, local preparations, hormones or other medications to relieve menopausal symptoms in the previous 3 months before inclusion to the study; lesions, scars or infection, active or recent (30 days) of the genitourinary tract; abnormal uterine bleeding; history of photosensitivity disorder or use of photosensitising drugs; genital prolapse (grade 2 to 3 classification POP-Q); and serious or chronic illness that could interfere with the study.
Technique	Laser treatment device: non-ablative 2940 nm Er:YAG laser (XS Fotona Smooth, Fotona, Slovenia). Patients had 3 treatment sessions at 30-day intervals. The procedures were done in an outpatient clinical setting without any preparation, anaesthesia or post-treatment medications. Before the procedure, the vagina was cleaned with disinfectant solution and dried with a swab. All patients had circular treatment of the vaginal wall followed by treatment of the vestibule and introitus. Patients with stress urinary incontinence had additional laser treatment of the anterior vaginal wall. After treatment, all patients were advised to abstain from sexual intercourse for 1 week. Control group: local treatments consisted of hormonal (estriol gel twice weekly) or non-hormonal therapies such as hyaluronic acid-based preparations or different moisturisers and lubricants for 3 months.
Follow-up	**24 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: A total of 235 women were treated by laser but only 205 completed the study; 11 patients left the study for personal reasons, 13 because of other pharmacological or surgical interventions, and 1 patient who complained of discomfort after the first application. The follow-up period in the control group ended at 6 months because most patients started a new local or systemic treatment. The paper states that 23 (16.6%) patients were lost to follow-up, but it is unclear whether this refers to the whole cohort or just those women with stress urinary incontinence.

Study design issues: Prospective longitudinal single centre study. The study does not describe how patients were allocated to each treatment group. The aim of the study was to evaluate the long-term efficacy of vaginal laser treatment for the management of genitourinary syndrome of menopause. Subjective symptoms (vaginal dryness and dyspareunia) were evaluated by a VAS (range 0 to 10, where 0=total absence of the symptom and 10=the worst possible symptom). The Vaginal Health Index Score (VHIS) was evaluated at every visit and the general acceptability and efficacy of laser therapy was assessed as excellent, good, acceptable, bad, or unacceptable. Patients were excluded from the analysis after they had a repeat procedure.

Population issues: There were no statistically significant differences in age, age at menopause, years since menopause and body mass index between the 2 groups at baseline. The basal VAS scores were also similar in the 2 groups. The mean number of years since menopause was 13 in both groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: 254 (205 laser treatment, 49 control)

Symptom scores before, during and after treatment, mean±standard error

Time period	n (laser group)	Atrophy (VAS)		Dyspareunia (VAS)		VHIS	
		Laser	Control	Laser	Control	Laser	Control
Basal	205	8.3±1.5	8.0±2.7	8.5±1.3	8.0±2.7	10.6±2.7	10.8±1.7
First laser treatment	205	5.2±1.7*	3.1±1.5	5.1±1.8*	4.5±1.5*	16.2±1.5*	18±2.5*
Second laser treatment	205	4.3±2.0*	3.0±2.0*	4.0±1.9*	4.2±2.0*	18.1±2.0*	19±2.4*
Third laser treatment	205	3.0±1.3*	4.0±2.1*	4.1±1.9*	3.8±2.1*	19.5±1.2*	18±2.6*
1 month after last laser treatment	204	3.0±1.1*	3.0±1.5*	3.5±1.0*	4.0±1.5*	20.1±1.3*	18±2.8*
3 months after last laser treatment	203	3.0±0.9*^	5.0±2.9	3.8±1.5*	6.8±1.5^	19.5±1.5*	16±2.7*
6 months after last laser treatment	163	3.5±1.2*	6.0±3.2^	4.2±2.0*	7.7±2.7^	18.7±1.5*	12±2.9*
12 months after last laser treatment	152	5.6±1.5*	-	5.3±2.2*	-	16.5±2.0*	-
18 months after last laser treatment	119	6.2±1.3	-	7.5±2.3	-	15.3±2.0*	-
24 after last laser treatment	66	7.0±1.0	-	8.2±2.4	-	12.7±2.7	-

* p<0.01 compared with baseline; ^p<0.05 compared with laser group

In the laser group, 3.9% (8/205) of patients stated that the treatment was not effective in reducing symptoms. Treatment was defined as effective up to 3 months by 23 patients (11.2%), up to 6 months by 18 patients (8.8%) and 73.6% (151/205) of patients stated that laser treatment was effective for 12 to 18 months.

Only 5 patients (2.4%) were still satisfied after 24 months from the last laser treatment session.

Proportion of patients who had a repeat procedure by follow-up period after last laser treatment

- 3 months=1.0% (2/205)
- 6 months=9.8% (20/205)
- 12 months=30.2% (62/205)
- 18 months=26.8% (55/205)
- 24 months=16.6% (34/205)
- Total=84.9% (174/205)

Safety

The paper states 'No adverse events related to the procedure were recorded throughout the study period' but it also states 'Less than 3% of patients discontinued treatment due to adverse events.'

Abbreviations used: ICIQ-UI SF, International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form; VHIS, Vaginal Health Index Score

Study 8 Filippini M (2020)

Details

Study type	**Case series**
Country	Italy (4 centres)
Recruitment period	2012 to 2018
Study population and number	**n=645** Postmenopausal women with genitourinary syndrome
Age	Median 56±7.9 years
Patient selection criteria	Inclusion criteria: menopausal status; more than 1 vulvovaginal symptom and VAS evaluation before and after the treatment; 3 to 4 CO_2 laser treatments; age between 18 and 75 years; vaginal atrophy; no uncontrolled psychiatric disorders; no symptomatic genital infections; no stenosis, trauma, or necrosis of the urethra; Eastern Cooperative Oncology Group performance status less than 2. Exclusion criteria: pregnancy; haematuria or urine clotting; alcohol or drug addictions; abscess, fistula, or any anatomical abnormality that could interfere with treatment; prolapse stage higher than 2 according to the Pelvic Organ Prolapse Quantification System; use of any form of local therapy within the previous 15 days.
Technique	A fractional CO_2 laser system was used (SmartXide^{2}V^{2}LR, Deka, Italy), with a vulvovaginal laser reshaping scanning system and appropriate handpieces for the vaginal area. All patients had 3 (n=595) or 4 (n=50) treatment sessions. The mean time of treatment was 6.5 months from the beginning of the first session to the end of the last session. No local therapy was recommended during or after the laser treatment.
Follow-up	**1 month**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Checks were scheduled each month during the treatment, at the end of treatment, after 6 to 12 months and then once a year depending on the protocol used. The paper only reports VAS results at 1-month follow-up.

Study design issues: Retrospective multicentre case series. Data were collected from a pre-existing database. The aims of the study were to assess the efficacy and effectiveness of CO_2 laser treatment in treating genitourinary syndrome of menopause, particularly vulvovaginal atrophy, and to evaluate possible early and late side effects. Symptoms were evaluated using a VAS.

Study population issues: Of the 645 included patients, 81% had a natural menopause and 19% had a medically induced menopause; 27% (171/645) were oncological patients (134 with breast cancer, 18 with gynaecological cancer, 16 with non-gynaecological cancer, 4 with non-specified cancer). The median age of menopause was 48 years.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **645**

Symptoms before treatment and 1 month after last treatment session (VAS)

Sign or symptom	Number of patients	%	Before treatment	After treatment	p
Dyspareunia	611	94.73	8.70	3.51	<0.0001
Pain at the vaginal orifice	238	36.90	8.07	2.94	<0.0001
Dryness or atrophy	645	100	8.30	2.97	<0.0001
Itching	257	39.84	6.09	1.32	<0.0001
Burning	293	45.43	6.12	1.78	<0.0001

The pH was measured in 299 women and changed from 5.82 before treatment to 5.61 after treatment (p<0.0001).

Improvement percentage by number of treatment sessions

Sign or symptom	4 sessions (n=50)	3 sessions (n=595)	3 or 4 sessions (n=645)
Dyspareunia	57%	60%	60%
Pain at the vaginal orifice	60%	67%	64%
Dryness	61%	65%	64%
Itching	72%	78%	78%
Burning	67%	72%	71%
pH	6%	1%	4%

Safety

The side effects were evaluated as pain greater than VAS 6 either after or during treatment, problems in sexual function either after or during the treatment, the presence of abrasions or ulcerations after the laser treatment. Patients did not report any of these side effects.

Abbreviations used: VAS, visual analogue scale

Study 9 Pieralli A (2017)

Details

Study type	**Case series**
Country	Italy
Recruitment period	2013 to 2016
Study population and number	**n=184** Postmenopausal women with 1 or more symptom related to vulvovaginal atrophy
Age	Mean 56 years (range 38 to 72)
Patient selection criteria	Inclusion criteria: menopause status (spontaneous menopause or menopause induced by chemotherapy or surgical adnexectomy), 1 or more vulvovaginal atrophy symptoms (itching, burning, reduced lubrication, postcoital bleeding or dyspareunia), negative Pap smear not older than a year or negative human papillomavirus test not older than 5 years. Exclusion criteria: the use of vaginal moisturising agents and lubricants within 30 days of study inclusion, the presence of active genital infection during the enrolment visit, prolapse stage 2 or above according to pelvic organ prolapse quantification system, previous reconstructive pelvic surgery or topical radiotherapy, previous vulvar, vaginal or cervical cancer.
Technique	Device: fractional microablative CO_2 laser (Smart Xide2; V2LR Monalisa Touch system, Italy). Each patient had 3 treatment sessions, 4 weeks apart. No local anaesthesia was used. Laser energy was released by 2 single shots oriented at 45° to each other, to treat the entire circular vaginal surface. Patients were not prohibited from having sexual activity before or after the treatment sessions.
Follow-up	**6 to 24 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: The final study group constituted 70% (184/262) of patients who were originally enrolled in the study: 12 patients were very dissatisfied with the treatment and decided to abandon the study and 66 patients were excluded from the study because they were unavailable for long-term follow-up. The paper states that 184 patients were available for long-term follow-up data but only reports patient satisfaction for 94 patients at 18 months and 16 patients at 24 months.

Study design issues: Prospective, single centre cohort study. The aim of the study was to evaluate long-term effects of the treatment. The main outcome was patient satisfaction measured on a 5-point Likert scale. All patients were called in September 2016 to evaluate treatment effects and the time of follow up was between 6 and 24 months after treatment.

Study population issues: The mean time from onset of menopause was 8 years (range 1 to 25) at baseline. Of the 184 patients, 128 (70%) had spontaneous menopause and 56 (30%) had oncological menopause (women with current or previous breast cancer).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **184** **Patient satisfaction by follow-up:** • 6 months=92% (170/184) • 12 months=72% (118/162) • 18 months=63% (60/94) • 24 months=25% (4/16) At the follow-up interview, 66.3% (122/184) of patients answered that they wanted to repeat the treatment; 17.4% (32/184) had decided to start or were making a new treatment cycle; 16.3% (30/184) did not want to repeat the treatment. **Patient satisfaction in patients with spontaneous menopause:** • 6 months=92% (118/128) • 12 months=69% (78/112) • 18 months=44% (22/50) • 24 months=0% (0/8) **Patient satisfaction in patients with oncological menopause:** • 6 months=93% (52/56) • 12 months=80% (40/50) • 18 months=86% (38/44) • 24 months=50% (4/8)	Safety data were not reported.

Study 10 Gordon C (2019)

Details

Study type	**Case series**
Country	US
Recruitment period	Not reported
Study population and number	**n=4** Patients with complications after laser treatment for genitourinary syndrome of menopause
Age	65, 61, 68 and 55 years
Patient selection criteria	Not applicable
Technique	All patients had 3 consecutive treatment sessions using a CO_2 laser.
Follow-up	**Not reported**
Conflict of interest/source of funding	One author is a paid consultant for Viveve Medical.

Key efficacy and safety findings

Case 1: vaginal lacerations after resumption of intercourse

65-year old postmenopausal woman with history of breast cancer presented with symptoms of severe vaginal dryness and moderate vaginal stenosis. She had previously tried vaginal oestrogen cream but discontinued it because of headaches. She had 3 laser treatments and engaged in intercourse a few weeks after the last session. She had heavy vaginal bleeding immediately afterwards. An examination under anaesthesia revealed 2 vaginal wall lacerations, which were repaired. There were areas of adhesive agglutination noted in the vaginal canal. Several months later, the patient presented with complaints of severe vaginal pain, dryness and inability to engage in penetrative intercourse. She had a foreshortened vaginal canal (about 2.5 cm in length) and fibrotic tissue was noted at the apex and within the canal of the vagina. She was offered intravaginal dehydroepiandrosterone, genitopelvic physical therapy and a vaginal dilator programme. At the 3-month follow-up, she was able to engage in intercourse using alternative sexual positions, copious amounts of silicone-based lubricant and use of dilators before coitus.

Case 2: persistent dyspareunia

61-year old woman with persistent painful intercourse 10 months after finishing 3 courses of laser treatment. She had mild dyspareunia before the laser treatment but the pain became progressively worse afterwards. On examination, there was moderate vaginal dryness with a vaginal pH of 6.5; she had a positive Q-tip test with vestibular inflammation and pelvic floor hypertonus with spasm of both levator and vaginal muscles. Treatment involved vaginal rehabilitation with topical hormones to the vestibule, intravaginal Valium and intravaginal sex steroid for moderate to severe dyspareunia.

Case 3: worsening dyspareunia and fibrous band mid vagina

68-year old woman with persistent and worsening painful intercourse after completing 3 courses of laser treatment. She had severe vaginal dryness, with burning and itching and associated coital pain. On examination, there was a crescent shaped fibrous band mid vagina, which impinged on the diameter of the vaginal canal, creating a partial obstruction and vaginal canal stricture. The vaginal pH was 6.5 and there was decreased rugae, pale, frail and inelastic tissues. Treatment involved vaginal rehabilitation with nightly intravaginal local prasterone coupled with vaginal moisturisers and a home vaginal dilator programme. At 1-month follow-up, she reported improvement in vaginal dryness but she was still concerned about resuming intercourse.

Case 4: dyspareunia and insertional pain

55-year old woman with persistent and progressively worsening painful intercourse after 3 laser treatments. She had a history of hysterectomy with a bladder sling, mesh erosion surgery with removal and fascial sling placement and a third operation to loosen the sling because of overtightening. Before the laser procedure, she had vaginal dryness and mild to moderate dyspareunia. After the laser treatments, sexual intercourse was severely painful, with increased pain on penile insertion. On examination, she had a moderate amount of pelvic floor hypertonus, and a moderate amount of levator ani spasms with minimal anterior and lateral wall scarring. Treatment involved vaginal moisturiser and nightly off-label use of intravaginal Valium, and self-dilation exercises.

Study 11 Ahluwalia J (2019)

Details

Study type	**Case series**
Country	US
Recruitment period	2015 to 2019
Study population and number	**n=45** Patients with adverse events related to laser and energy-based devices for 'vaginal rejuvenation'.
Age	Not reported
Patient selection criteria	Patients with adverse events related to laser and energy-based devices for 'vaginal rejuvenation'.
Technique	Devices: fractional CO_2 laser, non-ablative Er:YAG laser, hybrid fractional laser, radiofrequency devices.
Follow-up	**Not reported**
Conflict of interest/source of funding	One author has stock options in Zalea, Inmode, Cytrellis, La Jolla Nanoparticle, serves on the scientific advisory board for Zeltiq Aesthetics, Soliton Inc., Sciton Inc., and Sienna Biopharmaceuticals, and is a paid consultant for Merz and Alastin. One author is a member of the scientific advisory boards for Sciton, Merz, Inmode, Rodan and Fields, and Allergan, and is on the speakers bureau and receives honorarium from Sciton, Inmode, Alastin and Allergan.

Analysis

Study design issues: Cross-sectional analysis of the FDA Manufacturer and User Facility Device Experience (MAUDE) database. Events related to laser and energy-based devices for vaginal rejuvenation were identified. Of the 45 reports, 31 were reported by patients, 4 by distributors, 8 by manufacturers and 2 were not specified. Devices were operated by various specialists, including urologists (n=3), dermatologists (n=3), and gynaecologists (n=7). In 22 reports, the operator was unspecified. Events were consolidated for dates, to identify distinct events.

Study population issues: Patient medical histories included vaginal atrophy (n=3), cystitis (n=2), cervical cancer (n=1), urinary incontinence (n=4), vulvar pain (n=1), 'bladder surgery' (n=1), yeast infection (n=1) and Müllerian agenesis (n=1). Indications for the procedure included vaginal dilation (n=1), lichen sclerosis (n=1), dyspareunia (n=2), urethral or vulval pain (n=2), urinary incontinence (n=6), vaginal atrophy (n=9) and 'vaginal rejuvenation' (n=13); some patients had more than 1 indication. The indication was unspecified for 16 patients.

Other issues: Reports from the MAUDE database are subject to reporting and verification biases. Reports from the database cannot be used to determine the incidence of adverse events. The authors note that these adverse events likely represent a small fraction of the total number of procedures that have been done, but this cannot be validated.

Key efficacy and safety findings

Safety
Adverse events (patients may have had more than 1 adverse event) • Pain, n=19 • Burning or numbness, n=11 • Scarring or burns, n=7 • Dyspareunia, n=6 • Increased urinary frequency or incontinence, n=4 • Redness or irritation, n=3 • Infection, n=2 • Bladder or urethral pain, n=2 • Discomfort, n=2 • Miscellaneous, n=3 Treatment included triptan, gabapentin, pregabalin, duloxetine, bupropion, hormonal creams and vaginal suppositories, platelet-rich plasma, lidocaine, Vaseline, dilators, fluconazole, antibiotics, topical steroids, over-the-counter medications, physical therapy, and acupuncture. 33 patients (12 radiofrequency, 17 fractional CO_2 laser, 2 hybrid fractional laser, 1 non-ablative Er:YAG laser, 1 unknown) reported chronic symptoms, including long-term pain, numbness, burning, bladder disturbances, dyspareunia, worsening symptoms, aggravation of lichen sclerosis, scarring and disfigurement.

Validity and generalisability of the studies

- Several small randomised controlled trials were identified. One was a double-blinded sham-controlled trial and the other 3 compared laser treatment with vaginal oestrogen cream or vaginal lubricant.
- There were different types of lasers and different treatment regimens used in the studies.
- One systematic review only included women who had been treated for breast cancer.[2]
- The report from the US Food and Drug Administration MAUDE database included adverse events associated with radiofrequency devices as well as those associated with lasers. Vaginal atrophy was the indication for treatment in a small proportion of the patients.[11]
- None of the studies reported follow-up beyond 2 years.

Existing assessments of this procedure

A technical bulletin on intravaginal laser for genitourinary syndrome of menopause and stress urinary incontinence was published by the Society of Obstetricians and Gynaecologists of Canada in 2018.[12] The report includes the following recommendations:

1. ‘In patients declining or with apparent contraindications to local estrogen, intravaginal laser therapy may be considered for short-term relief of symptoms associated with genitourinary syndrome of menopause’.

2. ‘There is insufficient evidence to offer intravaginal laser therapy as an equivalent modality to local oestrogen for the treatment of genitourinary syndrome of menopause (including vulvovaginal atrophy, lower urinary tract symptoms, and sexual dysfunction)’.

3. ‘There is insufficient evidence to offer intravaginal laser therapy as an effective modality for the treatment of stress urinary incontinence over alternate managements such as pelvic floor physiotherapy, incontinence pessaries, or surgery’.

4. ‘Long-term use of intravaginal laser therapy for the management of genitourinary syndrome of menopause remains experimental and should remain within the protocols of well-executed clinical trials in attempts to establish its safety and efficacy’.

A best practice consensus document, developed by the International Society for the Study of Vulvovaginal Disease and the International Continence Society, was published in 2019.[13] With regard to urogenital atrophy, the report states: ‘There is currently not enough scientific data demonstrating efficacy and safety of LASER for treating vulvovaginal atrophy (level of recommendation 2b/3b, grade of recommendation C).’

A committee opinion on laser-based vaginal devices for treatment of stress urinary incontinence, genitourinary syndrome of menopause, and vaginal laxity was published by the International Urogynecological Association in 2019.[14] The report concluded: ‘The therapeutic advantages of nonsurgical laser-based devices in urogynecology can only be recommended after robust clinical trials have demonstrated their long-term complication profile, safety, and efficacy.’

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

NICE guidelines

- Menopause: diagnosis and management. NICE guideline 23 (2015). Available from http://www.nice.org.uk/guidance/NG23

Additional information considered by IPAC

Professional experts’ opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. One Professional expert questionnaire for transvaginal laser therapy for urogenital atrophy was submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 4 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Below is a list of ongoing trials:

- LASER and Radiofrequency as Alternative Treatment of Vaginal Vulvar Atrophy in Women Treated for Breast Cancer (NCT04081805); RCT; Brazil; n=195; estimated study completion date September 2023.
- The Use of Laser in the Treatment of Atrophic Vulvovaginitis (NCT04297319); RCT; Argentina; n=70; estimated study completion date December 2021.
- Laser Vaginal Treatment for GSM (NCT04042766); RCT; Canada; n=60; estimated study completion date April 2022.
- Effect of Hybrid Laser 10600+1540 nm on Vaginal Atrophy-genitourinary Syndrome of the Menopause (NCT03956563); RCT; Spain; n=30; estimated study completion date August 2020.
- Vaginal CO2 Laser and the Genitourinary Syndrome of Menopause (NCT03754205); RCT; Greece; n=60; estimated study completion date January 2021.
- Clinical Study to Compare the Efficacy of Erbium-Yag Laser or CO2RE Intimate Laser With Sham (COER) (NCT04039555); RCT; Spain; n=136; estimated study completion date May 2020.

- Randomized, Controlled Trial With Hybrid Fractional Laser (NCT03647189); RCT; US; n=25; estimated study completion date January 2020.
- Vaginal Laser Therapy in Breast Cancer Survivors (NCT03738605); RCT; Greece; n=50; estimated study completion date August 2020.
- Hybrid Fractional Laser for Symptoms of Genitourinary Syndrome of Menopause (NCT03178825); single group assignment; US; n=60; estimated study completion date March 2020.
- Laser Treatment of Genito-urinary Syndrome in Women (NCT03238053); RCT; Denmark; n=160; estimated study completion date December 2021.

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6. Politano CA, Costa-Paiva L, Aguiar LB et al. (2019) Fractional CO2 laser versus promestriene and lubricant in genitourinary syndrome of menopause: a randomized clinical trial. Menopause 26: 833–40
7. Gambacciani M, Levancini M, Russo E et al. (2018) Long-term effects of vaginal erbium laser in the treatment of genitourinary syndrome of menopause. Climacteric: the journal of the International Menopause Society 21: 148–52
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9. Pieralli A, Bianchi C, Longinotti M et al. (2017) Long-term reliability of fractioned CO2 laser as a treatment for vulvovaginal atrophy (VVA) symptoms. Archives of Gynecology and Obstetrics 296: 973–8
10. Gordon C, Gonzales S, Krychman ML (2019) Rethinking the techno vagina: A case series of patient complications following vaginal laser treatment for atrophy. Menopause 26: 423–7
11. Ahluwalia J, Avram MM, Ortiz AE (2019) Lasers and energy-based devices marketed for vaginal rejuvenation: A cross-sectional analysis of the MAUDE database. Lasers in Surgery and Medicine 51: 671–7

12. Walter JE, Larochelle A (2018) No. 358-Intravaginal laser for genitourinary syndrome of menopause and stress urinary incontinence. Journal of Obstetrics and Gynaecology Canada 40: 503–11

13. Preti M, Vieira-Baptista P, Digesu GA et al. (2019) The clinical role of LASER for vulvar and vaginal treatments in gynecology and female urology: an ICS/ISSVD best practice consensus document. Journal of Lower Genital Tract Disease 23: 151–60

14. Shobeiri SA, Kerkhof MH, Minassian VA et al. (2019) IUGA committee opinion: laser-based vaginal devices for treatment of stress urinary incontinence, genitourinary syndrome of menopause, and vaginal laxity. International Urogynecology Journal 30: 371–6

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	20/07/2020	Issue 7 of 12, July 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	20/07/2020	Issue 7 of 12, July 2020
MEDLINE (Ovid)	20/07/2020	1946 to July 17, 2020
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	20/07/2020	July 17, 2020
EMBASE (Ovid)	20/07/2020	1974 to 2020 July 17

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Laser Therapy/
2	Lasers/ or Lasers, Gas/ or Lasers, Solid-State/
3	VAGINAL DISEASES/ or Vagina/ or VULVA/
4	2 and 3
5	((treatment* or device* or therap* or appl* or fractional or surg* or scapel* or carbon dioxide* or non-ablative or transvaginal* or vagina* or procedure*) adj4 (laser* or lazer*)).ti,ab.

6	(Alma Pixel CO2 laser* or FEMILIFT CO2 LASER* or SMARTXIDE* or IntimaLase* or RenovaLase* or Incontilase* or Fotana*).mp.
7	1 or 4 or 5 or 6
8	exp Urinary Incontinence, Stress/
9	(SUI or (incont* adj4 (urin* or stress*))).ti,ab.
10	(sphincter adj4 (defic* or dysfunct*)).tw.
11	exp Urethra/
12	(urethra* adj4 hypermob*).ti,ab.
13	or/8-12
14	7 and 13
15	VAGINA/ or VULVA/
16	Atrophy/
17	PRURITUS/ or PRURITUS VULVAE/
18	DEHYDRATION/
19	DYSPAREUNIA/
20	16 or 17 or 18 or 19
21	15 and 20
22	VULVOVAGINITIS/ or Atrophic Vaginitis/ or Vaginitis/
23	FEMALE UROGENITAL DISEASES/
24	exp VULVAR DISEASES/
25	VAGINAL DISEASES/
26	vulvovagini*.ti,ab.
27	((vagina* or vulvovagina* or urogenital or genitourinary or genito-urinary) adj4 (atroph* or dry* or pruritis or sore* or irrita* or itch* or pain* or dyspar?euni* or dysuri* or discharge* or discomfort* or erosion or dehydrat* or thin* or inflam* or burn*)).ti,ab.
28	(vaginitis adj4 atroph*).ti,ab.
29	(genitourinary syndrome of the menopause or genito-urinary syndrome of the menopause or GSM).ti,ab.
30	or/21-29
31	7 and 30
32	Animals/ not Humans/
33	14 not 32
34	31 not 32

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Adabi K, Golshahi F, Niroomansh S et al. (2020) Effect of the fractional CO2 laser on the quality of life, general health, and genitourinary symptoms in postmenopausal women with vaginal atrophy: a prospective cohort. Journal of Lasers in Medical Sciences 11: 65–9	Case series n=140 FU=3 months	The fractional CO2 laser can be effective in treating vaginal atrophy and urinary symptoms. It improved the quality of life and the sexual function of post-menopausal women.	Case series with more patients or longer follow-up are included.
Alexiades MR (2020) Fractional CO2 laser treatment of the vulva and vagina and the effect of postmenopausal duration on efficacy. Lasers in Surgery and Medicine DOI 10.1002/lsm.23247	Case series n=18 FU=12 months	Fractional CO2 laser treatment of the vulva and vagina resulted in statistically significant improvements in VHI and FSFI compared with baseline in postmenopausal population that were sustained to 12-month follow-up. Restoration of normal VHI was observed in a statistically significant greater percentage in the recently postmenopausal cohort (1–3 years) as compared with postmenopausal cohort of >3 years, suggesting that early intervention is correlated with improved outcomes.	Case series with more patients or longer follow-up are included.
Angioli R, Stefano S, Filippini Maurizio et al. (2020) Effectiveness of CO2 laser on urogenital syndrome in women with a previous gynecological neoplasia: a multicentric study. International Journal of Gynecological Cancer: official journal of the International Gynecological Cancer Society 30: 590–95	Case series n=165 FU=4 weeks	Dryness improved by 66%, dyspareunia improved by 59%, burning improved by 66%, pain at introitus improved by 54%, and itching improved by 54%. No side effects were seen in any sessions.	Case series with more patients or longer follow-up are included.
Areas F, Valadares ALR, Conde DM et al. (2019) The effect of vaginal erbium laser treatment on sexual function and vaginal health in women with a history of breast cancer and symptoms of the genitourinary syndrome of menopause: A prospective study. Menopause 26: 1052–8	Case series n=24 FU=1 month	Vaginal health improved, as shown by an increased overall score ($p<0.001$). The effect size was large for vaginal elasticity, fluid volume, epithelial integrity, and moisture. The effect size was also statistically significant for the overall sexual function	Case series with more patients or longer follow-up are included.

		score and for the score in the dyspareunia domain.	
Arroyo C (2017) Fractional CO2 laser treatment for vulvovaginal atrophy symptoms and vaginal rejuvenation in perimenopausal women. International Journal of Women's Health 9: 591–5	Case series n=21 FU=6 to 8 months	82% of the patients showed a statistically significant improvement in VHI ($p<0.05$). Additionally, 81% of patients reported improvement in sexual gratification, 94% reported improvement in vaginal rejuvenation, and 100% reported satisfaction with treatment. VHI improvement remained significant at 6-8 months after treatments ($p<0.01$). Most patients (97%) reported no to mild discomfort with treatment.	Case series with more patients or longer follow-up are included.
Arunkalaivanan A, Kaur H, Onuma O (2017) Laser therapy as a treatment modality for genitourinary syndrome of menopause: a critical appraisal of evidence. International Urogynecology Journal 28: 681– 5	Systematic review 4 studies (n=220)	The collated data suggest that laser therapy may be valuable as a nonhormonal therapeutic modality in the management of GSM. Higher quality of evidence from randomized controlled trials is required to establish the efficacy of laser treatment in the management of GSM.	Another systematic review with a meta-analysis has been included, which includes all 4 studies described in this review.
Athanasiou S, Pitsouni E, Douskos A et al. (2020) Intravaginal energy-based devices and sexual health of female cancer survivors: a systematic review and meta-analysis. Lasers in Medical Science 35 (no. 1)	Systematic review 8 studies (n=274)	Serious adverse events were not observed in any of the studies. Intravaginal laser therapies appear to have a positive effect on dyspareunia, vaginal dryness, and FSFI of cancer survivors. However, the quality of evidence is "very low". Further research with high-quality RCTs and long-term follow-up is needed to evaluate the value of energy-based devices as a therapeutic option for cancer survivors with sexual problems.	Review focuses on patients who have had breast cancer or gynaecological cancer. A similar systematic review is already included (Jha et al., 2019).
Athanasiou S, Pitsouni E, Grigoriadis T et al. (2019) Microablative fractional CO2 laser for the genitourinary syndrome of menopause: Up to 12-month results. Menopause 26: 248–55	Case series n=94 FU=12 months	Laser therapy may provide significant improvement and/or absence of GSM symptoms up to 12 months follow-up, irrespectively to the number of laser therapies applied. Symptoms intensity 1 month after last laser therapy may be indicative of GSM symptoms intensity at 12 months. One month after third laser therapy is the critical time to decide whether	Case series with more patients or longer follow-up are included.

		treatment extension should be offered.	
Athanasiou S, Pitsouni E, Antonopoulou S et al. (2016) The effect of microablative fractional CO2 laser on vaginal flora of postmenopausal women. Climacteric: the journal of the International Menopause Society 19: 512–8	Case series n=53 FU=1 month	Microablative fractional CO_2-laser therapy is a promising treatment for improving the vaginal health of postmenopausal women by helping repopulate the vagina with normally existing Lactobacillus species and reconstituting the normal flora to premenopausal status.	Study focuses on the effect of laser therapy on the vaginal microenvironment of postmenopausal women. Study is included in Pitsouni et al. (2017).
Athanasiou S, Pitsouni E, Falagas ME et al. (2017) CO2-laser for the genitourinary syndrome of menopause. How many laser sessions? Maturitas 104: 24–28	Case series n=55 FU=end of treatment session	Results of this study indicate that CO_2-laser therapy may contribute to complete regression of dyspareunia and dryness and reestablishment of normal sexual function in postmenopausal women, in a dose-response manner. An extra fourth or fifth session may further increase the GSM symptom-free rate.	Case series with more patients or longer follow-up are included.
Baggish MS (2016) Fractional CO2 laser treatment for vaginal atrophy and vulvar lichen sclerosus. Journal of Gynecologic Surgery 32: 309–17	Case series n=23 (with vaginal atrophy)	22/23 women who previously complained of dryness and discomfort had these symptoms alleviated and vaginal microscopic exam showed significant changes in colour, elasticity, and wetness following 3 courses of CO_2 laser fractional treatment; additionally 20/23 women had elimination of urinary frequency and urgency, 18/21 women had alleviation of dyspareunia.	Case series with more patients or longer follow-up are included.
Barber MA, Eguiluz I (2016) Patient satisfaction with vaginal erbium laser treatment of stress urinary incontinence, vaginal relaxation syndrome and genito-urinary syndrome of menopause. Journal of the Laser and Health Academy 1: 18–23	Case series n=40	More than 80% of patients presenting with vaginal dryness experienced improvement after the procedure and 85% of these achieved important improvement.	Case series with more patients or longer follow-up are included.
Becorpi A, Campisciano G, Zanotta N et al. (2018) Fractional CO2 laser for genitourinary syndrome of menopause in breast cancer survivors: clinical, immunological, and microbiological aspects. Lasers in Medical Science 33: 1047–54	Case series n=20	The significant reduction of clinical symptoms related to GSM after the CO_2 laser treatment supports its efficacy as therapy in postmenopausal cancer survivors. The exact mechanism responsible for the clinical improvement is still to be elucidated and further studies are needed in this field	Case series with more patients or longer follow-up are included.

		to clarify its long-term efficacy and other effects.	
Behnia-Willison F, Sarraf S, Miller J et al. (2017) Safety and long-term efficacy of fractional CO2 laser treatment in women suffering from genitourinary syndrome of menopause. European Journal of Obstetrics, Gynecology, and Reproductive Biology 213: 39–44	Case series n=102 FU=12 months	84% of patients had statistically significant improvement in their symptoms after CO_2 laser treatment. Scores on measures of sexual function, dyspareunia, and bothersomeness of sexual issues were improved from pretreatment to long-term (12-24 month) follow-up. Furthermore, there were improvements on measures of bladder function (p=0.001), prolapse (p=0.001), vaginal sensation (p=0.001), vaginal lubrication (p<0.001) and urge incontinence (p=0.003) from the pretreatment assessment to the second assessment.	Case series with more patients or longer follow-up are included.
Bhide AA, Khullar V, Swift S et al. (2019) The use of laser in urogynaecology. International Urogynecology Journal 30: 683– 92	Review 25 studies	The use of lasers to treat these conditions may seem appealing; however, the lack of good-quality evidence in the form of multi-centre randomised placebo-controlled trials is concerning. The safety and effectiveness of these laser devices have not been established. Use of lasers may lead to serious adverse events such as vaginal burns, scarring, dyspareunia and chronic pain. Randomised placebo-controlled trials in addition to formal evaluation of the laser devices are required before this treatment modality can be recommended.	A systematic review that is more specific to the indication of urogenital atrophy has been included.
Bojanini JF (2016) Treatment of Genitourinary syndrome of menopause with Erbium:YAG laser: a prospective study of efficacy and safety of the treatment for women after menopause of natural origin and therapy-induced menopause in breast cancer survivors. Journal of the Laser and Health Academy 2016, No.1	Non-randomised comparative study n=40 FU=12 months	Statistically significant reduction of vaginal dryness and dyspareunia was observed in all 3 groups at all follow-ups up to 12 months posttreatment. Also improvement in patients' sexual life measured by patient evaluation of intercourse avoidance was statistically significant in all 3 groups at all follow-ups. There were no serious side effects noted. Patients were highly satisfied with the treatment.	Studies with more patients or longer follow-up are included.

Bojanini JF, Mejía AM (2014) Laser treatment of vaginal atrophy in post-menopause and post-gynecological cancer patients. Journal of the Laser and Health Academy 2014, No.1	Non-randomised comparative study n=40 FU=3 months	Results were similar for all treatment groups, independent of whether the patient had gynaecological cancer. Before treatment, all patients reported severe vaginal dryness and severe dyspareunia, and 98% of patients avoided having sex because of the symptoms. At 3 month follow-up, 70% of patients reported no vaginal dryness and 30% had only mild vaginal dryness; 90% of the patients said they did not have dyspareunia and no longer avoided sexual intercourse, while only 10% of the patients remained with mild dyspareunia and rare sex avoidance.	Studies with more patients or longer follow-up are included.
Burton R (2019) Vaginal Health and Wellness: Vaginal Laser Therapy. Plastic Surgical Nursing: official journal of the American Society of Plastic and Reconstructive Surgical Nurses 39: 97–102	Review	The CO_2 fractional laser treatment of VVA has been shown to alleviate symptoms of VVA by remodelling the vaginal epithelium and offers an additional effective treatment. The author's experience has shown short-term relief but lacks the evidence of longstanding relief of symptoms. This treatment is directed not only at symptom relief but also at counteracting the urogenital atrophy that occurs with menopause as well as other conditions. More data are needed to assess the long-term effects of this treatment.	All relevant studies are included in table 2 or the appendix.
Di Donato V, D'Oria O, Scudo M et al. (2020) Safety evaluation of fractional CO2 laser treatment in post-menopausal women with vaginal atrophy: A prospective observational study. Maturitas 135: 34–39	Case series n=53 FU=median 6 months	Fractional CO_2 laser for treatment of VVA seems a safe therapeutic option. No severe complications occurred. A minority of patients reported mild complications, but these resolved without the need for treatment. Most discomfort was related to probe introduction and rotation. Overall, patients were highly satisfied, and they would repeat laser treatment.	Case series with more patients or longer follow-up are included.
Eder SE (2018) Early effect of fractional CO2 laser treatment in post-menopausal women with	Case series n=28	The mean VHIS score improved at 1 month (13.89 compared with 11.93 at baseline, $p<0.05$), and	Case series with more patients or

vaginal atrophy. Laser Therapy 27: 41–47	FU=6 months	improved further at 3 and 6 months following all 3 laser treatments (16.43 and 17.46 respectively). Almost all vulvovaginal atrophy symptoms were improved at 1 month after the first treatment. A further statistically significant improvement in symptoms was noted at 3 and 6 months after the third laser session. The FSFI score increased (22.36 compared with 13.78 at baseline, p<0.05), and remained statistically significantly higher than baseline at the 3- and 6-month follow-up visits.	longer follow-up are included.
Eder SE (2019) Long-term safety and efficacy of fractional CO2 laser treatment in post-menopausal women with vaginal atrophy. Laser Therapy 28: 103–9	Case series n=20 FU=18 months	Almost all vulvovaginal atrophy symptoms were statistically significantly improved at 12 months after the third treatment compared to baseline and this improvement was sustained at 15 and 18 months. At 12 months, the total FSFI score increased significantly (n=15, 24.4 +/- 6.9; p<0.05), and at the 15-and 18-month follow-up visits, the total FSFI remained higher than baseline (22.2 +/- 6.7, 25.8 +/- 6.6).	Case series with more patients or longer follow-up are included.
Elia D, Gambacciani M, Berreni N et al. (2019) Genitourinary syndrome of menopause (GSM) and laser VEL: a review. Hormone Molecular Biology and Clinical Investigation 20190024	review	The vaginal Er:YAG laser (VEL) technology acts only by thermal effect and not by ablation on tissue. It is a safe solution in terms of side effects and potential complications. Studies have been increasing since 2012 and all demonstrate improvement in the GSM signs and symptoms, as well as an improved sexual life after VEL treatment. Double-blind, placebo-controlled, randomised studies are needed, to ultimately confirm the safety and effectiveness of VEL.	A systematic review with a meta-analysis has been included.
Filippini M, Del Duca E, Negosanti F et al. (2017) Fractional CO2 laser: from skin rejuvenation to vulvo-vaginal reshaping. Photomedicine and Laser Surgery 35: 171–5	Case series n=386 FU=2 months	After 3 treatments, patients reported improvement of symptoms (60% dryness, 56% burn, sensation, 49% dyspareunia, 56% itch, 73%	A larger and more recent study from the same author is included.

		soreness, and 49% vaginal introitus pain).	
Franic D, Fistonic I (2019) Laser therapy in the treatment of female urinary incontinence and genitourinary syndrome of menopause: an update. BioMed Research International 1576359	review	Additional studies are needed to explore the long-term safety and efficacy of various laser therapies for genitourinary symptoms.	A systematic review with a meta-analysis has been included.
Gambacciani M, Levancini M (2015) Short-term effect of vaginal erbium laser on the genitourinary syndrome of menopause. Minerva Ginecologica 67: 97–102	Case series n=65	VEL treatment statistically significantly improved vaginal dryness, dyspareunia, and mild-moderate SUI. Larger and long-term studies are needed to investigate the role of laser treatments in the management of GSM.	Case series with more patients or longer follow-up are included. Study is included in Pitsouni et al. (2017).
Gambacciani M, Levancini M, Cervigni M (2015) Vaginal erbium laser: the second-generation thermotherapy for the genitourinary syndrome of menopause. Climacteric: the journal of the International Menopause Society 18: 757–63	Non-randomised comparative study n=70 (45 laser)	VEL treatment induced a significant decrease of VAS of both vaginal dryness and dyspareunia ($p<0.01$), with a significant ($p<0.01$) increase of VHIS.	A larger and more recent study from the same author is included. Study is included in Pitsouni et al. (2017).
Gambacciani M, Levancini M (2017) Vaginal erbium laser as second-generation thermotherapy for the genitourinary syndrome of menopause: a pilot study in breast cancer survivors. Menopause 24: 316–9	Case series n=43 FU=18 months	This study suggests that the vaginal erbium laser is effective and safe for the treatment of genitourinary syndrome of menopause in breast cancer survivors.	Case series with more patients or longer follow-up are included. Included in Jha S et al., 2019.
Gambacciani M, Palacios S (2017) Laser therapy for the restoration of vaginal function. Maturitas 99: 10–15	Review	Although large randomised trials have not been reported, the evidence suggests that VEL can be offered as a safe and efficacious alternative to hormone replacement therapy for GSM, as well as a first-line treatment for mild to moderate SUI, before surgical procedures are resorted to. Randomised studies are needed to compare laser treatments with other therapies, as well as to assess the duration of the therapeutic effects and the safety of repeated applications.	A systematic review with a meta-analysis has been included.
Gaspar A, Brandi H, Gomez V et al. (2017) Efficacy of Erbium:YAG laser treatment compared to topical estriol treatment for symptoms of genitourinary syndrome of menopause. Lasers in Surgery and Medicine 49: 160–8	Non-randomised comparative study n=50 FU= up to 18 months	Er:YAG laser treatment successfully relieved symptoms of genitourinary syndrome of menopause and the results were more pronounced and longer lasting than topical estriol treatment.	Larger studies are included. Study is included in Pitsouni et al. (2017).

Gittens P, Mullen G (2019) The effects of fractional microablative CO2 laser therapy on sexual function in postmenopausal women and women with a history of breast cancer treated with endocrine therapy. Journal of Cosmetic and Laser Therapy: official publication of the European Society for Laser Dermatology 21: 127–31	Case series n=25	There was a statistically significant improvement in every domain of FSFI, WBFS, and FSDS-R when comparing baseline symptom scores to after treatment 3 symptom scores for all patients. The secondary outcome was to evaluate the differences, if any, in outcomes of sexual function between postmenopausal women and women with a history of breast cancer treated with endocrine therapy. Both groups had statistically significant improvements in many domains studied.	Case series with more patients or longer follow-up are included.
Hersant B, Werkoff G, Sawan D et al. (2020) Carbon dioxide laser treatment for vulvovaginal atrophy in women treated for breast cancer: Preliminary results of the feasibility EPIONE trial. Annales de Chirurgie Plastique et Esthetique doi.org/10.1016/j.anplas.2020.05.002	Case series n=20 FU=6 months	This pilot feasibility study showed that CO_2 laser treatment appears to be an effective and safe method to improve the trophicity and decrease vaginal mucosal dryness in women with vulvovaginal atrophy that developed after systemic breast cancer therapy.	Case series with more patients or longer follow-up are included.
Knight C, Logan V, Fenlon D (2019) A systematic review of laser therapy for vulvovaginal atrophy/genitourinary syndrome of menopause in breast cancer survivors. ecancer 13: 988	Systematic review n=163 (6 studies)	There are a number of small-scale studies which all suggest an improvement in vaginal health in women who have had breast cancer, both objectively and subjectively. However, there are no large-scale studies which discuss the acceptability of the intervention and which were randomised. There is a need to undertake large-scale prospective, randomised controlled trials to fully explore the benefits of vaginal laser as a therapy for vaginal atrophy and to gain a better understanding of whether this treatment can reduce symptom burden and improve QoL for postmenopausal women, particularly after breast cancer treatment.	A systematic review with a meta-analysis is included.
Lang P, Dell JR, Rosen L et al. (2017) Fractional CO2 laser of the vagina for genitourinary syndrome of menopause: Is the out-of-pocket cost worth the outcome of treatment?	Case series n=122	Patients 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	Case series with more patients or longer follow-up are included.

Lasers in Surgery and Medicine 49: 882–85		were satisfied with their treatment results.	
Lang P, Karram M (2017) Lasers for pelvic floor dysfunctions: is there evidence? Current Opinion in Obstetrics & Gynecology 29: 354–8	Review	The existing data is limited to mostly observational studies with additional quality randomised controlled trials and sham studies needed to ensure that physicians are providing the optimum evidence-based treatments to their patients. At the present time there is insufficient data to promote these therapies for stress incontinence, vaginal tightening, or other pelvic floor abnormalities.	A systematic review with a meta-analysis is included.
Lekskulchai O, Mairaing K, Vinayanuvattikhun N (2016) Fractional CO2 laser for vulvovaginal atrophy. Journal of the Medical Association of Thailand 99: 54–8	Case series n=112 FU=3 months	Fractional CO2 laser could ameliorate the vulvovaginal atrophy symptoms with at least 3 months of long lasting improvement of vaginal health with safety.	Case series with more patients or longer follow-up are included.
Lugo Salcedo F, Estrada Blanco Z (2020) Experience with ospemifene in patients with vulvovaginal atrophy treated with laser therapy: case studies. Drugs in Context 9: 2020-3-7	Case reports n=2	Postmenopausal women with VVA and severe dyspareunia can benefit from combined treatment with laser therapy and ospemifene. As shown in the case studies, ospemifene appears to be useful in preparing and conditioning the vaginal epithelium for laser therapy, at minimum allowing laser therapy to be performed and potentially augmenting its beneficial effects.	Case reports focusing on the use of ospemifene with laser therapy.
Marin J, Lipa G, Dunet E (2019) The results of new low dose fractional CO2 Laser - A prospective clinical study in France. Journal of Gynecology Obstetrics and Human Reproduction 101614	Case series n=50 FU=6 months	The new micro-fractionated laser device with low dose energy - 18W, demonstrated significant improvement of genitourinary syndrome in both non-menopausal and post-menopausal women with no important adverse events.	Case series with more patients or longer follow-up are included.
Mendoza N, Carrion R, Mendoza-Huertas L et al. (2020) Efficacy and safety of treatments to improve dyspareunia in breast cancer survivors: a systematic review. Breast Care	Systematic review 3 studies on laser	In the 3 prospective observational studies of this review, which globally analysed 113 women, the efficacy and safety of laser therapy were observed even when applied only once. There are not enough RCTs to determine its effectiveness and safety, although some trials are already in progress.	All relevant studies are already included in table 2 or the appendix.
Mothes AR, Runnebaum M, Runnebaum IB (2018) Ablative dual-phase Erbium:YAG laser treatment	Case series n=16	Pre-laser vaginal health index (VHI) scored 16 (SD 4.6) and post-laser VHI 20 (SD 3) with	Case series with more patients or

of atrophy-related vaginal symptoms in post-menopausal breast cancer survivors omitting hormonal treatment. Journal of Cancer Research and Clinical Oncology 144: 955–60	FU=8 weeks	p=0.01. 94% (15/16) of patients were satisfied regarding symptom relief.	longer follow-up are included. Included in Jha S et al., 2019.
Mothes AR, Runnebaum M, Runnebaum IB (2018) An innovative dual-phase protocol for pulsed ablative vaginal Erbium:YAG laser treatment of urogynecological symptoms. European Journal of Obstetrics, Gynecology, and Reproductive Biology 229: 167–71	Case series n=71 FU=6 weeks	In patients with genitourinary syndrome of menopause, pre- and post-treatment VHI and pH differed significantly [15.3 +/- 4.5 compared with 19.9 +/- 2.8 ($p<0.001$) and 5.2 +/- 0.6 compared with 4.8 +/- 0.4 ($p=0.024$), respectively]. Overall, 82% (n=58) of patients were satisfied with the treatment, 84% (47/56) post-menopausal patients were satisfied.	Case series with more patients or longer follow-up are included.
Pagano I, Gieri S, Nocera F et al. (2017) Evaluation of the CO2 laser therapy on vulvo-vaginal atrophy (VVA) in oncological patients: preliminary results. Journal of Cancer Therapy 8: 452–63	Case series n=33 FU=3 months	Fractionated CO2 laser therapy is a safe, effective and easy-to-perform treatment modality for menopause-related vaginal atrophy and stress urinary incontinence.	Case series with more patients or longer follow-up are included.
Pagano T, De Rosa P, Vallone R et al. (2018) Fractional microablative CO2 laser in breast cancer survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local treatments: a retrospective study. Menopause 25: 657–62	Case series n=82	This study shows that CO_2 laser treatment is effective and safe in breast cancer patients with iatrogenic menopause. However, the optimal number of cycles to administer and the need for retreatment remain to be defined. Prospective trials are needed to compare CO_2 laser therapy with therapeutic alternatives.	Case series with more patients or longer follow-up are included.
Pagano T, De Rosa P, Vallone R et al. (2016) Fractional microablative CO2 laser for vulvovaginal atrophy in women treated with chemotherapy and/or hormonal therapy for breast cancer: a retrospective study. Menopause 23: 1108–13	Case series n=26	Treatment resulted in a significant regression of vulvovaginal atrophy symptoms compared with baseline ($p<0.001$ in almost all cases). No adverse reactions were observed or reported by women.	Case series with more patients or longer follow-up are included.
Pearson A, Booker A, Tio M et al. (2019) Vaginal CO2 laser for the treatment of vulvovaginal atrophy in women with breast cancer: LAAVA pilot study. Breast Cancer Research and Treatment 178: 135–40	Case series n=26 FU=12 weeks	There was significant improvement in each of the vulvovaginal atrophy symptoms: dryness ($p<0.001$), itch ($p<0.001$), burning ($p=0.003$), dysuria ($p<0.001$) and dyspareunia ($p<0.001$). Patients also reported improvement in sexual function on the FSFI ($p\leq0.001$).	Case series with more patients or longer follow-up are included.

Perino A, Calligaro A, Forlani F et al. (2015) Vulvo-vaginal atrophy: a new treatment modality using thermo-ablative fractional CO2 laser. Maturitas 80: 296–301	Case series n=48 FU=30 days	There was a statistically significant improvement in vulvovaginal symptoms (vaginal dryness, burning, itching and dyspareunia) ($p<0.0001$) in patients who had 3 sessions of vaginal fractional CO2 laser treatment. Overall, 92% of patients were satisfied or very satisfied with the procedure and experienced considerable improvement in quality of life. There were no adverse events due to fractional CO_2 laser treatment.	Case series with more patients or longer follow-up are included. Study is included in Pitsouni et al. (2017).
Perrone AM, Tesei M, Ferioli M et al. (2020) Results of a phase I-II study on laser therapy for vaginal side effects after radiotherapy for cancer of uterine cervix or endometrium. Cancers 12, 1639; doi:10.3390/cancers12061639	Case series n=43 FU=6 months	Laser therapy improved vaginal length and VHI in women having pelvic radiotherapy; prospective studies are needed.	Case series with more patients or longer follow-up are included.
Phillips C, Hillard T, Salvatore S et al. (2020) Lasers in gynaecology. European Journal of Obstetrics and Gynecology and Reproductive Biology 251: 146–55	review	The authors recommend further independently or nationally funded, large multicentre randomised controlled trials are needed to assess efficacy and safety of each laser as well as any dose related effects. There are several studies underway and results should be available over the next few years. Best practice in treatments for incontinence and prolapse would also dictate that if used, a database of indication, assessment, treatment regimes: including energy settings, number of passes and follow up outcomes should be mandatory.	A systematic review with a meta-analysis is included.
Photiou L, Lin MJ, Dubin DP et al. (2019) Review of non-invasive vulvovaginal rejuvenation. Journal of the European Academy of Dermatology and Venereology DOI:10.1111/jdv.16066	review	It appears that there is more evidence in favour of the CO_2 laser than the erbium:YAG laser. Both lasers have more evidence than radiofrequency (RF). In conclusion, microablative CO_2 laser, erbium:YAG laser and RF may be offered to patients with vulvovaginal atrophy/genitourinary syndrome of menopause as an alternative or adjunct to conventional therapies.	A systematic review with a meta-analysis is included.

		Further well-conducted controlled studies are needed.	
Pieralli A, Fallani MG, Becorpi A et al. (2016) Fractional CO2 laser for vulvovaginal atrophy (VVA) dyspareunia relief in breast cancer survivors. Archives of Gynecology and Obstetrics 294: 841–6	Case series n=50 FU=mean 11 months	The treatment with fractionated CO_2 laser appeared to be a feasible and effective treatment for VVA dyspareunia in breast cancer survivors with contraindications to hormonal treatments.	Case series with more patients or longer follow-up are included. Included in Jha S et al., 2019 and Pitsouni E et al., 2017.
Pitsouni E, Grigoriadis T, Falagas M et al. (2017) Microablative fractional CO2 laser for the genitourinary syndrome of menopause: power of 30 or 40 W? Lasers in Medical Science 32: 1865–72	Case series n=50 FU=1 month	Comparison between 30 and 40 W revealed that mean improvement or presence of all GSM symptoms and clinical signs was not statistically significant different. CO_2 laser therapy may improve GSM symptoms and clinical signs. This improvement did not seem to associate to power of 30 or 40 W.	Case series with more patients or longer follow-up are included.
Pitsouni E, Grigoriadis T, Tsiveleka A et al. (2016) Microablative fractional CO2-laser therapy and the genitourinary syndrome of menopause: An observational study. Maturitas 94: 131–6	Case series n=53 FU=4 weeks	This study suggests that intravaginal CO_2-laser therapy for postmenopausal women with clinical signs and symptoms of GSM may be effective in improving both vaginal pathophysiology and reported symptoms.	Case series with more patients or longer follow-up are included. Study is included in Pitsouni et al. (2017).
Quick AM, Zvinovski F, Hudson C et al. (2019) Fractional CO2 laser therapy for genitourinary syndrome of menopause for breast cancer survivors. Supportive Care in Cancer: official journal of the Multinational Association of Supportive Care in Cancer https://doi.org/10.1007/s00520-019-05211-3	Case series n=64 FU=1 month	Fractional CO_2 laser treatment for breast cancer survivors is feasible and appears to reduce GSM symptoms across treatment and follow-up.	Case series with more patients or longer follow-up are included.
Rabley A, O'Shea T, Terry R et al. (2018) Laser therapy for genitourinary syndrome of menopause. Current Urology Reports 19: 83	Review	Although laser therapy for the treatment of the symptoms of GSM appears promising, there is currently a lack of high-level and long-term evidence regarding its safety and efficacy.	A systematic review with a meta-analysis is included.
Robinson D, Flint R, Veit-Rubin N et al. (2020) Is there enough evidence to justify the use of laser and other thermal therapies in female lower urinary tract dysfunction? Report from the ICI-RS 2019. Neurourology and Urodynamics	Review	While the evidence base supporting the use of laser therapy in GSM is relatively comprehensive, there remains a need for well-designed long-term studies to assess the efficacy and safety of these emerging technologies.	A systematic review with a meta-analysis is included.

Romero-Otero J, Lauterbach R, Aversa A et al. (2020) Laser-based devices for female genitourinary indications: position statements from the European Society for Sexual Medicine (ESSM). Journal of Sexual Medicine 17: 841–8	Review	It is too early in the evolution and research of laser-based devices to make decisive recommendations regarding vaginal treatments. There is need for randomised controlled trials with proper design for safety reasons, possible harm, and short- and long-term benefits for the different indications studied.	A systematic review with a meta-analysis is included.
Salvatore S, Nappi RE, Parma M et al. (2015) Sexual function after fractional microablative CO2 laser in women with vulvovaginal atrophy. Climacteric: the journal of the International Menopause Society 18: 219–25	Case series n=77 FU=12 weeks	Fractional microablative CO_2 laser treatment is associated with a statistically significant improvement of sexual function and satisfaction with sexual life in postmenopausal women with vulvovaginal atrophy symptoms.	Case series with more patients or longer follow-up are included. Study is included in Pitsouni et al. (2017).
Salvatore S, Athanasiou S, Candiani M (2015) The use of pulsed CO2 lasers for the treatment of vulvovaginal atrophy. Current Opinion in Obstetrics & Gynecology 27: 504–8	Review	Increasing evidence with histological and clinical data supports the use of pulsed CO_2 lasers in the treatment of vulvovaginal atrophy; however, no randomised control trial (sham compared with treatment) has yet been produced and no data on the duration of therapy are currently available.	A more recent systematic review with a meta-analysis is included.
Salvatore S, Pitsouni E, Del Deo F et al. (2017) Sexual function in women suffering from genitourinary syndrome of menopause treated with fractionated CO_2 laser. Sexual Medicine Reviews 5: 486–94	Review n=273 (6 studies)	Fractional CO_2 laser can improve sexual function in postmenopausal women affected by GSM by restoring a better trophism in the lower genitourinary tract.	Another systematic review, which includes more outcomes, is included.
Salvatore S, Nappi RE, Zerbinati N et al. (2014) A 12-week treatment with fractional CO2 laser for vulvovaginal atrophy: a pilot study. Climacteric 17: 363–9	Case series n=50 FU=12 weeks	Fractional CO_2 laser treatment was effective to improve vulvovaginal atrophy symptoms (vaginal dryness, vaginal burning, vaginal itching, dyspareunia, dysuria; $p<0.001$) as well as the VHIS (13.1 ± 2.5 at baseline compared with 23.1 ± 1.9; $p<0.001$). Both physical and mental scores of quality of life were significantly improved in comparison with baseline ($p<0.001$). Satisfaction with the laser procedure was reported by 42 women (84%).	Case series with more patients or longer follow-up are included. Study is included in Pitsouni et al. (2017).
Samuels JB, Garcia MA (2019) Treatment to external labia and vaginal canal with CO2 laser for symptoms of vulvovaginal atrophy in	Case series n=40 FU=12 months	Fractional CO_2 laser treatments were well tolerated and were associated with improvement in vaginal health and amelioration of symptoms	Case series with more patients or longer follow-up are included.

postmenopausal women. Aesthetic Surgery Journal 39: 83–93		of vulvovaginal atrophy. Histological changes in the epithelium and lamina propria after treatment correlated with clinical restoration of vaginal hydration and pH to premenopausal levels.	
Siliquini GP, Tuninetti V, Bounous VE et al. (2017) Fractional CO2 laser therapy: a new challenge for vulvovaginal atrophy in postmenopausal women. Climacteric: the journal of the International Menopause Society 20: 379–84	Case series n=87 FU=15 months	This study shows that CO_2 laser treatment induces a significant and long-lasting improvement of symptoms.	Case series with more patients or longer follow-up are included.
Singh P, Chong CYL, Han HC (2019) Effects of vulvovaginal laser therapy on postmenopausal vaginal atrophy: A prospective study. Journal of Gynecologic Surgery 35: 99–104	Case series n=45 FU=6 months	Vulvovaginal laser therapy appears to be a promising option for managing genitourinary symptoms of menopause. Further randomised controlled trials with long-term follow-up data are needed before routine use of the therapy for this indication.	Case series with more patients or longer follow-up are included.
Sipos AG, Kozma B, Poka R et al. (2019) The effect of fractional CO2 laser treatment on the symptoms of pelvic floor dysfunctions: Pelvic Floor Distress Inventory-20 questionnaire. Lasers in Surgery and Medicine: 51: 882–6	Case series n=40 FU=4 weeks	Three sessions of microablative fractional CO_2 vaginal laser treatment significantly improves patient reported urinary and pelvic organ prolapse symptoms.	Case series with more patients or longer follow-up are included.
Sokol ER, Karram MM (2017) Use of a novel fractional CO2 laser for the treatment of genitourinary syndrome of menopause: 1-year outcomes. Menopause 24: 810–4	Case series n=30 FU=1 year	Based on study data up to 1 year, the fractional CO_2 laser may be an effective and safe treatment for women suffering from symptoms of GSM, although additional studies with larger populations and placebo control is needed to confirm these results.	Case series with more patients or longer follow-up are included.
Sokol ER, Karram MM (2016) An assessment of the safety and efficacy of a fractional CO2 laser system for the treatment of vulvovaginal atrophy. Menopause 23: 1102–7	Case series n=30 FU=3 months	In this sample, the data suggest that the fractional CO_2 laser is effective and safe for treatment of the symptoms associated with GSM.	Case series with more patients or longer follow-up are included. Study is included in Pitsouni et al. (2017).
Song S, Budden A, Short A et al. (2018) The evidence for laser treatments to the vulvo-vagina: Making sure we do not repeat past mistakes. The Australian & New Zealand Journal of Obstetrics & Gynaecology 58: 148–62	Systematic review n=761 (vulvovaginal symptoms) FU=none to 2 years	Current scientific evidence in support of laser therapy is limited to observational data and is not enough to demonstrate robust clinical safety and efficacy. While this treatment may well be safe and efficacious, these claims	A systematic review with a meta-analysis is included.

		must be validated through large-scale randomised controlled trials, which can provide stronger evidence, to ensure responsible representation of this new treatment to the public.	
Tovar-Huamani J, Mercado-Olivares F, Grandez-Urbina JA et al. (2019) Efficacy of fractional CO2 laser in the treatment of genitourinary syndrome of menopause in Latin-American Population: First Peruvian experience. Lasers in Surgery and Medicine 51: 509–15	Case series n=60 FU=4 months	In this sample, the data suggests that fractionated CO_2 laser is an effective alternative for GSM treatment with positive outcomes that persists over time.	Case series with more patients or longer follow-up are included.
Tranoulis A, Georgiou D, Michala L (2019) Laser treatment for the management of genitourinary syndrome of menopause after breast cancer. Hope or hype? International Urogynecology Journal 30: 1879–86	Systematic review n=192 (6 studies)	The findings suggest that lasers appear to be effective and practical treatment options in breast cancer survivors with GSM. Evidence on long-term effects is lacking. The rationale for repeated treatment remains uncertain. Randomised controlled trials that collate different frequencies, intensities and durations are warranted to ascertain a dose-response relationship and adherence.	A systematic review with a meta-analysis is included.
Vizintin Z, Lukac M, Kazic M et al. (2015) Erbium laser in gynecology. Climacteric: the journal of the International Menopause Society 18: 4-8	Review	The results show that SMOOTH-mode erbium laser seems to be an effective and safe method for treating vaginal laxity, stress urinary incontinence, pelvic organ prolapses and vaginal atrophy.	A more recent systematic review with a meta-analysis is included.