

Nonhormonal Approaches

RECOMMENDATION STATEMENTS

- Nonhormonal methods should be considered first-line treatment for urogenital symptoms in individuals with a history of estrogen-dependent breast cancer.
- Gynecologists should be familiar with different non-hormonal treatment options as trials of multiple options may be needed to find effective treatment for any individual patient.
- Non-hormonal treatments that have been reported to be effective in treating vulvovaginal symptoms include silicone, polycarbophil, and water-based lubricants, hyaluronic acid, polyacrylic acid, and vitamin E and D vaginal suppositories. There are insufficient data to indicate that one approach is superior to others.

SUPPORTING EVIDENCE

Related Guidelines

North American Menopause Society (NAMS) 2020: The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society

- Choice of therapy depends on the severity of symptoms, the effectiveness and safety of treatments for the individual patient, and patient preference. Nonhormone therapies available without a prescription provide sufficient relief for most women with mild symptoms.

Category I

Systematic Reviews

Mixed Vaginal Moisturizers

Seav 2015: The review found that regular and prolonged use of vaginal moisturizers was effective in improving vaginal dryness, dyspareunia, and sexual satisfaction. Educational and counseling interventions targeting sexual dysfunction showed consistent improvement in various aspects of sexual health.

Sinha 2013: Vaginal moisturizers applied on a regular basis have an efficacy equivalent to topical vaginal estrogen for the treatment of vulvar and vaginal atrophy (VVA)-related symptoms and should be offered to women wishing to avoid the use of estrogen. Over-the-counter lubricants do not address the underlying condition of VVA and are usually used during sexual

Category II

Observational Studies

Mixed Vaginal Moisturizers

Carter 2021: Hyaluronic acid (HLA) moisturization improved vulvovaginal health/sexual function of cancer survivors. While HLA administration 1–2x/week is recommended for women in natural menopause, a 3–5x/week schedule appears to be more effective for symptom relief in cancer survivors.

Juraskova 2013: In a study evaluating the efficacy of a novel intervention (Olive Oil, Vaginal Exercise, and MoisturizeR [OVERcome]), treatment resulted in significant improvements in dyspareunia, sexual function, and quality of life over time (all P<0.001). Pelvic floor muscle (PFM) relaxation training was reported to be effective (P<=0.001). Maximum benefits were

Category III

Narrative Reviews

Mixed Vaginal Moisturizers

Amori 2018: Recently, a new non-invasive product, containing hyaluronic acid, oligopeptides, and antioxidants was introduced to the market. The aim of this product is to allow a vulvovaginal bio stimulation and considered simple, safe, and satisfactory

Derzko 2007: For breast cancer patients taking aromatase inhibitors, first-line therapy for urogenital symptoms, notably vaginal dryness and dyspareunia, should be the non-hormonal group of preparations such as moisturizers and precoital vaginal lubricants.

intercourse to provide temporary relief from vaginal dryness and dyspareunia, but there is no evidence that they have any long-term therapeutic effects.

Randomized Controlled Trials

Loprinzi 1997: During the first 4 weeks, average vaginal dryness decreased by 62% and 64% in the placebo and Replens groups, respectively (P = .3). Average dyspareunia scores also improved by 41% and 60%, respectively (P = .05). Crossover analysis indicated that the bulk of the beneficial effects appeared within the first 2 weeks of the first treatment and remained constant thereafter. Both treatments were relatively well tolerated.

Hickey 2016: In a post hoc analysis, pain/discomfort during penetration improved more during silicone-based lubricant use than during water-based lubricant use (odds ratio 5.4, 95% CI 1.3-22.1, p = 0.02). Almost twice as many women preferred silicone-based to water-based lubricant than the converse (n = 20, 65%, vs. n = 11, 35%). 88% continued to experience clinically significant sexually related distress despite use of either lubricant.

Lidocaine

Goetsch 2014: In breast cancer survivors with dyspareunia, exquisite sensitivity was vestibular and reversible with aqueous lidocaine. Vaginal tenderness was rare despite severe atrophy.

Goetsch 2015: Breast cancer survivors with menopausal dyspareunia can have comfortable intercourse after applying liquid lidocaine compresses to the vulvar vestibule before penetration

Acid based moisturizer

Juliato 2017: In women with breast cancer treated with Tamoxifen, those treated with polyacrylic acid showed a decrease in sexual dysfunction from 96% to 24% (p < 0.0001) and the lubricant group showed a decrease from 88.9% to 55.6% (p = 0.0027).

Suppositories

Keshavarzi 2019: These data support that vitamin D and E vaginal suppositories were beneficial in improving vaginal atrophy in women with breast cancer receiving tamoxifen.

Vaginal Gel

observed at week 12. Most women rated PFM relaxation exercises (92%), vaginal moisturizer (88%), and olive oil (73%) as helpful, indicating that the intervention was acceptable. Unexpectedly, six cases (11%) of vaginal stenosis were noted during initial screening.

Vaginal Cream

Biglia 2010: Eighteen patients receiving estriol cream 0.25 mg (n = 10) or estradiol tablets 12.5 microg (n = 8) twice/week for 12 weeks were evaluated and compared with eight patients treated with polycarbophil-based moisturizer 2.5 g twice/week. Both low-dose vaginal ET are effective for relieving urogenital atrophy, while non-hormonal moisturizer only provides transient benefit. The increase of serum estrogens levels during treatment with vaginal estrogen at these dosages is minimal.

Chatsipirois 2019: This study demonstrates that the investigated cream is an effective and safe non-hormonal, topical option in the treatment of vulvovaginal dryness symptoms in patients undergoing breast cancer treatment for. However, the study duration and follow-up time of 4 weeks as well as the non-randomized trial design are limitations of the study.

Krychman 2013: Many of the sexual health issues experienced by cancer survivors can be addressed in clinical practice. A multimodal treatment paradigm is necessary to effectively treat these sexual complaints in this special patient population.

Sussman 2019: Patients with breast cancer receiving antiestrogen therapy, specifically aromatase inhibitors, often suffer from vaginal dryness, itching, irritation, dyspareunia, and dysuria, collectively known as genitourinary syndrome of menopause. First-line treatment includes nonhormonal therapy with vaginal moisturizers, lubricants, and gels.

Kim 2017: The pH-balanced vaginal gel is not superior to the placebo in improving dyspareunia and overall sexual function.

Lee 2011: Vaginal dryness and dyspareunia improved more in the pH-balanced gel group than in the placebo group (baseline mean 8.20 compared with end-point mean 4.23 [P=.001] and 8.23 compared with 5.48 [P=.040], respectively). There was no significant difference in adverse effects between the two groups except for mild irritation at the early time of pH-balanced gel administration.

Hormonal Approaches: Vaginal Estrogen

RECOMMENDATION STATEMENT

- If nonhormonal treatments have failed to adequately address symptoms, after discussion of risks and benefits, low-dose vaginal estrogen may be used in individuals with a history of breast cancer, including those on tamoxifen. For individuals on aromatase inhibitors, low-dose vaginal estrogen can be used after shared decision-making between the patient, gynecologist, and oncologist.

SUPPORTING EVIDENCE

Related Guidelines

North American Menopause Society (NAMS) 2020: The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society

- For women with a history of breast or endometrial cancer, management depends on a woman's preferences, symptom severity, and understanding of potential risks after consultation with her oncologist. [Level C]. Although product labeling for low-dose vaginal estrogen therapy notes risks associated with systemic hormone therapy (including coronary heart disease, stroke, venous thromboembolism, breast and endometrial cancer), these risks are highly unlikely given minimal systemic absorption and reassuring findings from clinical trials and observational studies. [Level B]

Category I

Systematic Reviews/ Meta-Analyses

Mixed Vaginal Estrogen Methods

Collaborative Group on Hormonal Factors in Breast Cancer 2019: Every menopausal hormone therapy type, except vaginal estrogens, was associated with excess breast cancer risks, which increased steadily with duration of use and were greater for estrogen-progestogen than estrogen-only preparations

Harris 2020: The risks of hormone therapy should be assessed on an individual basis, with consideration of age, type of hormone therapy, dose, duration of use, regimen, route, and prior exposure. Systemic hormone therapy is not recommended in breast cancer survivors, whereas vaginal low-dose estrogen appears safe.

Mazzarello 2015: One study of 98 patients suggested that vaginal pH-balanced gel (mean VHI 5.00 +/- 0.816, mean Vaginal Health Index 51.18 +/- 3.753) was more efficient than placebo (VHI 16.98 +/- 3.875, $p < 0.001$, VMI 47.87 +/- 2.728, $p < 0.001$) at 12 weeks in providing vaginal symptom relief. In

Category II

Observational Studies

Mixed Vaginal Estrogen Methods

Biglia 2010: Eighteen patients receiving estriol cream 0.25 mg (n = 10) or estradiol tablets 12.5 microg (n = 8) twice/week for 12 weeks were evaluated and compared with eight patients treated with polycarbophil-based moisturizer 2.5 g twice/week. Both low-dose vaginal estrogen therapy are effective for relieving urogenital atrophy, while non-hormonal moisturizer only provides transient benefit. The increase of serum estrogens levels during treatment with vaginal estrogen at these dosages is minimal.

Crandall 2018: Among women with an intact uterus, the risks of stroke, invasive breast cancer, colorectal cancer, endometrial cancer, and pulmonary embolism/deep vein thrombosis were not significantly different between vaginal estrogen users and nonusers, whereas the risks of coronary heart disease, fracture, all-cause mortality, and global index event (GIE) were lower in users than in nonusers (GIE adjusted hazard ratio 0.68, 95% confidence interval 0.55-0.86).

Category III

Editorials

Manson 2014: This commentary summarizes the activities of several clinicians and researchers to encourage modifications to the labeling of low-dose vaginal estrogen.

Mixed Vaginal Estrogen Methods

Case Series

Zuo 2018: Low-dose vaginal estrogen use for 1 or more years in a small cohort of women with genitourinary syndrome of menopause did not appear to be associated with any changes in breast density or Bi-RADS breast cancer risk scores in the majority of study participants, including three breast cancer survivors

Narrative Reviews

Crean-Tate 2020: Hormonal therapies must be used with caution in women with estrogen-dependent cancers. For many cancer survivors, local vaginal estrogen or dehydroepiandrosterone therapy can be considered with

patients who used lidocaine, 90 % had reduced dyspareunia compared to saline in a study of 46 patients. Although increased serum estradiol occurred, both Estring and Vagifem were shown to improve quality of life and VMI in a study of seven patients.

Pavlovic 2019: For women on aromatase inhibitors, after 8 weeks of local hormonal treatment, there was no change in the serum levels of luteinizing hormone and estradiol, whereas sex hormone binding globulins were low, and follicle stimulating hormone was almost doubled compared with the baseline. Adverse effect rates of vaginal discharge, facial hair growth, urinary tract or yeast infection, and vaginal or vulvar itching and/or irritation did not show significant changes in the sensitivity analysis, with exception of a single trial.

Randomized Controlled Trials

Low Dose Estriol Gel

Hirschberg 2020: Sixty-one women who had been treated with aromatase inhibitors were included: 50 received 0.005% estriol vaginal gel and 11 received placebo. Active treatment significantly improved maturation value and pH, vaginal dryness and global scores of symptoms and signs. Active treatment also increased the total Female Sexual Functioning Index (FSFI) score and all the FSFI domains, with the exception of pain.

Vaginal Ring

Melisko 2017: In postmenopausal women with early-stage breast cancer receiving aromatase inhibitors, treatment with a vaginal ring or intravaginal testosterone cream over 12 weeks met the primary safety end point. Baseline elevation in E2 was common and complicates this assessment. Vaginal atrophy, sexual interest, and sexual dysfunction were improved.

Dew 2003: Subjects who used a topical estrogen alone for menopausal symptoms had an uncorrected hazard ratio of 0.30 (95% confidence interval (CI) 0.11-0.80, $p = 0.02$). The corrected hazard ratio was 0.57 (95% CI 0.20-1.58, $p = 0.28$). Although the small numbers of this study preclude a definitive result, topical estrogen usage does not appear to be associated with an increased risk of recurrence of breast cancer.

Decker 2003: In these selected patients, estrogen replacement therapy relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases.

Le Ray 2012: Overall, the use of local hormonal therapy (LHT) was not associated with an increased risk of recurrence (RR: 0.78, 95 % CI 0.48-1.25) compared with non-use. In stratified analyses, LHT did not increase the risk of recurrence among tamoxifen-treated patients (RR: 0.83, 95 % CI 0.51-1.34), while the risk was not estimable among AI-treated patients since no patients receiving LHT experienced a recurrence. The use of LHT is not associated with an increase in breast cancer recurrence among women receiving a hormone therapy.

Lyttinen 2006: Altogether, 2,171 women with breast cancer were identified. The standardized incidence ratio of breast cancer with systemic estradiol for less than 5 years was 0.93 (95% confidence interval 0.80-1.04), and for estradiol use for 5 years or more, 1.44 (1.29-1.59). Estradiol for 5 years or more, either orally or transdermally, means 2-3 extra cases of breast cancer per 1,000 women who are followed for 10 years. Oral estradiol use for less than 5 years, oral estriol, or vaginal estrogens were not associated with a risk of breast cancer

O'Meara 2001: The authors observed lower risks of recurrence and mortality in women who used hormone replacement therapy (HRT) after breast cancer diagnosis than in women who did not. Although residual confounding may exist, the results suggest that HRT after breast cancer has no adverse impact on recurrence and mortality.

Vaginal Estrogen Tablets

Buchholz 2015: Local vaginal therapy with Gynoflor containing 0.03 mg estriol daily in breast cancer survivors on AIs relieving atrophic vaginitis could be considered as a useful treatment for the quality of sexual life. Vaginal dryness continuously improved from a median score of 8 at entry to a score of 4 at the end of initial therapy, and a median score of 2 at the end of maintenance therapy.

informed shared decision making. Clinicians should consult the woman's oncologist when considering these therapies.

Lupo 2015: the authors conducted an integrative review investigating recurrence and mortality data among breast cancer survivors who have used hormone replacement therapy (HRT). They recommend a stepwise algorithm for treating vaginal symptoms in breast cancer survivors: (1) start with nonhormonal treatments; (2) progress to a detailed discussion among patients and health-care professionals about the current known risks and benefits of vaginal estrogen; and (3) conclude with mutual decision-making between health-care providers and patients regarding the use of vaginal estrogen treatment.

Donders 2014: The low-dose 0.03 mg E3 (ultra-low-dose .03mg estradiol) and Lactobacillus acidophilus vaginal tablets application in postmenopausal breast cancer patients during AI treatment suffering from vaginal atrophy lead to small and transient increases in serum E3, but not E1 (estrone) or E2 (estradiol), and therefore can be considered as safe and efficacious for treatment of atrophic vaginitis in breast cancer patients taking non-steroidal aromatase inhibitors.

Donders 2015: The vaginal use of ultra-low dose estriol and lactobacilli results in rapid and enduring improvement of all markers of the vaginal microflora and epithelial vaginal cell quality in women with breast cancer on AI with dyspareunia. Candida may develop soon after its use, but rapidly disappears again upon their prolonged use. Due to its excellent safety profiles and clinical efficacy we recommend this product as first choice in women on AI with severe dyspareunia.

Kendall 2006: The vaginal estradiol tablet Vagifem significantly raises systemic estradiol levels, at least in the short term. This reverses the estradiol suppression achieved by aromatase inhibitors in women with breast cancer and is contraindicated.

Pfeiler 2011: Two weeks of daily vaginal estriol treatment (Ovestin, 0.5mg) in women using AIs did not change serum estradiol or estriol levels. However, significant decreases in levels of serum follicle stimulating hormone ($p = 0.01$) and luteinizing hormone ($p = 0.02$) were observed. Five out of six breast cancer patients noticed an improvement in vaginal dryness and/or dyspareunia.

Wills 2012: For women on AIs, mean pre-insertion E2 levels in patients using VE tablets were not significantly different than those of controls ($P = .48$), and postinsertion levels were 76 pmol/L higher than pre-insertion ($P < .001$).

Vaginal Ring

Streff 2021: In women treated with aromatase inhibitors, there was no significant difference between baseline and week 16 estradiol levels ($p = 0.81$). In addition, patients in the prospective group reported subjective improvement in their vaginal dryness symptoms questionnaires.

Dehydroepiandrosterone (DHEA) and Testosterone

RECOMMENDATION STATEMENT

- If vaginal estrogen is not an option, vaginal dehydroepiandrosterone (DHEA) or testosterone may help with dyspareunia and improve vaginal tissue health.

Category I

DHEA

Randomized Controlled Trials

Barton 2018/Support Care Cancer 2018;26:643-50. doi: 10.1007/s00520-017-3878-2: Neither DHEA dose was statistically significantly different from PM at 12 weeks (6.25 mg, $p=.08$; 3.25 mg, $p=0.48$), although a significant difference at 8 weeks for 6.5 mg DHEA was observed ($p=0.005$). Women on the 6.5 mg arm of DHEA reported significantly better sexual health on the Female Sexual Functioning Index (FSFI) ($p<0.001$). There were no significant differences in provider-graded toxicities and few significant differences in self-reported side effects.

Testosterone

Systematic Reviews

Bell 2018: Taken together, the studies suggest that intravaginal testosterone may lower vaginal pH, increase the proportion of vaginal lactobacilli, and possibly improve the vaginal maturation index. The lack of a placebo treatment in four studies, and failure to adjust for baseline differences, resulted in uncertainty of the effect on sexual function. Safety remains uncertain because of the small number of women exposed, short study durations, and inconsistent and incomplete outcome reporting for sex steroid levels.

Lemke 2017: Vaginal testosterone shows preliminary promise as an option to manage sexual side effects of aromatase inhibitor therapy in postmenopausal cancer survivors; however, available data are too limited to draw practice-changing conclusions.

Randomized Controlled Trials

Category II

Observational Studies

DHEA

Barton 2018/ Support Care Cancer 2018;26:1335-43. doi: 10.1007/s00520-017-3960-9: Circulating dehydroepiandrosterone-sulfate and testosterone levels were significantly increased in those on vaginal DHEA in a dose-dependent manner compared to the plain moisturizer group. Estradiol was significantly increased in those on 6.5 mg/day DHEA but not in those on 3.25 mg/day DHEA ($p < 0.05$ and $p = 0.05$, respectively), and not in those on AIs.

Testosterone

Dahir 2014: The use of a compounded testosterone vaginal cream applied daily for 4 weeks improves reported sexual health quality of life in women with breast cancer taking aromatase inhibitors. When compared with baseline FSFI scores, there was a statistically significant improvement for individual domain scores of desire ($P = 0.000$), arousal ($P = 0.002$), lubrication ($P = 0.018$), orgasm ($P = 0.005$), satisfaction ($P = 0.001$), and pain ($P = 0.000$).

Witherby 2011: A 4-week course of vaginal testosterone was associated with improved signs and symptoms of vaginal atrophy related to AI therapy without increasing estradiol or testosterone levels. Estradiol levels remained suppressed after treatment to <8 pg/mL. Mean total symptom scores improved from 2.0 to 0.7 after treatment ($p<.001$) and remained improved 1 month thereafter ($p=.003$). Dyspareunia ($p=.0014$) and vaginal dryness ($p<.001$) improved. The median vaginal pH decreased from 5.5 to 5.0 ($p=.028$).

Category III

Testosterone

Case Series

Krychman 2007: The improved sexual functioning is a quality-of-life parameter for these patients, and the unknown testosterone safety profile is an individually accepted level of risk. As studies emerge reporting beneficial effects of testosterone on libido and sexual function, the use of testosterone-containing therapies can be expected to increase among postmenopausal women

Davis 2018: Intravaginal testosterone significantly improved sexual satisfaction and reduced dyspareunia in postmenopausal women on aromatase inhibitor (AI) therapy. The low reporting of UI among women on AI therapy merits further investigation.

Melisko 2017: In postmenopausal women with early-stage breast cancer receiving aromatase inhibitors, treatment with a vaginal ring or vaginal testosterone cream over 12 weeks met the primary safety end point. Baseline elevation in E2 was common and complicates this assessment. Vaginal atrophy, sexual interest, and sexual dysfunction were improved.

Ospemifene/Selective estrogen receptor modulators

RECOMMENDATION STATEMENT

- Ospemifene, an orally administered selective estrogen receptor modulator, has been found to improve symptoms in a general population of menopausal individuals and may be considered as an option for individuals with a history of estrogen-dependent breast cancer. Although there is no indication that ospemifene is associated with increased risk of recurrence, long-term safety data are limited.

Category I

Systematic Reviews

Di Donato 2019: In the group of patients treated with ospemifene, there was a slightly higher rate of hot flushes (OR:2.36, 95% CI 1.26-4.42; p = 0.007) and urinary tract infection (OR:1.97, 95% CI 1.23-3.14, p = 0.005) at 12 weeks of treatment, but no differences were noted after 52 weeks.

Randomized Controlled Trials

Archer 2019: Ospemifene significantly improved (P < 0.0001) the percentages of parabasal and superficial cells, vaginal pH, and severity of vaginal dryness severity compared with placebo at week 12; significant between-group differences were noted by week 4.

Constantine 2014: Ospemifene substantially improved clinical signs of vulvar and vaginal atrophy. Within the placebo group, there was no difference in physiologic effects in lubricant users vs. nonusers. Based on gynecologic evaluation of the vagina, benefits were apparent at 12 weeks and sustained for 52 weeks in the ospemifene-treated subjects with significant improvement over placebo.

Category II

Observational Studies

Cai 2020: No difference in recurrence was observed between ospemifene-treated and matched untreated patients. Ten (32.3%) treated vs. 25 (40.3%) controls in the 1:2 matched analysis had a recurrence.

Category III

Narrative Reviews

Cagnacci 2020: Because ospemifene is a selective estrogen receptor modulator, it can be administered also in women with a history of breast cancer, and this makes it more acceptable by any woman. Available data indicate that women using ospemifene have higher adherence to treatment, higher persistence and lower discontinuation rate. Satisfaction is higher than with other local therapies and overall health care cost is lower.

Other Approaches: Fractional CO₂ Laser Treatment

SUPPORTING EVIDENCE

Related Guidelines

U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to safeguard women's health from deceptive health claims and significant risks related to devices marketed for use in medical procedures for "vaginal rejuvenation." The FDA has cleared or approved laser and energy-based devices for the treatment of serious conditions like the destruction of abnormal or pre-cancerous cervical or vaginal tissue, as well as condylomas (genital warts). But the safety and effectiveness of these devices hasn't been evaluated or confirmed by the FDA for "vaginal rejuvenation." In addition to the deceptive health claims being made with respect to these uses, the "vaginal rejuvenation" procedures have serious risks. In some cases, these devices are being marketed for this use to women who have completed treatment for breast cancer and are experiencing symptoms caused by early menopause. The deceptive marketing of a dangerous procedure with no proven benefit, including to women who've been treated for cancer, is egregious.

Category I

Systematic Reviews

Athanasiou 2020: Intravaginal laser therapies appear to have a positive effect on dyspareunia, vaginal dryness, and the Female Sexual Function Index of cancer survivors. However, the quality of evidence is "very low," with no data on intravaginal radiofrequency therapy

Jha 2019: Vaginal laser was effective in treating genitourinary syndrome of menopause in breast cancer survivors with improvement in the Vaginal Health Index and the Visual Analogue Scale score for dyspareunia and vaginal dryness, sexual function, and overall satisfaction in the short term with minimal adverse events.

Category II

Observational Studies

Vaginal Erbium Laser

Areas 2019: For women with a history of breast cancer treated with vaginal erbium laser, vaginal health improved, as shown by an increased overall score (P < 0.001). The effect size was large between pretreatment and post-treatment scores for vaginal elasticity, fluid volume, epithelial integrity, and moisture. The effect size was also significant for the overall sexual function score and for the score in the dyspareunia domain between pretreatment and 1 month after the final treatment session.

Gambacciani 2015: Vaginal Erbium laser treatment was effective to improve genitourinary syndrome of menopause (GSM) symptoms. Both subjective and objective scores significantly improved in comparison with baseline values (p < 0.01). No adverse events were recorded during the study period. These results suggest that Vaginal Erbium Laser is effective and safe for the treatment of GSM in postmenopausal Breast Cancer Survivors.

Gambacciani 2017: From baseline values of 8.5 +/- 1.0 cm, vaginal dryness Visual Analog Scale (VAS) scores were 4.4 +/- 1.2 cm after the third treatment and 5.5 +/- 1.5 cm 12 months after the treatment (P < 0.01 vs basal values), whereas they were 7.5 +/- 1.8 cm after 18 months from the last laser application (NS vs basal values). From baseline values of 7.5 +/- 1.5 cm, dyspareunia VAS values decreased to 4.2 +/- 0.9 cm after the third treatment and 5.1 +/- 1.8 cm 12 months from the

Category III

Consensus Statements

Donders 2019: Expert opinion: Laser therapy requires validation and safety data, as is can potentially cause vaginal fibrosis and stenosis, and safer and cheaper alternatives are available.

last laser application ($P < 0.01$ vs basal values), whereas they were 6.5 +/- 1.8 cm after 18 months from the last laser application (NS vs basal values). Vaginal Health Index Score, from baseline values of 8.1 +/- 1.3, was 21.0 +/- 1.4 after the third treatment and 18 +/- 1.8 12 months from the last laser application ($P < 0.01$ vs basal values), whereas they were 14.8 +/- 1.5 cm after 18 months from the last laser application (NS vs basal values). No adverse events were recorded during the study.

Mothes 2018: All ablative vaginal laser outpatient procedures were successfully completed, all patients returned to daily activities without a need for analgetic medication. Evaluation was performed after 8.3 (SD 2.5) weeks. Pre-laser vaginal health index scored 16 (SD 4.6) and post-laser VHI 20 (SD 3) with $p = 0.01$. Patients were satisfied in 94% ($n = 15$) regarding symptom relief.

CO₂ Laser

Gittens 2019: In a retrospective study evaluating fractional ablative CO₂ laser, there was a statistically significant improvement in every domain of the Female Sexual Functioning Index, the Wong-Baker Faces Scale, and the Female Sexual Distress Scale—Revised when comparing baseline symptom scores to after treatment three 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.

Pagano 2016: Fractional microablative CO₂ laser treatment is associated with a significant improvement of vulvar and vaginal atrophy (VVA) symptoms in women affected by hormone-driven breast cancer. This procedure has the advantage of relieving iatrogenic/physiological VVA symptoms without resorting to contraindicated estrogen preparations, which have been the most effective therapy thus far.

Pagano 2018: In a retrospective study on CO₂ laser treatment, pre versus post-treatment differences in mean visual analog scale scores were significant for sensitivity during sexual intercourse, vaginal dryness, itching/stinging, dyspareunia and dysuria ($P < 0.001$ for all), bleeding ($P = 0.001$), probe insertion ($P = 0.001$), and movement-related pain ($P = 0.011$). Multivariate analyses confirmed that results were significant, irrespective of patients' age and type of adjuvant therapy.

Pieralli 2016: Data indicated a significant improvement in vulvar and vaginal atrophy dyspareunia ($p < 1.86e-22$) in breast cancer

survivors who had undergone 3 sessions of vaginal fractional CO₂ laser treatment. Moreover, Vaginal Health Index scores were significantly higher 30 days post-treatment (T4) ($p < 0.0001$). 76 % of patients were satisfied or very satisfied with the treatment results. The majority (52 %) of patients were satisfied after a long-term follow-up (mean time 11 months). No adverse events due to fractional CO₂ laser treatment occurred. (9% on AIs, 91% on Tamoxifen)

Quick 2019: CONCLUSION: Fractional CO₂ laser treatment for breast cancer survivors is feasible and appears to reduce genitourinary syndrome of menopause symptoms across treatment and follow-up. Most participants were receiving endocrine therapy (n= 54, 92%), most commonly aromatase inhibitors (AI; n= 40, 68%).

Quick 2021: In breast cancer survivors with genitourinary syndrome of menopause, the total and individual domain scores of the Female Sexual Function Index (FSFI) and Female Sexual Distress Scale Revised (FSDS-R) improved after fractional CO₂ laser therapy.

Salvatore 2021: Microablative fractional CO₂ laser was safe and effective in treating vulvovaginal symptoms in women with a history of breast cancer, irrespective of being previously or currently on endocrine therapies.

Veron 2021: Among women with breast cancer, fractional microablative CO₂ laser is effective on the long term on vulvovaginal symptoms and gynecological quality of life.