Review

For reprint orders, please contact: reprints@futuremedicine.com

Journal of **Comparative Effectiveness Research**

Vaginal laser therapy for gynecologic conditions: re-examining the controversy and where do we go from here

Ralph Zipper[1] & Georgine Lamvu*[,2]

[1]Zipper Urogynecology & Associates, Melbourne, FL, 32935 USA

[2]University of Central Florida College of Medicine, Department of Clinical Sciences, Obstetrics and Gynecology, Orlando, FL, 32827 USA

*Author for correspondence: Tel.: +1 407 461 1189; georginelamvu@gmail.com

Despite significant controversy, vaginal laser therapy continues to be used for treatment of many gynecologic and pelvic conditions including vaginal atrophy, vaginal dryness, dyspareunia, urinary incontinence and pelvic pain. This commentary reviews the controversy surrounding vaginal laser therapy and summarizes the important distinction between ablative and non-ablative vaginal lasers. While much research is still needed, the article describes what is important for healthcare professionals to know before making the decision to integrate this technology into their clinical practice.

First draft submitted: 11 November 2021; Accepted for publication: 27 April 2022; Published online: 21 June 2022

Keywords: atrophy • genitourinary syndrome of menopause • pain • photobiomodulation • vaginal laser • vaginal low-level laser therapy

Since being introduced into the US market in 2014, vaginal lasers have been widely promoted for off-label office use with claims of treating different gynecologic conditions including urinary incontinence, vaginal atrophy, dryness and pain. Lasers are also being used for the treatment of vaginal laxity in a procedure known as vaginal 'rejuvenation'. Although vaginal laser devices do not have US FDA marketing approval or clearance for any of these indications, the technology has been aggressively marketed, resulting in widespread use. Evidence in support of such off-label use is limited to a small group of predominantly observational studies [1–12]. Rare reports of complications – such as vaginal fibrosis, scarring, agglutination and pain – have accumulated, and by 2018, FDA commissioner Scott Gottlieb issued a statement warning clinicians against the use of vaginal lasers for vaginal rejuvenation [13]. Shortly thereafter multiple societies, including the American College of Obstetricians and Gynecologists [14], the International Urogynecological Association, the International Continence Society [15], and the International Society for the Study of Vulvovaginal Diseases [16], published guidelines stating that there is not enough evidence to support efficacy and that long-term data on side effects was lacking. These guidelines and advisories largely discouraged the use of vaginal lasers and concluded that use of these devices should be limited to clinical trials.

More recent research is disparate from the FDA safety communication. In 2020 Guo *et al.* [17] conducted a review of the medical literature, the Manufacturer and user Facility Device Experience (MAUDE) database and the Bloomberg Law database, for evidence on the safety of vaginal laser therapy. In their review the authors noted that the FDA wrongly "*equates vaginal laser therapy for the treatment of genitourinary syndrome of menopause (GSM) with 'vaginal rejuvenation' and elective cosmetic vaginal procedures such as bleaching, as having similar evidence and justification*" (Guo p. 1183). Guo *et al.* [17] point out that it may be incorrect to compare the risk–benefit ratio of vaginal lasers used for cosmetic indications to those used for relief of GSM symptoms, which include vaginal atrophy, dryness and dyspareunia. They concluded that strong evidence of significant risk from vaginal laser treatment of GSM is lacking and that most reported 'adverse events' should actually be classified as lack of treatment effects. Ahluwalia and colleagues conducted a separate review of the MAUDE database and identified only 45 individual records, out of hundreds of procedures performed [18]. The paucity of complications in the MAUDE database prompted several authors to suggest that the FDA warning against the use of vaginal lasers was

Future Medicine

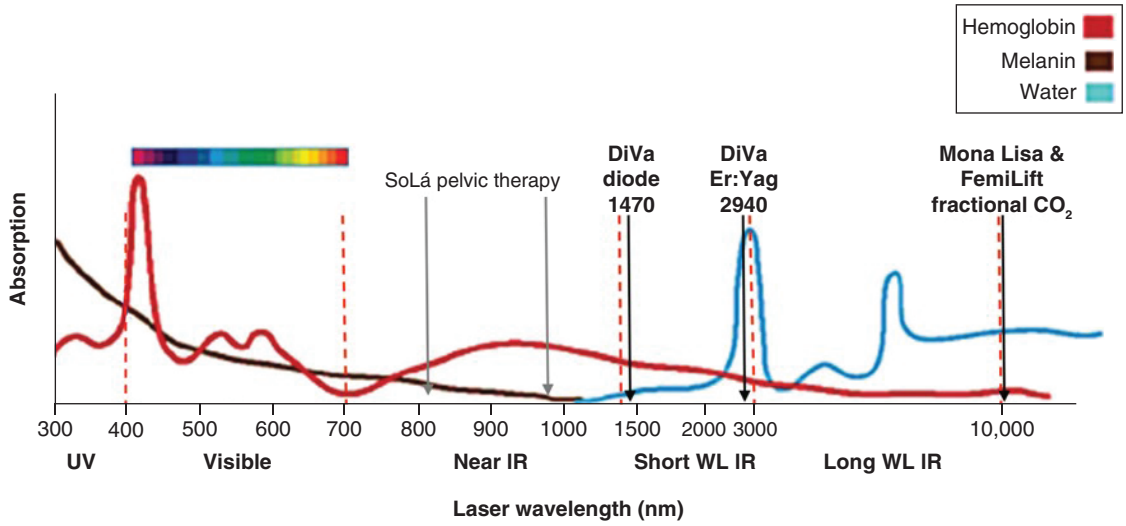

Figure 1. Wavelengths of vaginal lasers, absorption wavelengths for human chromophores and wavelengths of commercial vaginal lasers.
Er:Yag: Erbium-doped yttrium aluminum garnet laser; IR: Infrared; UV: Ultraviolet WL: Wavelength.

premature, motivated by gender bias and fear of litigation, and may result in women not having access to potentially effective therapy for debilitating vaginal symptoms [18,19].

In May of 2020 the American Urogynecology Society published its consensus statement on vaginal energy-based devices (EBD) [20]. Focusing mostly on GSM they stated that "*For patients experiencing vaginal atrophy (VVA) and dyspareunia associated with medical menopause it was agreed that EBD therapy has demonstrated short-term efficacy. The benefits associated with factional laser treatment for menopausal dyspareunia last up to 1 year, and CO_2 and Er: YAG laser may improve VVA for 1 year*" (Alshiek, p.289). They also concluded that EBD has a beneficial effect on sexual function in the short-term, whereas longer duration is unknown[20].The authors noted that adverse events include vaginal discharge, vaginal spotting immediately after treatment, bacterial vaginosis, urinary tract infection and mild discomfort at the sight of treatment, scarring and burning [20]. However, they also emphasized that serious adverse events are 'infrequent' when used to treat women with menopausal dyspareunia and atrophy, and that EBD therapies have a 'favorable safety profile' [20].

Gynecologists are now challenged by the conflicting opinions and limited evidence relating to the use of laser energy in the vagina. Although the marketing of vaginal lasers continues, most manufacturers, in accordance with FDA guidance, no longer make marketing claims for the treatment of vaginal atrophy, dryness, dyspareunia or incontinence. When considering expert opinions, the peer-reviewed literature and specialty society guidance, one must thoughtfully consider the fact that not all lasers are the same and that their efficacy is not proven in most vaginal conditions. The objective of this manuscript is to review the important differences between various types of lasers available for transvaginal therapy. The authors hope that this review will help physicians navigate the confusing waters of this evolving area of medicine.

What is a laser? Not all lasers are the same

Electromagnetic energy is characterized by its wavelength (WL): gamma-rays ($<10^{-12}$ m), x-rays (1 pm–1 nm), ultraviolet (1 nm–400 nm), visible (400 nm–750 nm), near infrared (NIR) (700 nm–1300 nm), short infrared (1300 nm–3000 nm), long (thermal) infrared (3000 nm–30,000 nm), microwaves (30,000 nm–1 mm) and radio waves (>1 mm) (Figure 1). The word laser is an acronym for 'light amplification by stimulated emission of radiation'. A laser is a device that is capable of delivering nearly monochromatic (single WL) electromagnetic energy that is coherent (i.e., phase differences between waves are constant). Non-laser sources of light energy such as incandescent bulbs, halogen bulbs and light emitting diodes, regardless of color, deliver light waves that are out of phase with multiple WLs. When using light energy as a form of medical therapy, one can think of non-laser light energy as being a pill that has a small amount of the desired therapeutic medicine mixed in. In order to provide

enough of the therapeutic medicine, the pill becomes too big and too dangerous to swallow. The laser, on the other hand, can deliver pure medicine. Yet, similar to a medication that might be taken by mouth, delivering an effective therapeutic dose to the target organ is not as simple as swallowing the pill. After determining the appropriate medication (i.e., WL), one must consider the device and method requirements to deliver a therapeutic dose of energy to the target organ(s) without sacrificing safety.

Chromophores are molecules in a given material or tissue that absorb particular WLs of light. To deliver electromagnetic energy to a given organ in order to exert a therapeutic effect, that organ must have a chromophore to absorb that specific WL of energy. If intervening tissues contain chromophores for that same WL, they may absorb the energy and prevent delivery of therapeutic dosing to the target tissue. One might try to overcome this problem by delivering more energy at the surface (increasing the power). However, this typically results in injury to the intervening tissues.

Examples of human chromophores include melanin, red blood cell hemoglobin and water; their corresponding absorption WLs are shown in Figure 1. As the human body is composed predominantly of water, the energy emitted by short- and long-infrared lasers will be rapidly absorbed the moment it interacts with human tissue. In contrast, NIR is poorly absorbed by water and has the ability to penetrate deeply into human tissue, reaching target tissues without damaging intervening tissues. Although NIR energy is absorbed by chromophores melanin and hemoglobin, melanin is absent from the vaginal mucosa, and hemoglobin molecules are present in only in minute amounts. The remarkable difference in chromophores separates lasers into two distinct categories, ablative and non-ablative.

Lasers that emit WLs strongly absorbed by water (Er:Yag [erbium-doped yttrium aluminum garnet laser], CO_2) are typically ablative. The rapid absorption of electromagnetic energy by water results in heating and destruction of tissue. The therapeutic effect of ablative lasers is thought to be achieved by destruction of tissue followed by tissue healing. Lasers that emit WLs that are poorly absorbed by water (NIR) are said to be non-ablative. The electromagnetic energy is minimally absorbed by water, allowing a non-thermal effect. The therapeutic mechanism of action is a non-destructive process called photobiomodulation (PBM). This is a process in which light triggers biochemical changes within cells. Photons are absorbed by the mitochondrial chromophore, cytochrome c oxidase, and initiate a chain of intracellular chemical reactions. Although PBM is a non-thermal, non-ablative modality, at high enough powers (e.g., >15 W with power density >3 W/cm^2), even lasers emitting light in the NIR range can be ablative.

To date, the most common WLs used inside the vagina have been in the short WL and long infrared categories, ablative lasers (Figure 1). The newest laser deployed inside the vagina (SoLá Pelvic Therapy, Uroshape, LLC) is in the NIR range. This laser is distinct, in that it is the first non-ablative vaginal laser.

Achieving a therapeutic outcome with laser therapy depends not only on the pathology and the effect of a given WL of light on such pathology, but also on the ability of the laser system to deliver a correct dose of energy to the target tissue. The dosing of laser is described by irradiance (power density) and fluence (power × time). As a certain percentage of energy will be absorbed by chromophores encountered between the laser probe and the target tissue, increasing the power (W/cm) emitted from the probe will allow a greater amount to reach the target. For ablative lasers, the consequences of increasing power are typically unacceptable (destruction of healthy tissue). However, for non-ablative lasers, increasing power in the 2–15 W range is an effective means of delivering therapeutic doses of energy to deep vaginal/pelvic target tissues [21].

Vaginal lasers

Several studies initially reported that fractional ablative CO_2 lasers (Mona Lisa Touch®, FemiLift®) and Er:Yag lasers (diVa®) effectively treat vaginal symptoms associated with GSM, such as vaginal dryness, atrophy, pain and incontinence. In some cases, these lasers are being used to treat a poorly defined condition known as vaginal 'laxity' through a controversial elective cosmetic procedure called vaginal rejuvenation. Ablative lasers are thought to induce controlled thermal injury to the epithelial layer of the vaginal skin, which then stimulates tissue repair and remodeling through the process of wound healing. It has been suggested that this process induces fibroblasts to produce collagen [22–24]. Er:Yag lasers have 10–15-times the affinity for water absorption compared with CO_2 lasers. This may enable a deeper thermal effect without burning the vaginal epithelium [15], and sometimes leads people to erroneously classify Er:Yag as a non-ablative laser. In comparison, CO_2 lasers cause more superficial tissue injury before subsequent collagen remodeling [15]. Secondary to the affinity for water, the therapeutic effects of ablative WLs are less likely limited to more superficial conditions.

Despite the lack of knowledge of the precise mechanisms by which ablative lasers exert a superficial therapeutic effect, they have become widely used by gynecologists. This may be secondary to the minimally invasive nature of the procedures, the ease of use in office settings, the fact that the treatments are generally short (5–10 min at intervals of 4–6 weeks) and well tolerated with rare adverse events, and that patients experience minimal downtime. The disadvantages are that the devices are costly, and treatments are not covered by insurance. Therapeutic effects, whatever they may be, are limited to the superficial vaginal tissues, and although adverse events are rare, tissue destruction can sometimes lead to severe burns and scarring.

An important limitation of vaginal lasers is the paucity of randomized clinical trials (RCTs) evaluating their efficacy and safety. Ablative vaginal lasers are used for many clinical indications including urinary incontinence, prolapse, atrophy, dryness and dyspareunia associated with menopause or GSM. In 2018 Cruz *et al.* published the first randomized, double-blind, placebo-controlled clinical trial comparing fractional CO_2 laser to topical estriol for the treatment of vaginal atrophy in postmenopausal women [10]. The study contained three treatment arms: laser plus estriol, laser plus placebo, and estriol plus sham laser. The investigators found that after 20 weeks of therapy, laser and estriol led to significant improvements in GSM symptoms including burning, dryness, dyspareunia and sexual function. The estriol arm showed improvement only in dryness, while laser alone improved in all domains except for a worsening of the pain domain reported on the female sexual function index, although the total female sexual function index score improved [10]. The researchers concluded that fractional CO_2 laser alone or in combination with topical estriol is 'a good treatment option for vulvovaginal atrophy' although 'sexual-related pain with vaginal laser treatment' alone 'might be of concern' [10]. As of 2022, several additional RCTs have been published. The VeLVET trial published by Paraiso and colleagues enrolled 69 women and randomized (unblinded) them into two study arms, laser versus estrogen cream. Although the trial was closed due to breech of FDA Investigational Device Exemption, the investigators were able to collect enough data to demonstrate that at 6 months, CO_2 vaginal laser and vaginal estrogen resulted in similar improvement in GSM symptoms [25]. A second study conducted by Ruanphoo and Bunyavejchevin randomized 88 women to vaginal CO_2 laser or sham procedures every 4 weeks for 12 weeks. They reported on the outcomes of dryness, irritation, soreness and dyspareunia, and showed that compared with sham, vaginal laser was superior at improving all four outcomes [26]. Another three-arm, unblinded randomized study compared CO_2 laser to promestriene (vaginal estrogen) and vaginal lubricant for treatment of stress incontinence, nocturia, and urgency and urge incontinence in women with GSM. This study only followed participants for 2 weeks and concluded that laser was superior to the other two treatments in treating these symptoms [27]. Another small unblinded randomized trial enrolled 50 women into one of two study arms: CO_2 laser versus topical Premarin. After 3 months of therapy, the authors reported that the women in the laser group showed greater improvement in sexual desire, orgasms and sexual satisfaction, and had less dyspareunia and better overall sexual function compared with the women in the Premarin group [28]. In contrast, a double-blinded, sham-controlled RCT conducted by Li and colleagues in 2021 showed that, in 90 women followed over 12 months, treatment with fractional CO_2 laser did not improve vaginal symptoms of GSM [29]. Nonetheless, systematic reviews published from 2021 to 2022 provide reassuring support for the use of ablative vaginal lasers for treatment of GSM symptoms. However, authors comment that due to methodological issues more research is needed [30,31]. A smaller body of evidence comments on the use of vaginal laser therapy for sexual dysfunction [32,33], incontinence, prolapse [34] and interstitial cystitis/bladder pain syndrome (IC/BPS) [35], and although results show that vaginal ablative lasers are generally beneficial, most studies are plagued by methodologic inadequacies such as lack of blinding, small sample size and short-term follow-up. Therefore, at this time, the best available evidence only supports judicious use of ablative lasers for short-term relief of GSM symptoms.

Non-ablative lasers are used in what was previously referred to as low-level laser therapy (LLLT), and is now known as PBM. The terminology has changed to emphasize that this type of laser therapy does not involve destruction of tissue. PBM is a form of NIR-light (Figure 1) therapy shown in several systematic reviews to improve pain in musculoskeletal and arthritic conditions such as low back pain, fibromyalgia, and knee and shoulder pain [36–38]. PBM uses non-ablative NIR to affect the mitochondrial chromophore cytochrome c oxidase (COX) [39]. Mitochondria are 'power plants' within cells because they can use oxidative phosphorylation to convert food and oxygen into energy in the form of adenosine triphosphate [40]. Nitric oxide (NO), is a mitochondrial waste product that is capable of binding to COX and displacing oxygen, especially in injured or hypoxic cells [41]. It is believed that PBM photo-dissociates NO from COX, resulting in the release of NO [42] and increased production of adenosine triphosphate. NO is a powerful relaxer of both smooth and skeletal muscle, and it is also capable of reducing muscle pain and improving circulation to oxygen-deprived tissues [40,43,44]. Additional benefits are

Figure 2. SoLá Pelvic Therapy, a novel transvaginal photobiomodulation system.

believed to be secondary to activation of various transcription factors that result from mitochondrial stimulation as well as the modulation of reactive oxygen species [45]. PBM also modulates cyclooxygenase activity decreasing prostaglandin E2 production [46–50]. The link between prostaglandin E2 production and pain is well described in the general medical as well as the gynecologic literature [51–55].

Although PBM is routinely used to treat musculoskeletal and arthritic pain, until recently there was no gynecologic applications for this type of technology. This changed in 2017 when Lev-Sagie and colleagues published a placebo-controlled randomized study using LLLT (PBM) versus sham laser in women with provoked vestibulodynia [9]. 34 women were randomized into the two study arms and followed for 1 year. The investigators reported that although that clinical exam findings of pain during tampon insertion and pain during intercourse were similar between the two groups, 78% of the LLLT (PBM) group reported overall improvement compared with 44% in the sham group ($p = 0.042$). Despite being very small, this study emphasized the possible vaginal application of PBM. Most importantly, there were no adverse events reported in this cohort even after long-term follow-up.

Besides the non-thermal properties, PBM has the added advantage of safer deeper tissue penetration, leading researchers to speculate that, as it is the case when PBM is used externally, internal vaginal application of PBM may be used to target deeper pelvic tissues and lead to pain relief in conditions associated with chronic pelvic pain such as IC/BPS, endometriosis-associated pelvic pain and pelvic myalgia. Based on the reported benefits of PBM for treating non-pelvic pain, a transvaginal PBM (TV-PBM) laser system was developed for the treatment of chronic pelvic pain (SoLá Pelvic Therapy, Uroshape, LLC, Figure 2) [21]. This novel system has been used on-label since 2019 as a class IV NIR non-ablative laser, by gynecologists for the temporary relief of pelvic muscle spasm and pain. In 2021, a report was published on the use of SoLá Pelvic Therapy in 144 women who had chronic pelvic pain. Of 93 eligible participants, 65% showed clinically significant improvement in pelvic pain and pain with sitting, standing, urination, defecation and intercourse [56]. Additional pilot data indicates that the therapeutic effect may last as long as 6 months [57]. Therapy was well tolerated with minimal adverse events; however, larger controlled studies will be needed to confirm these findings.

SoLá Pelvic Therapy is capable of transmitting its 810 nm and 980 nm WLs to generate therapeutic irradiance at the vaginal mucosa, levator ani muscles and the bladder [21]. At a power of 5 W the non-ionizing and non-thermal effect emitted by the device avoids the serious side effects including vaginal scarring and burns reported [22] when traditional lasers (CO_2 and Er:Yag lasers) are used to treat vaginal conditions such as atrophy, laxity and

incontinence [16,20]. Consistent with the non-thermal properties of the technology, the manufacturer of this device reports that over 5000 treatments have been performed with no unexpected adverse events. Although MAUDE does not have claims related to this device, safety claims have not yet been substantiated with rigorous research.

Conclusion

Laser technologies are rapidly emerging as a treatment option for various vaginal conditions, including vaginal atrophy, dryness, dyspareunia, pelvic pain, urinary urgency and incontinence. Although vaginal ablative devices were initially introduced into the market without sufficient prospective randomized research, newer data is confirming that, when appropriately used, ablative lasers are generally safe. They show promise in the treatment of GSM; however, there is still not enough data to draw a meaningful conclusion on long-term safety and efficacy. Data for other vaginal conditions (not necessarily associated with menopause), such as sexual dysfunction, vulvar pain, pelvic pain and IC/BPS, is emerging but not yet sufficient. More research is needed to determine the duration and magnitude of effect as well as a standard dosing that should be applied in each condition. Until then, clinicians should consider ablative devices with caution following careful patient selection and extensive discussion of risks and benefits (especially long-term outcomes, which are largely unknown). Concerns about vaginal injury, scarring and pain must be specifically discussed, especially with patients who do not have a history of vaginal pain. Importantly, risk–benefit considerations are not the same for patients undergoing laser therapy for cosmesis or rejuvenation as they are for patients with conditions that significantly impair quality of life, such as atrophy, dryness and pain.

Clinicians should understand the difference between ablative and non-ablative devices. TV-PBM delivered at powers below 10 W is void of safety concerns associated with ablative lasers. TV-PBM can target deeper pelvic tissues such as the pelvic floor muscles and the bladder. For these reasons, TV-PBM is now being used in patients with pelvic pain conditions. However, more research is needed to confirm the efficacy, effect duration and long-term safety of TV-PBM. Given that millions of women are affected by conditions that can be targeted by ablative and non-ablative lasers (both external and transvaginal) the potential impact of vaginal lasers should not be underestimated, and research on these technologies should not be delayed.

Despite a lack of sufficient evidence to guide treatment protocols and a recent call to put vaginal lasers on 'pause' [58], they are widely used by clinicians and requested by patients – a trend that may be difficult to reverse. Therefore, in addition to research, we must continue to disseminate education about laser technology and conditions for appropriate use. For now, recent recommendations made by American Urogynecologic Society [20] regarding ablative lasers seem prudent; clinicians may continue to use these technologies with caution and following extensive patient counseling regarding both cost and limited knowledge of efficacy and safety.

Future perspective

Over the next 5–10 years we speculate that research will specify which conditions benefit most from vaginal laser therapy, and laser type (ablative or non-ablative), irradiance and fluence will be condition specific. Non-ablative lasers may be developed for external application, to treat superficial vaginal conditions, while transvaginal application will be used to target deeper pelvic tissues in conditions associated with pelvic pain and dysfunction.

Executive summary

- Vaginal lasers are used for treatment of various vaginal conditions that negatively impact women, including vaginal atrophy, dryness, prolapse, incontinence and dyspareunia.
- Evidence supports the use of ablative vaginal lasers for symptoms of atrophy, dryness and pain associated with genitourinary syndrome of menopause; however, the duration of effect and long-term efficacy are unknown.
- When used appropriately, ablative lasers are generally safe with a low prevalence of injury, scarring and post-treatment pain; however, risk–benefit considerations are not the same in cases where lasers are being used for cosmetic indications.
- Evidence is lacking to guide treatment protocols; therefore, vaginal ablative lasers should only be used with caution and following extensive patient counseling regarding limited evidence on efficacy and safety.
- Clinicians should understand the difference between ablative and non-ablative lasers (photobiomodulation); non-ablative lasers may have a lower risk of injury and can target deeper vaginal and pelvic tissues.
- Early research suggests transvaginal photobiomodulation may improve pain originating from deeper vaginal and pelvic tissues; however, more research is needed.

Financial & competing interests disclosure

G Lamvu serves in a consultant role as the Chief Science Officer for Uroshape, LLC, the manufacturer of SoLá Pelvic Therapy. R Zipper is the Chief Executive Officer of Uroshape, LLC, the manufacturer of SoLá Pelvic Therapy. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Lee MS. Treatment of vaginal relaxation syndrome with an erbium:YAG laser using 90 degrees and 360 degrees scanning scopes: a pilot study &and short-term results. *Laser Ther.* 23(2), 129–138 (2014).
2. Gambacciani M, Levancini M. Short-term effect of vaginal erbium laser on the genitourinary syndrome of menopause. *Minerva Ginecol.* 67(2), 97–102 (2015).
3. Gambacciani M, Levancini M, Cervigni M. Vaginal erbium laser: the second-generation thermotherapy for the genitourinary syndrome of menopause. *Climacteric* 18(5), 757–763 (2015).
4. Perino A, Calligaro A, Forlani A *et al.* Vulvo-vaginal atrophy: a new treatment modality using thermo-ablative fractional CO_2 laser. *Maturitas* 80(3), 296–301 (2015).
5. Anger JT. CO_2 laser treatment is effective for symptoms of vaginal atrophy. *J. Urol.* 198(6), 1228–1229 (2017).
6. Arroyo C. Fractional CO_2 laser treatment for vulvovaginal atrophy symptoms and vaginal rejuvenation in perimenopausal women. *Int. J. Womens Health* 9, 591–595 (2017).
7. Gambacciani M, Levancini M. Vaginal erbium laser as second-generation thermotherapy for the genitourinary syndrome of menopause: a pilot study in breast cancer survivors. *Menopause* 24(3), 316–319 (2017).
8. Gambacciani M, Palacios S. Laser therapy for the restoration of vaginal function. *Maturitas* 99, 10–15 (2017).
9. Lev-Sagie A, Kopitman A, Brzezinski A. Low-level laser therapy for the treatment of provoked vestibulodynia – a randomized, placebo-controlled pilot trial. *J. Sex. Med.* 14(11), 1403–1411 (2017).
10. Cruz VL *et al.* Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO_2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. *Menopause* 25(1), 21–28 (2018).
11. Eder SE. Early effect of fractional CO_2 laser treatment in post-menopausal women with vaginal atrophy. *Laser Ther.* 27(1), 41–47 (2018).
12. Kwon TR *et al.* Fractional CO_2 laser treatment for vaginal laxity: a preclinical study. *Lasers Surg. Med.* 50(9), 940–947 (2018).
13. FDA. 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' (2018). www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-efforts-safeguard-womens-health-deceptive-health-claims (Accessed 3 August 2021).
14. ACOG. Fractional laser treatment of vulvovaginal atrophy and US Food and Drug Administration clearance (2018). www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/fractional-laser-treatment-of-vulvovaginal-atrophy-and-us-food-and-drug-administration-clearance (Accessed 3 August 2021).
15. Shobeiri SA *et al.* IUGA committee opinion: laser-based vaginal devices for treatment of stress urinary incontinence, genitourinary syndrome of menopause, and vaginal laxity. *Int. Urogynecol. J.* 30(3), 371–376 (2019).

• **Consensus and opinion statements on use of ablative vaginal lasers.**

16. Preti M *et al.* The clinical role of laser for vulvar and vaginal treatments in gynecology and female urology: an ICS/ISSVD best practice consensus document. *J. Low Genit. Tract. Dis.* 23(2), 151–160 (2019).

• **Consensus and opinion statements on use of ablative vaginal lasers.**

17. Guo, JZ *et al.*Vaginal laser treatment of genitourinarysyndrome of menopause: does the evidence support the FDA safety communication?. *Menopause*. 27(10), 1177–1184 (2020).
18. Ahluwalia J, Avram MM, Ortiz AE. Lasers and energy-based devices marketed for vaginal rejuvenation: a cross-sectional analysis of the MAUDE database. *Lasers Surg. Med.* 51(8), 671–677 (2019).
19. Wallace SL, Sokol ER, Enemchukwu EA. Vaginal energy-based devices: characterization of adverse events based on the last decade of MAUDE safety reports. *Menopause* 28(2), 135–141 (2020).
20. Alshiek J *et al.* Vaginal energy-based devices. *Female Pelvic. Med. Reconstr. Surg.* 26(5), 287–298 (2020).

21. Zipper R, Pryor B. Evaluation of a novel deep tissue transvaginal near-infrared laser and applicator in an ovine model. *Lasers Med. Sci.* 7(1), 639–643 (2021).
22. Preti M *et al.* The clinical role of laser for vulvar and vaginal treatments in gynecology and female urology: an ICS/ISSVD best practice consensus document. *Neurourol. Urodyn.* 38(3), 1009–1023 (2019).

• **Consensus and opinion statements on use of ablative vaginal lasers.**

23. Salvatore S *et al.* Early regenerative modifications of human postmenopausal atrophic vaginal mucosa following fractional CO_2 laser treatment. *Open Access Maced. J. Med. Sci.* 6(1), 6–14 (2018).
24. Zerbinati N *et al.* Microscopic and ultrastructural modifications of postmenopausal atrophic vaginal mucosa after fractional carbon dioxide laser treatment. *Lasers Med. Sci.* 30(1), 429–436 (2015).
25. Paraiso MFR *et al.* A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: the VeLVET trial. *Menopause* 27(1), 50–56 (2020).
26. Ruanphoo P, Bunyavejchevin S. Treatment for vaginal atrophy using microablative fractional CO_2 laser: a randomized double-blinded sham-controlled trial. *Menopause* 27(8), 858–863 (2020).
27. Aguiar LB *et al.* Efficacy of fractional CO_2 laser, promestriene, and vaginal lubricant in the treatment of urinary symptoms in postmenopausal women: a randomized clinical trial. *Lasers Surg. Med.* 52(8), 713–720 (2020).
28. Eftekhar T *et al.* The effect of the CO_2 fractional laser or premarin vaginal cream on improving sexual function in menopausal women: a randomized controlled trial. *J. Lasers Med. Sci.* 11(3), 292–298 (2020).
29. Li FG *et al.* Effect of fractional carbon dioxide laser vs sham treatment on symptom severity in women with postmenopausal vaginal symptoms: a randomized clinical trial. *JAMA* 326(14), 1381–1389 (2021).
30. Filippini M *et al.* CO_2-laser therapy and genitourinary syndrome of menopause: a systematic review and meta-analysis. *J. Sex Med.* 19(3), 452–470 (2022).

•• **Systematic reviews on vaginal lasers for the treatment of genitourianry syndrome of menopause, incontinence and prolapse.**

31. Mension E *et al.* Vaginal laser therapy for genitourinary syndrome of menopause – systematic review. *Maturitas* 156, 37–59 (2021).

•• **Systematic reviews on vaginal lasers for the treatment of genitourianry syndrome of menopause, incontinence and prolapse.**

32. Lou W *et al.* A randomized controlled study of vaginal fractional CO_2 laser therapy for female sexual dysfunction. *Lasers Med. Sci.* 37(1), 359–367 (2021).
33. Sathaworawong A *et al.* The efficacy of erbium-doped yttrium aluminum garnet (Er:YAG) laser in the treatment of decreased sexual sensation: a randomized, placebo-controlled trial. *Lasers Med. Sci.* 37(1), 581–588 (2021).
34. Mackova K *et al.* Laser therapy for urinary incontinence and pelvic organ prolapse: a systematic review. *BJOG* 127(11), 1338–1346 (2020).

•• **Systematic reviews on vaginal lasers for the treatment of genitourianry syndrome of menopause, incontinence and prolapse.**

35. Okui N, Okui M, Vizintin Z. Effects of non-ablative vaginal erbium:YAG laser treatment for interstitial cystitis/bladder pain syndrome: a case series (UNICORN-2 study). *Climacteric* 23(Supp1.), S14–S17 (2020).
36. Clijsen R *et al.* Effects of low-level laser therapy on pain in patients with musculoskeletal disorders: a systematic review and meta-analysis. *Eur. J. Phys. Rehabil. Med.* 53(4), 603–610 (2017).
37. Glazov G, Yelland M, Emery J. Low-level laser therapy for chronic non-specific low back pain: a meta-analysis of randomised controlled trials. *Acupunct. Med.* 34(5), 328–341 (2016).
38. Yeh SW *et al.* Low-level laser therapy for fibromyalgia: a systematic review and meta-analysis. *Pain Physician* 22(3), 241–254 (2019).
39. Anders JJ, Lanzafame RJ, Arany PR. Low-level light/laser therapy versus photobiomodulation therapy. *Photomed. Laser Surg.* 33(4), 183–184 (2015).
40. Cotler HB *et al.* The use of low level laser therapy (LLLT) for musculoskeletal pain. *MOJ Orthop. Rheumatol.* 2(5), 2015).
41. Brown GC. Nitric oxide regulates mitochondrial respiration and cell functions by inhibiting cytochrome oxidase. *FEBS Lett.* 369(2-3), 136–139 (1995).
42. Lane N. Cell biology: power games. *Nature* 443(7114), 901–903 (2006).
43. de Freitas LF, Hamblin MR. Proposed mechanisms of photobiomodulation or low-level light therapy. *IEEE J. Sel. Top. Quantum Electron.* 22(3), (2016).
44. Hamblin MR. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. *AIMS Biophys.* 4(3), 337–361 (2017).
45. Chung H *et al.* The nuts and bolts of low-level laser (light) therapy. *Ann. Biomed. Eng.* 40(2), 516–533 (2012).
46. Tomazoni SS *et al.* Photobiomodulation therapy is able to modulate PGE2 levels in patients with chronic non-specific low back pain: a randomized placebo-controlled trial. *Lasers Surg. Med.* 53(2), 236–244 (2021).
47. Lim W *et al.* Anti-inflammatory effect of 635 nm irradiations on *in vitro* direct/indirect irradiation model. *J. Oral Pathol. Med.* 44(2), 94–102 (2015).

48. Tomazoni SS *et al.* Effects of photobiomodulation therapy and topical non-steroidal anti-inflammatory drug on skeletal muscle injury induced by contusion in rats-part 1: morphological and functional aspects. *Lasers Med. Sci.* 32(9), 2111–2120 (2017).

49. Castano AP *et al.* Low-level laser therapy for zymosan-induced arthritis in rats: importance of illumination time. *Lasers Surg. Med.* 39(6), 543–550 (2007).

50. Tomazoni SS *et al.* Effects of photobiomodulation therapy, pharmacological therapy, and physical exercise as single and/or combined treatment on the inflammatory response induced by experimental osteoarthritis. *Lasers Med. Sci.* 32(1), 101–108 (2017).

51. Jang Y, Kim M, Hwang SW. Molecular mechanisms underlying the actions of arachidonic acid-derived prostaglandins on peripheral nociception. *J. Neuroinflammation* 17(1), 30 (2020).

52. Ghlichloo I, Gerriets V. Nonsteroidal anti-inflammatory drugs (NSAIDs). In: *StatPearls.* FL, USA (2021). www.ncbi.nlm.nih.gov/books/NBK547742/ (Accessed 31 May 2022).

53. Lumsden MA, Kelly RW, Baird DT. Primary dysmenorrhoea: the importance of both prostaglandins E2 and F2 alpha. *Br. J. Obstet. Gynaecol.* 90(12), 1135–1140 (1983).

54. Creatsas G *et al.* Prostaglandins: PGF2 alpha, PGE2, 6-keto-PGF1 alpha and TXB2 serum levels in dysmenorrheic adolescents before, during and after treatment with oral contraceptives. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 36(3), 292–298 (1990).

55. Iacovides S, Avidon I, Baker FC. What we know about primary dysmenorrhea today: a critical review. *Hum. Reprod. Update* 21(6), 762–778 (2015).

56. Kohli N *et al.* An observational cohort study of pelvic floor photobiomodulation for treatment of chronic pelvic pain. *J. Comp. Eff. Res.* 10(17), 1291–1299 (2021).

•• **Preliminary data on non-ablative photobiomodulation for treatment of pelvic pain.**

57. Zipper R, Pryor B, Lamvu G. Transvaginal photobiomodulation for the treatment of chronic pelvic pain: a pilot study. *Womens Health Rep. (New Rochelle)* 2(1), 518–527 (2021).

58. Adelman M, Nygaard IE. Time for a 'pause' on the use of vaginal laser. *JAMA* 326(14), 1378–1380 (2021).

• **Consensus and opinion statements on use of ablative vaginal lasers.**