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Authors
Iglesia, Cheryl B
Choi, Jennie Eunsook
Tadir, Yona

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Lasers in Gynecology

Cheryl B. Iglesia, MD, *Jennie Eunsook Choi,* MD, *and Yona Tadir,* MD

The first published reports on the use of laser for cervical pathology date back to 1973. Technical advancements in flexible and rigid laser fibers revolutionized video laser laparoscopy in the 1990s. Fractionated lasers have been used to treat vulvovaginal symptoms associated with genitourinary syndrome of menopause, lichen sclerosus, and urinary incontinence. Review of available data suggests that fractionated lasers can improve both subjective and objective signs of vaginal atrophy and lichen sclerosus, but the evidence is weak because most of the trials are underpowered, are at risk for bias, and lack long-term follow-up. There is no strong evidence to support fractionated laser therapy for urinary incontinence or low-level laser therapy for chronic pelvic pain. Although short-term, single-arm trials suggest benefit of fractionated laser therapy for genitourinary syndrome of menopause, lichen sclerosus, and urinary incontinence, additional adequately powered, prospective, randomized, and longer-term comparative trials are needed before lasers can be recommended for these specific conditions. The purpose of this Clinical Expert Series is to review basic laser biophysics and the mechanism of action for modern fractionated lasers as relevant to the gynecologist. We also summarize safety and effectiveness data for lasers used for some of the most commonly studied gynecologic conditions: the vulvovaginal atrophy component of genitourinary syndrome of menopause, lichen sclerosus, and urinary incontinence.

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The first published report in *Obstetrics & Gynecology* on the use of laser for gynecologic conditions dates back 50 years to 1973 when Kaplan et al[1] published a series of 11 patients treated with carbon dioxide (CO_2) lasers for cervical erosions (Appendix 1, available online at http://links.lww.com/AOG/D708).[2] Colposcopy-guided delivery of the laser beam to premalignant cervical intraepithelial neoplasia lesions and other HPV-related genital warts was quickly adapted and, through the years, has been deemed a cost-effective treatment. The uterine cervix served as an ideal model for use of a laser beam as a "light scalpel" creating bloodless tissue destruction. By the early 1980s, technical progress in delivery systems, including rigid and flexible laser fibers, allowed the use of intraperitoneal CO_2 lasers to precisely ablate endometrial implants, perform tubal sterilization, treat adnexal conditions and adhesions, and, with the addition of neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, perform hysteroscopic endometrial ablations. Early studies involving lasers in gynecology hailed from Israel, Germany, and the United States.[1,3–8]

In the early 1990s, video laser laparoscopy was introduced. The use of video cameras and monitors during laparoscopy widened the operative field and revolutionized minimally invasive gynecologic surgery.[9,10] By 1991, the integration of various laser wavelengths led to advances in in vitro fertilization with the use of laser for piercing the zona pellucida

From the Division of Urogynecology and Reconstructive Pelvic Surgery, MedStar Health and Georgetown University School of Medicine, Washington, DC; and Beckham Laser Institute and Medical Clinic, University of Irvine, Irvine, California.

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Corresponding author: Cheryl B. Iglesia, MD, MedStar National Center for Advanced Pelvic Surgery, Georgetown University School of Medicine, Washington, DC; Cheryl.iglesia@medstar.net.

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and for laser-assisted hatching, which opened the field of pre-embryo genetic diagnosis. Use of CO_2 laser for vulvar intraepithelial neoplasia and lichen sclerosus was described starting in 1984.[11–15] Lasers played a very important role in the transition of gynecologic surgery from laparotomy to laparoscopy in the 1990s, but perhaps because of improved alternatives in laparoscopic, robotic, and hysteroscopic electrosurgery devices, coupled with difficulties with laser setup, cost, and maintenance, laser use in gynecology started to wane. Around 2000, low-energy and fractionated lasers gained increased popularity for cutaneous use by aesthetic dermatologists and plastic surgeons for skin conditions such as age spots, wrinkles, and photodamaged skin. First reports of laser labiaplasty and vaginal fractional CO_2 were published in 2006 and 2011.[16,17] Although lasers were cleared in 1997 by the U.S. Food and Drug Administration (FDA) for "incision, excision, ablation and/or, vaporization of and coagulation of body soft tissues" in gynecology, modern-day fractionated lasers were cleared between 2006 and 2015.[18] In 2018, the FDA issued a warning to manufacturers and health care professionals that the safety and effectiveness had not been established for vaginal rejuvenation devices or other aesthetic genitourinary applications and called for further research through premarket approval trials on fractionated laser and other energy-based devices used for specific genitourinary indications, such as vaginal atrophy and urinary incontinence.[19]

BIOPHYSICS OF LASERS AND LASER TERMINOLOGY

The acronym LASER stands for light amplification by stimulated emission of radiation.[20,21] *Lasers* are devices in which an external energy source stimulates a suitable medium to emit artificial energy waves of coherent light (laser beams). The three basic elements of a laser include an excitable medium (gas, liquid, or solid), a resonator cavity with mirrors to bounce the light back and forth, and an energy source to excite the medium. These elements are housed within the delivery system of a console, which also contains a cooling system. The goal of any medical laser application is the absorption of photonic energy by the desired or targeted chromophores where the biological response is initiated. A chromophore is any chemical group with cells that are capable of light absorption. Laser light is absorbed on the basis of the interaction of the selected laser wavelength with the respective tissues. The main chromophore examples for human tissue include hemoglobin, melanin, water, and foreign bodies such as tattoo ink. Lasers emit light energy at their own unique wavelengths (Fig. 1).

The goal of laser devices is to deliver photons to the specific chromophores where the interaction is ideally desired without absorption by other incidental substances. Basic laser biophysics terminology is listed in Table 1. In particular, energy is reported in joules, and the rate at which the laser energy is delivered is known as *power*, reported in watts (watts=joules/sec). Power density and fluence, or energy per square centimeter, are important when reviewing different treatment protocols using various laser units. An excellent educational resource about medical laser safety and the scientific basis of medical lasers is the American Institute of Medical Laser Applications (AIMLA.org). The laser safety modules offered on their website provide an excellent overview and can be used toward certification for laser safety officers at hospitals and in medical offices.[22] Basic laser terminology and biophysics are shown in Table 1.

LASER–TISSUE INTERACTIONS

To get absorption of the photons into the target cells, the wavelength of the laser must be matched to the absorption spectrum of the desired chromophore (melanin, hemoglobin, water).[21] In simplistic terms, the light is absorbed by the chromophore and transformed into heat, which is transmitted to surrounding tissues. Selecting the desired wavelength (nanometers) and pulse length (milliseconds) can determine penetration depth and absorption rate. Tissue interactions can be photothermal, photomechanical, or photochemical. Photothermal effects use prolonged energy exposure to increase chromophore temperature, leading to cellular vaporization such as in laser hair removal. Photomechanical effects use shorter pulses to create acoustic waves to break up the target material such as in tattoo removal. Photochemical reactions occur when laser light is used to change specific chemicals in the body, such as photodynamic therapy, in which laser light assists in attacking cancer cells within the body. Photobiomodulation is a type of photochemical biostimulation in which laser light is used by chromophores on cellular mitochondria to transfer adenosine diphosphate to adenosine triphosphate for tissue healing.[22] Cytochrome c oxidase is the key membrane protein photoreceptor on the mitochondria and promotes the release of nitric oxide and adenosine triphosphate, resulting in decreased inflammation, accelerated wound healing, angiogenesis, and analgesia. Photobiomodulation, now currently being evaluated in gynecology for pelvic myofascial pain, involves low-level laser therapy within the red or

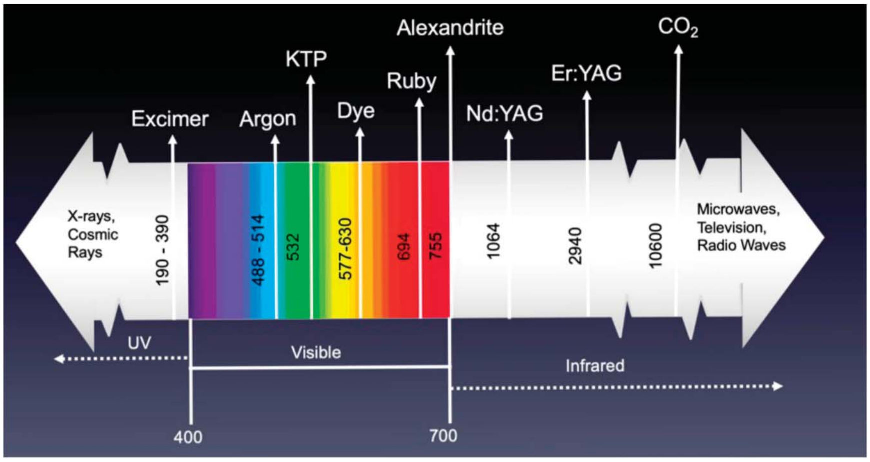

Fig. 1. The electromagnetic spectrum and laser wavelengths. The electromagnetic spectrum describes all the wavelengths of light. The left side includes harmful ultraviolet (UV) x rays, cosmic and gamma rays all of which have higher frequency and shorter wavelength than visible light. Visible light falls between 380 to 740 nanometers. The right side of the spectrum includes far infrared light which is lower in frequency and longer in wavelength and less harmful. Microwaves and television waves which constantly surround us are not harmful. Most of the lasers used for vulvovaginal treatment like Er:YAG and CO_2 have far infrared (2940 nm and 10,600 nm) wavelengths. Nd:YAG, neodymium-doped yttrium aluminum garnet; Er:YAG, erbium YAG. Reprinted with permission from Lumenis company, Yokneam, Israel, *and* Fodor L, Ullmann Y, Elman M. Light tissue interactions. In: Aesthetic applications of intense pulsed light. Springer, London; 2011. https://doi.org/10.1007/978-1-84996-456-2_2

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near-infrared spectrum to alter cell function using noncoherent laser light (operating at different frequencies and wavelengths) and differs from therapeutic laser treatments such as fractionated CO_2 and erbium, which is composed of photons oscillating at the same or coherent wavelength and phase and can generate much more heat. Absorption by mitochondrial chromophores and the cytochrome c oxidase membrane is a major pathway for low-level laser pain management and has been used most frequently in sports medicine.

MODERN FRACTIONATED LASERS

Carbon dioxide and erbium-doped yttrium aluminum garnet (Er:YAG) lasers are considered the gold standard lasers for skin resurfacing in dermatology.[2,23,24] The CO_2 laser emits a 10,600-nm wavelength, which is strongly absorbed by water as the tissue chromophore. Er:YAG emits a wavelength of 2,940 nm in the infrared range, and depth of penetration is 1–3 micrometers of tissue per joule per square centimeter compared with 20–30 micrometers seen with CO_2.[23] Fractionated laser beam technology thermally ablates microscopic columns of tissue in regularly spaced arrays while preserving normal tissue between the laser columns (Fig. 2). Fractionated lasers can be nonablative, sparing the superficial epidermis, or ablative with microthermal zones, ablating both the superficial and deeper tissue layers. Hybrid lasers have multiple laser wavelength options, allowing both ablative and nonablative treatment. Table 2 includes currently available fractionated laser options and dates of clearance for use by the FDA through the 510k process, meaning that the lasers were cleared on the basis of similar prior predicate devices.[25]

Although lasers have been cleared for mostly general soft tissue use in a multitude of medical and surgical specialties, as listed in Table 2, lasers have not been approved for specific genitourinary conditions such as vulvovaginal atrophy, vulvar skin conditions, including lichen sclerosus, and urinary incontinence. This clinical expert review article outlines the current safety and effectiveness data for fractionated laser treatments of these conditions.

GENITOURINARY SYNDROME OF MENOPAUSE

Genitourinary syndrome of menopause, a term introduced by the North American Menopause Society in 2014, is a common condition of perimenopausal and postmenopausal patients with a prevalence as high as 50%.[26,27] Genitourinary syndrome of menopause comprises vulvovaginal, urinary, and sexual symptoms driven by estrogen deficiency and includes vaginal dryness, burning, itching, dyspareunia, urinary urgency, dysuria, and urinary tract infections. Clinical signs include pallor, thinning, and loss of elasticity. Histologically, the postmenopausal vaginal tissue has reduced blood supply in the lamina propria, diminished glycogen stores, decreased superficial cells, and increased parabasal cells.[28] Despite the significant effect on quality of life, self-esteem, and sexual relationships, studies have shown that patients often do

Table 1. Glossary of Basic Laser Biophysics Terminology

Term	Definition
Spot size (meters)	The diameter of the laser beam on the target tissues
Wavelength (meters)	The dimension over which the wave repeats
Frequency (hertz)	Pulses per second (Hz=1/s)
Energy (joules)	No. of photons emitted in a laser
Power (watts)=joules/s	Energy (joules)/time (sec) is the rate at which energy is emitted
Power density=W/cm^2	Power (watts)/spot size (cm^2) is the concentration of power output
Fluence/dosage=J/cm^2	Energy (joules)/area (cm^2); laser medical procedures will report dosages delivered on 1 cm^2

not seek treatment.[29] Commercially available vaginal estrogens are commonly recommended by clinicians when treatment is offered and have been shown to be effective for genitourinary syndrome of menopause.[30] However, a multitude of reasons exist for patients or their health care professionals to prefer nonestrogen alternatives such as genitourinary syndrome of menopause symptoms refractory to prior estrogen therapy, a personal history of breast or other estrogen-responsive cancer, personal concerns about hormone use, cost, or other medical contraindications to the use of estrogen. The Women's EMPOWER study, surveying 1,858 postmenopausal patients online in North America, found that, of patients started on a form of local treatment for genitourinary syndrome of menopause, only a striking 7% were using the prescribed therapy, citing concerns about messiness, cost, and safety, including perceived increased risk of estrogen-dependent cancers.[31] Therefore, patients and investigators have been investigating alternative therapies, including fractionated vaginal laser, for treatment. Laser settings for fractional CO_2 include Dot power of 30–40 W, dwell time of 800–1,000 microseconds, dot spacing of 800–1,000 micrometers, and smart stack of 1–3 with three treatment sessions spaced out every 4–6 weeks.[32–40] For fractional Nd:YAG, there is a larger heterogeneity in settings across studies according to several systematic reviews because of the proprietary nature of these lasers.[41,42] Sham laser settings are based on probe placement or insertion with low-energy settings imparting no tissue effect.

Outcomes for treatment of genitourinary syndrome of menopause include subjective and objective measures. Subjective measures include assessments of vaginal dryness, dyspareunia, itching, or burning. Validated questionnaires include the VAS (Vaginal Assessment Scale) or VuAS (Vulvar Assessment Scale) for vulvovaginal atrophy, the FSFI (Female Sexual Function Index) for sexual function, and the UDI-6 (Urinary Distress Inventory-Short Form) and ICIQ (International Consultation on Incontinence Questionnaire) for urinary symptoms. Objective measures can be performed with the VMI (Vaginal Maturation Index) and VHI (Vaginal Health Index). The VMI score quantifies the estrogenization of vaginal tissue through assessment of the relative proportion of three epithelial cell types (parabasal, intermediate, and superficial cells) through cytology, whereas the VHI score evaluates five parameters: vaginal elasticity, vaginal secretions, vaginal pH, presence of petechiae on the epithelial surface, and vaginal hydration. A few studies have also looked at histologic comparisons before and after vaginal laser therapy across various time points after laser treatments.

A systematic review by Mortensen et al[41] identified 70 studies evaluating effects of CO_2 and Er:YAG lasers on genitourinary syndrome of menopause and vulvovaginal atrophy, including 10 randomized controlled trials (RCTs) with 524 patients and observational studies totaling 3,668 patients. Four RCTs randomized patients to receive either CO_2 or sham laser.[34,35,43,44] Although all four trials found symptom improvement after CO_2 laser, three trials reported similar improvement between CO_2 and sham laser groups; Salvatore et al[44] found that the CO_2 group reported a significantly higher improvement on a visual analog scale of symptom severity compared with the sham group. Similarly, Mortensen et al[41] found that when studies compared laser with topical hormone therapy or lubricants, there was improvement with CO_2 laser, but comparative results in RCTs were heterogeneous. One study found that CO_2 laser provided significantly higher improvement compared with vaginal estrogen or lubricant[45]; another found no difference in improvement when CO_2 was compared with vaginal estrogen.[32] Promisingly, a review of data from 64 observational studies using either CO_2 or Er:YAG lasers has shown improvement in severity

Table 2. Current U.S. Food and Drug Administration Approval Status of Devices in Genitourinary Applications

Device	510k	Date	Indications
Joule Profile Multi-Platform System, diVA (Sciton), Er:YAG 2940 nm, 1470 nm	K060033 K101916	1/4/2006 3/18/2011	At 2940 nm: ablation, vaporization, and coagulation of soft tissue and for skin resurfacing and at 1470 nm: ablation, vaporization, hemostasis, or coagulation of soft tissue.
Lumenis Femtouch CO_2	K100415	4/12/2010	Vaporization, incision, excision, ablation or photocoagulation of soft tissue in the surgical specialities of ENT, gynecology, laparoscopic surgery, including gyn laparoscopy, esthetic surgery, dental and oral surgery, neurosurgery, orthopedics, general surgery and podiatry.
SP DYNAMIS (Fotona), Er:YAG 2940 nm; Nd:YAG 1064 nm	K101817 K143723	11/22/2010 4/9/2015	Surgical applications requiring the ablation, vaporization, excision, incision, and coagulation of soft tissue in medical specialties, including aesthetic surgery (dermatology and plastic surgery), podiatry, gynecology, neurosurgery, orthopedics (soft tissue), arthroscopy.
FemiLift (Alma) CO_2	K103501	1/14/2011	Laser incision, excision, ablation and/or vaporization of soft tissue in gynecology for the treatment of conization of the cervix, including cervical intraepithelial neoplasia, vulvar and vaginal intraepithelial neoplasia; condyloma acuminate, including cervical, genital, vulvar, perineal, and Bowen's disease (erythroplasia of Queyrat), and Bowenoid papulosa (BP) lesions; leukoplakia (vulvar dystrophies), incision and drainage of Bartholin's and nabothian cysts, herpes vaporization, urethral caruncle vaporization; urethral caruncle vaporization; cervical dysplasia, benign and malignant tumors, hemangiomas.
ThermiVA (Thermi), RF	K130689	11/15/2013	For use in dermatological and general surgical procedures for electrocoagulation and hemostasis.
SmartXide2 MonaLisa Touch, El En/DEKA/Cynosure	K133895	9/15/2014	Incision, excision, vaporization and coagulation of body soft tissues in medical specialties, including aesthetic (dermatology and plastic surgery), podiatry, otolaryngology (ENT), gynecology, neurosurgery, orthopedics, general and thoracic surgery (including open and endoscopic), dental and oral surgery and genitourinary surgery. The use with the scanning unit is indicated for ablative skin resurfacing
CORE Intima (Syneron), CO_2	K151655	9/14/2015	Surgical applications requiring the ablation, vaporization, excision, incision, and coagulation of soft tissue in medical specialties, including esthetic surgery (dermatology and plastic surgery), podiatry, gynecology, neurosurgery, orthopedics (soft tissue), arthroscopy
HPM6000UF	K181497	11/14/2018	Noninvasive electromagnetic stimulation of pelvic floor musculature for the purpose of rehabilitation of weak pelvic muscles and restoration of neuromuscular control for the treatment of male and female urinary incontinence
Esmella, BTL			https://www.accessdata.fda.gov/cdrh_docs/pdf18/K181497.pdf

Reprinted with permission from Alexiades MR, Iglesias C, Sokol E, Gaspar A, Tadir Y. Light and energy-based therapeutics for genitourinary applications: consensus on protocols and best practices. Lasers Surg Med 2023 Jul;55(5):444–454. doi: 10.1002/lsm.23672. The table in Alexiades et al was modified from Alexiades M. Device-based treatment for vaginal wellness. Semin Cutan Med Surg 2018;37(4): 226–32. doi: 10.12788/j.sder.2018.052.

of both the subjective and objective measures after laser therapy. Reassuringly, no serious adverse events were identified in the review of 99 studies totaling 51,094 patients undergoing vaginal or vulvar laser treatment.

A recent systematic review by Casiano Evans et al[46] published outcomes on alternative, nonestrogen products commercially available in the United States and Europe for treatment of genitourinary syndrome of menopause. Fractional laser therapy (Er:YAG and CO_2) was one of the seven alternative options of interest. The authors reviewed six RCTs comparing CO_2 laser with topical estrogen, four RCTs comparing CO_2 with sham laser, one three-arm study (CO_2 laser, sham, and topical estrogen), and 41 single-group studies. Use of Er:YAG laser was reviewed in two RCTs comparing

Fig. 2. Fractionated laser pattern after CO2 laser treatment of vaginal epithelium. Photo courtesy of Cheryl B. Iglesia, MD.

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Er:YAG with topical estrogen and three single-arm studies. A meta-analysis was unable to be performed because of data heterogeneity, but review of the available data by the authors concluded that Er:YAG and CO_2 lasers can improve both subjective and objective signs of atrophy, whereas CO_2 can further improve sexual function and urinary symptoms. Therefore, the authors concluded that laser therapy can be suggested as an alternative to local estrogen therapy. Similarly, Gunawan et al[47] performed a meta-analysis of six RCTs comparing CO_2 with sham laser and found results favoring CO_2 over sham for improvement in VAS, UDI-6 symptoms, satisfaction rate, and resolution of vaginal dryness.

To summarize, available data on comparative laser compared with sham trials for genitourinary syndrome of menopause show no difference in improvement up to 1 year, but most of these studies involve small numbers with heterogeneous data. Although fewer studies comparing laser with local estrogen have been published, most of these studies are also underpowered with limited follow-up. The data suggest some potential benefit of laser for genitourinary syndrome of menopause but no quantifiable difference over estrogen. No significant adverse events were reported from vaginal laser use in these systematic reviews, including burns, eye injury, and device malfunction. Future studies may need to assess the need for estrogen for pretreatment of vaginal epithelium before fractionated laser therapy and consideration for combination laser and local estrogen because the laser could serve as a method of improving drug delivery to vaginal tissues.

Laser Use in Breast Cancer Survivors

Breast cancer survivors have been shown to have a higher prevalence of urogenital symptoms of up to 70% compared with menopausal patients with no history of breast cancer.[48] Higher rates of genitourinary syndrome of menopause symptoms could be attributable to cancer treatments, including chemotherapy and antiestrogenic adjuvant therapies.[42] Health care professionals have some reluctance when prescribing hormone-based therapy for genitourinary syndrome of menopause symptoms in breast cancer survivors. Furthermore, patient report of bothersome genitourinary syndrome of menopause symptoms does not consistently correlate with severity of signs on clinical examination. The lack of early recognition of vulvovaginal atrophy remains a barrier to adequate and timely care.[49–51] Therefore, treatment of genitourinary syndrome of menopause in breast cancer survivors represents a significant gap in medical care.[52]

A systematic review by Cucinella et al[42] included 16 studies evaluating the safety and efficacy of CO_2 laser and four studies evaluating Er:YAG laser therapy in a total of 789 breast cancer survivors. Although most studies focused exclusively on breast cancer survivors, one of these studies evaluated estrogen-dependent gynecologic cancer survivors,[38] and three comparative studies included healthy menopausal patients as a comparator group.[40,53,54] The treatment protocol, laser settings, and adverse events across the studies were reported in this systematic review. The settings were largely homogeneous across studies using fractionated vaginal CO_2 laser, performed at three monthly laser sessions with a power of 30–40 W. There was more heterogeneity across studies on Er:YAG laser treatments. In several observational retrospective cohort studies comparing menopausal women with and without a history of breast cancer, there were significant improvements in both vulvovaginal symptoms[39,40,54] and sexual function[40,53] with the use of vaginal fractional CO_2 laser. In one of these studies, however, participants in the breast cancer survivor group had slower improvement compared with the control group as assessed by VHI scores, possibly as a consequence of more severe genitourinary syndrome of menopause symptoms at baseline in the breast cancer survivor group.[39] Regardless, the results were promising, with significant improvement in VHI and Vulvovaginal Health Index scores at any session and maintained through 12 months of follow-up. Cucinella et al concluded that vaginal laser had an overall positive effect on genitourinary syndrome of menopause symptoms, with high tolerability of treatments and no relevant identified adverse events.

A recent study by Casiraghi et al[37] investigated the histologic changes in 15 postmenopausal individuals treated with at least two cycles of CO_2 laser for genitourinary syndrome of menopause in the prior 2 years. When comparing histology before and after the subsequent treatment cycle, they found a statistically significant increase in squamous epithelial thickness, number of glycogen-filled cells, and number of papillae. Scores from six validated questionnaires reporting subjective symptom severity also correlated with the histologic changes. Notably, the presence of neovascularization, no signs of fibrosis, and no adverse events were reported with this study protocol, suggesting that annual treatment cycles could be considered for maintenance therapy. Figure 3A and B demonstrates the increased epithelial thickness after laser treatment, whereas Appendix 2, available online at http://links.lww.com/AOG/D708, demonstrates vaginal epithelial cells stained for glycogen with increased papillae at 1 month after fractionated laser therapy. Future studies investigating the long-term efficacy and safety of vaginal laser for genitourinary syndrome of menopause should include adequate controls or comparators, such as vaginal estrogen, and other moisturizers, such as hyaluronic acid. Analysis of combination laser and estrogen therapy would also be of interest.

Summary of Laser Use for Genitourinary Syndrome of Menopause

Many studies have demonstrated feasibility, tolerability, and positive effects of vaginal laser on genitourinary conditions; however, data quality has been deemed low and very low, and higher-quality clinical trials are needed to change current clinical practice recommendations. A recent consensus article by Alexiades et al[25] reviewed clinical trial data for lasers on genitourinary conditions and aimed to develop protocols and practices for the use of laser in future clinical trials, which may allow comparable data and meta-analyses. The consensus document lists common brands of CO_2 and Er:YAG laser devices and their manufacturer-recommended settings and describes a treatment schedule of three treatments at 1-month intervals, with a maintenance treatment between 6 and 12 months of follow-up.

LASERS FOR LICHEN SCLEROSUS

Lichen sclerosus is a chronic, inflammatory skin condition that affects the genital area and is associated with symptoms of severe itching, pain, dyspareunia, skin changes of hypopigmentation, fissures, loss of labia minora, and phimosis or fusion of the clitoral hood. Topical corticosteroid therapy is the first-line therapy for lichen sclerosis.[55] In 2020, the American Urogynecologic Society published a clinical consensus statement based on review of the available evidence on energy-based device use for vulvovaginal disorders. The group reconvened in 2022 to update the consensus statement.[56,57] The overall executive summary, unchanged from 2020 to 2022, was as follows:

> The absence of consensus on many statements about EBD [energy-based device] therapy practices currently in clinical use … exposes a significant knowledge gap about the efficacy and safety profile of the vulvovaginal EBD therapies, their indications, contraindications, maintenance regimens, comparison with available current treatments, and long-term benefits.

The conclusion for the 2022 American Urogynecologic Society consensus statement was that laser therapy may be effective for lichen sclerosus. Subsequently, two additional systematic reviews were published on the use of laser for lichen sclerosus in May 2021 and March 2022.[41,58] The 2021 systematic

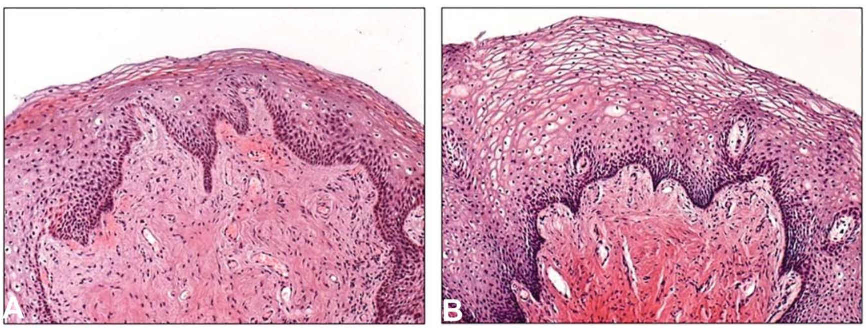

Fig. 3. 4L Hematoxylin-eosin, biopsies for measurement of epithelial thickness. Baseline (**A**) and one month after last laser treatment (**B**). Reprinted with permission from Casiraghi A, Calligaro A, Zerbinati N, Doglioli M, Ruffolo AF, Candiani M, Salvatore S. Long-term clinical and histological safety and efficacy of the CO2 laser for treatment of genitourinary syndrome of menopause: an original study. Climacteric 2023;26(6):605–12a. doi: 10.1080/13697137.2023.2246886

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review by Tasker et al,[58] based on 24 studies with a total of 610 patients, including six RCTs, suggests benefit of laser therapy for lichen sclerosus for clinical symptoms and signs, quality of life, and sexual function; however, the authors concluded that there was not strong enough evidence to support the use of laser for the treatment of genital lichen sclerosis because most of the trials were underpowered, at risk for bias, and lacked long-term follow-up. The 2022 Mortensen et al[41] review identified 11 studies with a total of 263 patients treated with vulvar laser for lichen sclerosus (nine using CO_2, one Er:YAG, and one Nd:YAG) with maximum follow-up for the three RCTs at 6 months after the last laser session. Significant improvement in vulvar lichen sclerosis symptoms was noted from different outcome measures in eight of the nine trials, with no reported serious adverse events. One study, with the primary outcome of histopathologic change before and after CO_2 laser, showed no significant difference between the 20 women receiving laser and the 20 women receiving sham laser at 2 months after the last treatment. The conclusion echoed the previous consensus statement and systematic review showing overall improvement in short-term outcomes but stressed the need for larger, long-term, and higher-quality RCTs with improved standardization of treatment protocols before laser can be considered for routine treatment for lichen sclerosis.

Since 2022, two additional trials have been published. Krause et al[59] performed a randomized trial of normal-dose MonaLisa Touch fractional CO_2 laser at 24 W compared with low-dose 0.5-W fractional laser in 63 patients with lichen sclerosus. The lower dose was supposed to serve as a placebo laser dose; however, significant improvement in the visual analog scale scores was noted in both groups with no difference between groups at 18 weeks. No reactivation of lichen sclerosus was noted, and no serious adverse events were reported, leaving the authors to conclude that even low-energy density laser could lead to improvement in lichen sclerosus. Dieter et al[60] found positive histologic changes after three monthly CO_2 treatments without concomitant corticosteroid in 10 patients with lichen sclerosus. The histologic findings demonstrated in Figure 4A and B also correlated with improvement in subjective skin symptoms.

Still, none of the trials published to date provide enough evidence to recommend laser for the primary treatment of genital lichen sclerosus, and a review of ClinicalTrials.gov shows three different randomized trials using fractionated CO_2 currently recruiting internationally, including the VULVIE (Fractionated CO2 Laser With and Without Clobetasol for Treatment of Vulvar Lichen Sclerosus) trial comparing CO_2 laser with and without concomitant clobetasol, a multicenter trial in the United States; CO_2 laser with steroid compared with steroid alone in Alabama; and CO_2 laser compared with clobetasol in Germany.[61–63] Results from these trials, in particular the VULVIE trial, will likely be useful in determining whether laser could be a first-line therapy for some patients or whether lasers serve as a mechanism for improved steroid drug delivery to the area of inflammatory infiltrate associated with this debilitating condition. Viereck et al[64] have also proposed a randomized trial of a hybrid Nd:YAG/Er:YAG compared with topical steroid for lichen sclerosus with a 2-year follow-up. This long-term surveillance is much needed to determine laser safety and efficacy. Appendix 3, available online at http://links.lww.com/AOG/D708, lists laser

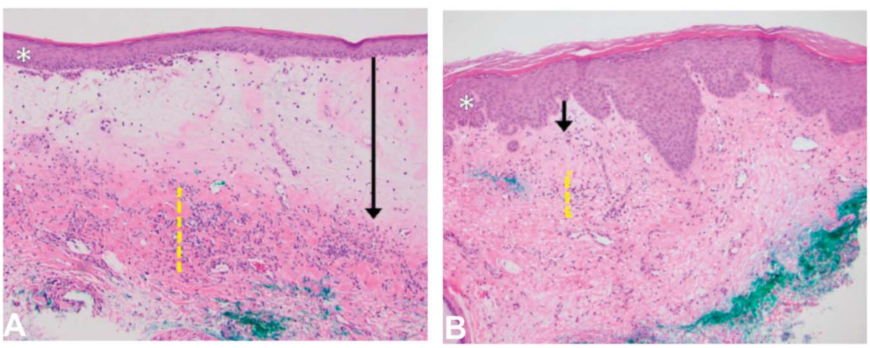

Fig. 4. Hematoxylin-eosin, magnification × 40; The *asterisk* shows epidermal expansion pre-to 4 weeks-post third laser. The *dark arrow* shows sclerosis, edema, and telangiectasias improved pre-to post-laser. *Yellow bars* show diminished sclerotic zone of inflammatory infiltrate. Pretreatment (**A**) and four weeks-post laser treatment (**B**). Reprinted with permission from Dieter AA, Iglesia CB, Lee JH, Etcheverry MJ, Gonzales MK, Sokol AI, Tefera E, Cardis MA. A prospective pilot study to assess for histologic changes on vulvar biopsies in postmenopausal women with lichen sclerosus treated with fractionated CO2 laser therapy. Lasers Surg Med 2023 Aug;55(6):521–527. doi: 10.1002/lsm.23669

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protocols for published clinical trials involving lasers for lichen sclerosus.

Although many studies suggest fractional laser as an alternative to steroids for lichen sclerosus, there are still insufficient data to recommend laser as first-line treatment, and we await the results of more comparative, multicenter, and long-term trials.

LASERS FOR URINARY INCONTINENCE

In a 2022 systematic review, Mortensen et al[41] analyzed 30 studies involving lasers in patients with urinary incontinence, including two RCTs. One RCT showed no difference between CO_2 laser and vaginal hormonal treatment in 72 women with a range of stress and urgency urinary incontinence symptoms, although follow-up was limited to just 2 weeks after the last laser treatment.[65] A second RCT showed a significant improvement at 3 months based on a validated urinary incontinence questionnaire in 114 women with stress urinary incontinence receiving Er:YAG laser treatment compared with sham laser, with outcomes reported 3 months after the last laser treatment.[66] The most recent RCT, published after the systematic review by Mortensen et al, evaluated 101 women with stress urinary incontinence and showed no difference in objective and subjective outcomes related to urinary incontinence at 3 months after the last treatment with fractionated CO_2 laser compared with sham laser.[67] In summary, there is an overall lack of high-quality evidence to support the use of laser to treat urinary incontinence.

PHOTOBIOMODULATION (LOW-LEVEL LASER THERAPY) FOR PELVIC PAIN

As discussed Laser–Tissue Interactions section, low-level laser therapy operates in the red and near-infrared spectrum, close to the visible light range. *Photobiomodulation* light energy targets the mitochondrial cytochrome c oxidase chromophore, and this low-level laser therapy is noncoherent and nonablative.[68] Photobiomodulation has been used to treat musculoskeletal low back pain, fibromyalgia, and knee and hip pain. One of the first randomized clinical trials using photobiomodulation was a pilot study of 34 patients with provoked vestibulodynia receiving low-level laser therapy or sham therapy twice weekly for 6 weeks. Significant improvement in subjective clinical pain was reported in the active arm compared with the sham control but not in other objective measures such as Q-tip testing, pain with tampon insertion, and dyspareunia, with the authors concluding that low-level laser therapy cannot be recommended to provoked vestibulodynia.[69] In another pilot trial of 13 patients with chronic myofascial pelvic pain treated with low-power (5 W) transvaginal photobiomodulation, 60% showed clinically significant improvement in pain lasting up to 6 months.[70] One other pilot study of 53 patients with bladder pain syndrome found clinically significant improvement in symptoms immediately after eight transvaginal photobiomodulation treatments.[71] Clearly, data are very preliminary for low-light laser therapy and pelvic pain, and more high-quality research is needed, particularly comparative studies.

FUTURE USE: OPTICAL COHERENCE TOMOGRAPHY

Scientific data on posttreatment changes of the vaginal wall are lacking mainly because repeated biopsies are not ethically justified. Therefore, a noninvasive optical biopsy probe has been developed that is based on a technique that uses light to capture micrometer-resolution images. *Optical coherence tomography* is based on a phenomenon of interference of waves, analogous to ultrasound imaging, using a relatively long near-infrared light that allows penetration into a scattering medium, resulting in a backscattered light traveling to a detector that interprets the signals into images. Unlike the target resolution of pelvic ultrasound imaging, which is 50–200 micrometers, depending on the sound frequency used, optical coherence tomography may define images at 5–20 micrometers, depending on the target tissue and light wavelength.

Optical coherence tomography can monitor in situ changes such as vaginal epithelial thickness and blood vessel density in the lamina propria. This technology may redefine, in statistically significant and quantifiable terms, the severity of genitourinary syndrome of menopause at baseline and posttreatment tissue remodeling in vaginal and vulvar pathologies to provide individualized patient management from local therapies, hormonal therapy, or energy-based devices.

Several optical biopsies of the vaginal wall already comparing before and after menopausal changes and before and after fractional pixel CO_2 laser treatment have been published.[72,73] A large CO_2 laser study that is aimed to define in vivo changes of vaginal epithelial thickness and blood vessel density is ongoing.[74] Optical coherence tomography angiography images of the same vaginal wall from four visits before and after each of three sessions of fractional CO_2 laser therapy are illustrated in Figure 5.[1]

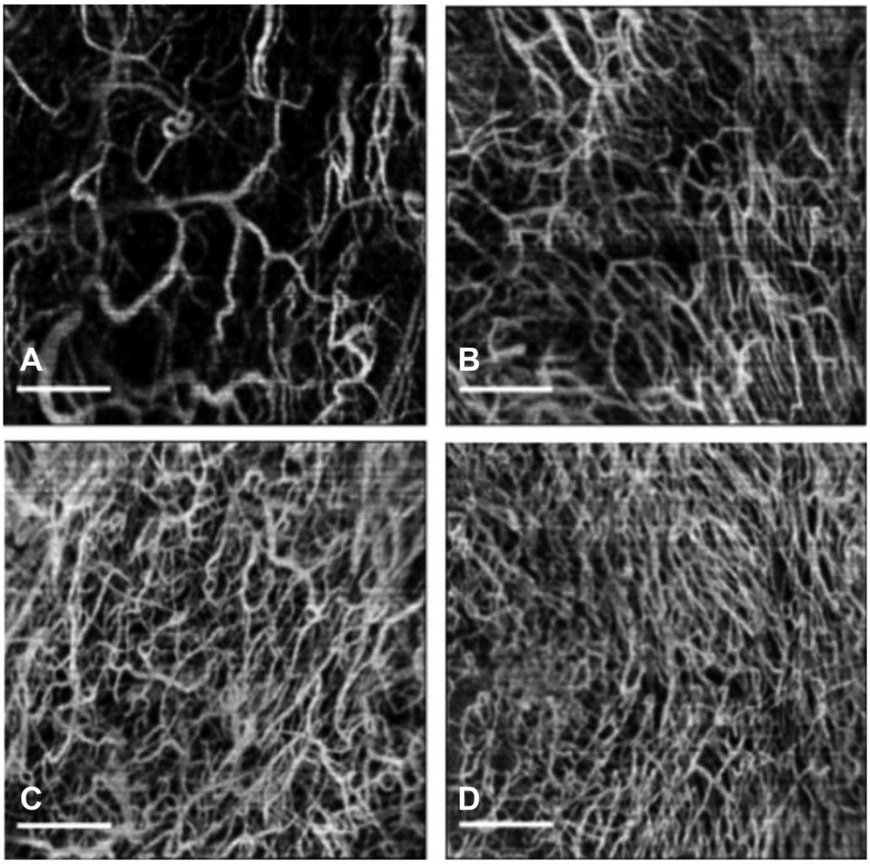

Fig. 5. Four OCT-Angiography (OCT-A) images of the same vaginal wall location: before and after 3 monthly treatment sessions of fractional-pixel CO_2 laser: first pre-treatment (**A**), after first treatment session (**B**), after second session (**C**), and after third session (**D**). Scale bar 1 mm. The blood vessel density increases after fractionated CO_2 laser treatment, indicative of improved tissue health, and suggests that laser treatments are effectively promoting angiogenesis. Reprinted from Qiu S, Arthur A, Jiang Y, Miao Y, Li Y, Wang J, Tadir Y, Lane F, Chen Z. OCT angiography in the monitoring of vaginal health. APL Bioeng 2023 Nov 7;7(4):046,112.[75] Qiu et al is an open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. doi: 10.1063/5.0153461

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CONCLUSION

Laser use in gynecology over the past 50 years has evolved from devices operated at high temperature to destroy abnormal tissues such as genital warts, precancerous lesions, and endometriosis implants to fractionated and low-temperature lasers used for tissue regeneration. Although initial studies using lasers for urogenital and vulvovaginal indications showed promising short-term results, more robust trials with appropriate controls and higher-quality evidence have tempered results. Few serious adverse events are reported with the use of fractionated lasers by trained experts. Without better-quality, comparative, multicenter, randomized trials with longer-term follow-up, the evidence is insufficient to recommend laser as first-line therapy for vaginal dryness for menopausal women, breast cancer survivors, and patients with lichen sclerosis and urinary incontinence. Future directions should evaluate the effect of priming with vaginal estrogen or topical steroid before laser therapy, the concomitant use of laser and drug therapy, and the need for maintenance laser therapy, as well as long-term safety and overall cost-effectiveness, especially because these energy-based devices are expensive and the treatments are not covered by most major insurers. As noted in the American Urogynecologic Society clinical consensus publication on vaginal energy-based devices,[56] research on modern fractionated lasers is limited by the variety of devices and published clinical protocols, and the efficacy is hard to determine from the limited use of validated outcome measures in underpowered studies of short duration. Registry data and larger, long-term comparative-effectiveness trials for each specific vulvovaginal condition are needed before routine fractionated laser treatment can be recommended for genitourinary syndrome of menopause, lichen sclerosus, and urinary incontinence.

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CME FOR THE CLINICAL EXPERT SERIES

Learning Objectives for "Lasers in Gynecology"

After completing this continuing education activity, you will be able to:

- Discuss the biophysics of medical lasers;
- Differentiate fractionated and low-level laser therapies; and
- Implement plans to expand the use of clinical lasers for very limited situations in gynecology.

Instructions for Obtaining *AMA PRA Category 1 Credits*™

Continuing Medical Education credit is provided through joint providership with The American College of Obstetricians and Gynecologists.

Obstetrics & Gynecology *includes CME-certified content that is designed to meet the educational needs of its readers. This article is certified for 2 **AMA PRA Category 1 Credits***.™ This activity is available for credit through August 31, 2027.

Accreditation Statement

ACCME Accreditation

The American College of Obstetricians and Gynecologists is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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In accordance with the College policy, all faculty and planning committee members have signed a conflict of interest statement in which they have disclosed any financial interests or other relationships with industry relative to article topics. Such disclosures allow the participant to evaluate better the objectivity of the information presented in the articles.

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Contact Information

Questions related to transcripts may be directed to cme@acog.org. For other queries, please contact the *Obstetrics & Gynecology* Editorial Office at obgyn@greenjournal.org. For queries related to the CME test online, please contact ceconnection@wolterskluwer.com or 1-800-787-8985.