

The Use of CO₂ Laser

in the Treatment of Stress Urinary Incontinence

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Introduction

Stress Urinary Incontinence (SUI) is a common problem that affects 35%-40% of women worldwide [1,2]. SUI occurs when a woman experiences involuntary leakage of urine with physical activities that increase intra-abdominal pressure such as exercise, cough, sneeze, or laugh [3]. Risk factors include age, parity, pregnancy, vaginal delivery, chronic cough, constipation, obesity, pelvic floor weakness, post-menopausal state, and prior pelvic surgery.

SUI can significantly affect quality of life (QOL) since women may avoid certain activities or exercises that cause leakage or they may be embarrassed to go out in public due to fear of leakage. Pads are often used as a management strategy but these are costly and inconvenient. The economic burden on the healthcare system and affected population is significant with the total annual cost of urinary incontinence in the United States estimated to be \$16.3 billion with women accounting for 91% and SUI 82% of the cost. Furthermore, costs for women over the age of 65 years are twice those for their younger counterparts [4].

The ideal treatment for SUI is a therapy that is effective at relieving symptoms, minimally invasive, nearly painless, durable and would restore normal urethral supportive function. Historic treatments such as a Burch urethral suspension or Marshall-Marchetti-Krantz (MMK) required an abdominal incision, an inpatient hospitalization and have failure rates that increase with time from surgery [5 ,6]. In addition, these procedures can be associated with significant complications such as hemorrhage, obstructive voiding, enterocele and osteitis pubis.

Currently, the main treatment options for SUI consist of a vaginal approach and placement of a synthetic midurethral slings, a biologic bladder neck sling or urethral bulking agents. The midurethral sling (MUS) accomplishes many of these goals of ideal SUI treatment and is considered the gold standard treatment for SUI. A MUS can be performed as an outpatient surgery with a small vaginal incision, and using trocars through the retropubic or transobturator space to place the sling in the midurethral area.

Alternatively, single incision or mini slings do not require external needle passage and the sling anchors into the obturator membrane. However, there are limitations to slings and not every patient with SUI is a candidate for a sling. These patients may require a tight bladder neck sling which can be associated with urgency-frequency, obstructive voiding and post operative pain, especially if autologous fascia is used. Urethral bulking agents are minimally invasive but durability is lacking and repeat injections are typically necessary.

The recent controversy surrounding the use of transvaginal mesh may be an impetus to look at the treatment of SUI differently. While the focus has been primarily on warnings by the Food & Drug Administration about the use of transvaginal mesh for pelvic organ prolapse repair, the MUS is not without its own unique set of risks, including mesh exposure, mesh erosion into surrounding organs, dyspareunia, pelvic pain, and need for further surgery. Despite the proven safety and efficacy of mesh MUS, an aggressive mesh MUS legal environment still exists. The ideal treatment of SUI is still lacking.

CO₂ laser therapy is widely used for delicate tissue management in specialties such as gynecology, Ear Nose and Throat and for skin rejuvenation and scar and soft tissue reconstruction in the field of plastic surgery. Recently, CO₂ vaginal laser therapy has been utilized by gynecologists and urologists for the treatment of vulvovaginal atrophy in women [7], and the Er:YAG laser has been introduced as a treatment for SUI in women [8]. Minimally invasive Lumenis CO₂ laser treatment offers a unique therapeutic option for women with SUI. We believe that further research and future clinical studies will continue to prove the safety and tolerability of treatment as well as demonstrate the desired clinical outcomes. In this white paper, we present the scientific evidence supporting laser treatment for SUI and discuss goals for future study.

Background

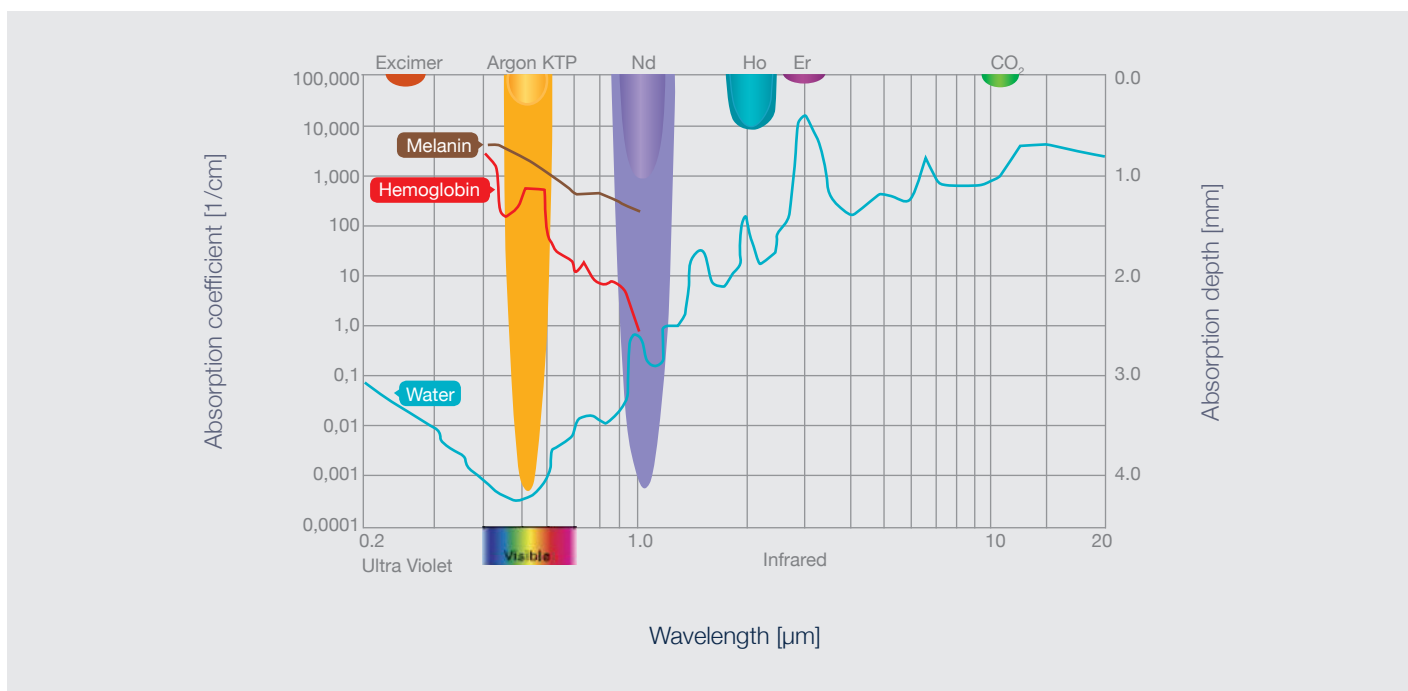
Laser stands for light amplification by the stimulated emission of radiation. In a laser, the tube is pumped via flash-lamp, RF or high voltage DC, to give out high-intensity light which then bombards a resonator cavity with photons. The atoms in the resonator cavity are excited to a higher energy state while most of the photons create heat, with less than 5% being absorbed. Meanwhile the electrons are excited by the movement of the photons and jump to higher orbitals. Due to the instability of these excited state orbitals, there is rapid decay of the electrons, which emit a photon. The emitted photon has the energy needed to interact with other excited state atoms. If this occurs, further electron orbital decay and photon emission are induced.

The emitted photon has the same characteristics and travels in the same direction as the original photon and they leave the resonator cavity as a coherent light beam. This is known as stimulated emission of radiation and is the operating principals of lasers [9]. Polanyi et al described the surgical interest in CO₂ lasers in 1970 [10]. This laser is a high-powered

continuously operating laser with a wavelength in the infrared spectrum at 10.6 μm, allowing almost complete absorption by the water in the tissue (Figure 1).

This results in a precise localized volume of tissue treated. Water absorbs CO₂ laser energy so efficiently that 90% is used up in the first 0.1 mm depth allowing precise tissue treatment. In addition, the laser beam can focus to a very small spot size further limiting adjacent tissue damage. Once absorbed, CO₂ laser energy instantly transforms into heat and the resulting tissue effect depends on how quickly and how high the tissue temperature rises, as well as laser dwell time. The CO₂ laser can be delivered using a pulse setting (fractional) which minimizes tissue damage due to overheating.

Figure 1: Laser absorption and tissue penetration



Pulsed CO₂ lasers have been used safely and effectively for remodeling tissue properties in many body areas. Fractional CO₂ lasers are widely used in dermatology for conditions including scars and skin rejuvenation. Histologic changes occur due to a microablative and thermal effect that stimulates tissue remodeling.

Heat shock proteins 43, 47 and 70 (HSP70) are released in response to the thermal laser energy that leads to a cascade of events. Transforming growth factor B activates fibroblast and collagen formation,

basic fibroblast growth factor stimulates angiogenic activity, epidermal growth factor stimulates re-epithelization, platelet derived growth factor stimulates fibroblasts to produce extracellular matrix components and vascular endothelial growth factor helps to regulate vasculogenesis and angiogenesis [11]. After 30 days, these combinations of events activate fibroblasts to synthesize a new extracellular matrix consisting of collagen, elastic fibers and vessels [7].

Genitourinary Symptoms of Menopause

Vulvovaginal atrophy (VVA) is a condition secondary to aging, menopause and subsequent lack of estrogen. Genitourinary syndrome of menopause (GSM) is the new term to describe changes of the vulva, vaginal and urinary tract.

This common condition after menopause leads to symptoms of vaginal dryness, itching, burning, dysuria, dyspareunia and recurrent UTIs.

Histologic changes consist of the alteration of type I collagen fibrils to type III collagen ratio.

Fibrils become flattened, less elastic and hypovascular. The acidic pH environment is changed and there is less lubrication. The epithelium becomes thin, flat and pale as a result and can lead to shortening and narrowing of the vaginal canal [11].

Topical vaginal estrogen is first line treatment of

VVA however, compliance is poor due in part to cost, as well to risks of unopposed estrogen in certain conditions (deep vein thrombosis, other thromboembolic events) and gynecologic cancers such as breast or ovarian. Other topical treatments such as sesame or coconut oil, due to their moisturizing properties, are often offered as an alternative but have limited efficacy and durability.

Laser Treatment for the Genitourinary Symptoms of Menopause

Zerbinati et al evaluated the effect of pulsed CO₂ laser on the vaginal epithelium of post-menopausal women [12]. Vaginal biopsies were performed on 5 patients with severe VVA changes and symptoms. These were performed at baseline on the left lateral wall and then two months post treatment on the right lateral wall. At 2 months, they report the restoration of a thick squamous stratified vaginal epithelium, presence of glycogen rich epithelial cells and a large content of blood vessels in the connective tissue. In fibroblasts, there was a large population of rough endoplasmic reticulum and vesicles for the synthesis of procollagen molecules. Golgi bodies were well developed with presence of vesicles for the glycosylation of proteins and the synthesis of molecular components of the ground substance [12].

VVA symptom improvement after laser treatment was first reported by Gaspar in 2011, in a study that was aiming to demonstrate the use of CO₂ fractional laser with local administration of platelets rich plasma for atrophy symptoms [13].

In this study group, 40 patients were treated and an important improvement of vaginal mucus histology, and a decrease in discomfort during sex were observed in most patients after CO₂ treatment. Salvatore et al [14] reported in 2014 in an observational study demonstrating the subjective and objective efficacy of CO₂ treatment in 50 women. Following 3 treatments over 12 weeks, symptoms of vaginal dryness, itching, burning, dysuria and dyspareunia significantly improved ($p < 0.001$). Vaginal health index scores improved from 13.1 to 23.1 ($p < 0.001$) and minimal side effects were reported.

The Rationale for Laser Treatment for SUI

Although risk factors for SUI have been identified, the exact etiology of this condition is poorly understood. The endopelvic fascia is rich in collagen, making up 80% of its protein content [15]. Collagenesis decreases with the aging process but is also affected by the destruction of collagen fibrils due to vaginal birth [16] and can even be associated with certain genetic polymorphisms [17]. SUI can also be associated with GSM due to hormonal deficiencies that affect the pelvic floor musculature. Estrogen receptors have been identified in the musculature of the pelvic floor with the exception of the levator ani muscles [18, 19] and Chen et al. found ER in the vaginal walls and uterosacral ligaments of premenopausal women despite being absent in postmenopausal women [20]. One theory suggests that SUI occurs due to an alteration of collagen arrangement and metabolism [21]. Over 20 years ago, Falconer et al performed

skin biopsies in women with SUI and found 30% less collagen compared to continent women [22]. More recently, Han et al looked specifically at the ultrastructure and content of collagen by obtaining samples of the cardinal ligaments, uterosacral ligaments and paraurethral tissue in women who underwent an abdominal or vaginal hysterectomy [23]. Patients with pelvic organ prolapse (POP) and SUI were compared to those without. POP and SUI patients had diffuse atrophy of smooth muscles, active fibroblast metabolism, swollen metabolism and visible Golgi apparatus.

The collagen fibril diameters were greater and the levels of Type I and Type III collagen were significantly lower in the SUI and POP group. Lastly, pelvic tissues were frail and smooth muscle cells were disorganized. They concluded that these changes could be associated with POP and SUI.

While the mechanism for the decrease in collagen has not been determined, a study by Chen et al demonstrated no difference in collagen synthesis in the endopelvic fascia or skin of women with or without SUI [24]. This suggests that increased breakdown, rather than decreased synthesis, may be responsible for these changes. In fact, these hypermetabolic changes may be a result of increased fibroblast activity and subsequent increased fibroblast secretion of matrix metalloproteinase 1 (MMP-1), the enzyme responsible for collagen breakdown [25, 26]. A recent study questions whether these changes are a result of the POP or SUI rather than the cause [27], but the fact that collagen is intricately involved in the supporting mechanism of the pelvic floor is difficult to dispute.

The application of the CO₂ laser to the vaginal canal, can yield healthier and more elastic tissue of the anterior wall which in turn, may serve as a strong support to the urethral support mechanism. In addition, the external treatment to the vestibule area, may penetrate to the lower pelvic floor muscles, and supply a more comprehensive treatment that can increase the elasticity of the pelvic floor muscle, and potentially increase the efficacy of the external urethral sphincter, yielding again, better support, and potentially better control of urine emptying.

Laser Therapy for SUI

Assuming that SUI is due in part to a deficiency or alteration in collagen in women, the use of the CO₂ laser to modify the matrix composition and elasticity of the vaginal supportive systems seems a viable option as a minimally invasive treatment for SUI.

Recently, the vaginal Er:Yag (erbium in yttrium aluminum-garnet crystal) laser has been used in the treatment of SUI in women. This laser, with a wavelength of 2940 nm, distributes non-ablative heat approximately 100 microns deep into the mucosal surface. This provides a limited deep thermal effect without ablation and avoids the risk of perforation with accidental lesions of the urethra, bladder and rectum. Fistonc et al evaluated 39 patients with mild to moderate SUI who underwent single treatment with this Er: YAG laser to the anterior vaginal wall and vestibule [28]. Patients were evaluated at 1 (39 patients), 3 (22 patients) and 6 months (6 patients). Scores on International Consultation on Incontinence Questionnaire (ICIQ) and PISQ-12 improved significantly at all time points and Q tip angle

decreased at 6 months to 22.5 degrees less than at baseline. Vaginal muscle strength and duration as measured by perineometry improved significantly at all time points compared to baseline.

The same group evaluated 73 women at 1 month and again at 2-6 months following a single treatment with the same laser [15]. Patients lost to follow up (38%) were assumed to be treatment non-responders and a significant improvement in ICIQ was still noted at 2-6 month follow up (12 (6-16) vs. 7 (0-13); P= <0.001). Side effects were minimal and included slight vaginal warmth or pricking or mild vulvar edema. 95% had a VAS score of 0 with a VAS of 2 the highest reported. While treatment for SUI is promising, in one study only 34% of women with mixed urinary incontinence had significantly improved incontinence at 1 year compared to 77% patients with pure stress incontinence [8].

CO₂ Laser vs Er:YAG

The possible consequence of laser energy onto tissue is divided into two major aspects: ablation and thermal effect. Tissue ablation occurs due to vaporization of layers near the surface and can penetrate into deeper layers. The thermal effect is the coagulation necrosis of cells on the borders of the residual layers. Both these processes can trigger a chain of events from the molecular level to yield eventual renewal of collagen and elastin fibers, and a new, healthier and more elastic tissue.

The major chromophore that absorbs the CO₂ and Er:YAG laser wavelengths is water, however there are differences in the absorption coefficient of these two wavelengths. At the 10.6- μm wavelength, CO₂ laser absorption coefficient is 600 cm^{-1} in skin, so the CO₂ laser optical energy is absorbed in a layer 15 to 20 μm thick. For the 2.9- μm wavelength Er:YAG laser,

the absorption coefficient is 10,000 cm^{-1} , and the optical energy is absorbed in a layer about 1 μm thick. This means that the Er:YAG laser is absorbed about 15 times better in water than the CO₂ wavelength, and as a result, operates at a more superficial level.

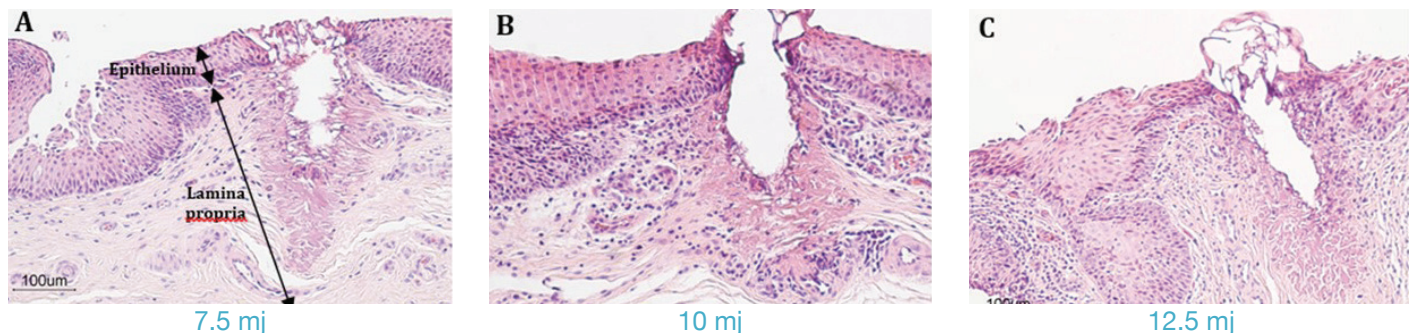
The CO₂ laser is considered gold standard for high precision incisions, skin resurfacing and tissue remodeling, and has already proven to reach depth of several hundred microns in preclinical and clinical work exploring the effect on the vaginal tissue (Figure 2). Because of the relatively low absorption coefficient of the CO₂ laser, the depth of penetration when using the CO₂ laser can easily be controlled by determining the power used according to the clinical state, and can reach from several microns to hundreds of microns.

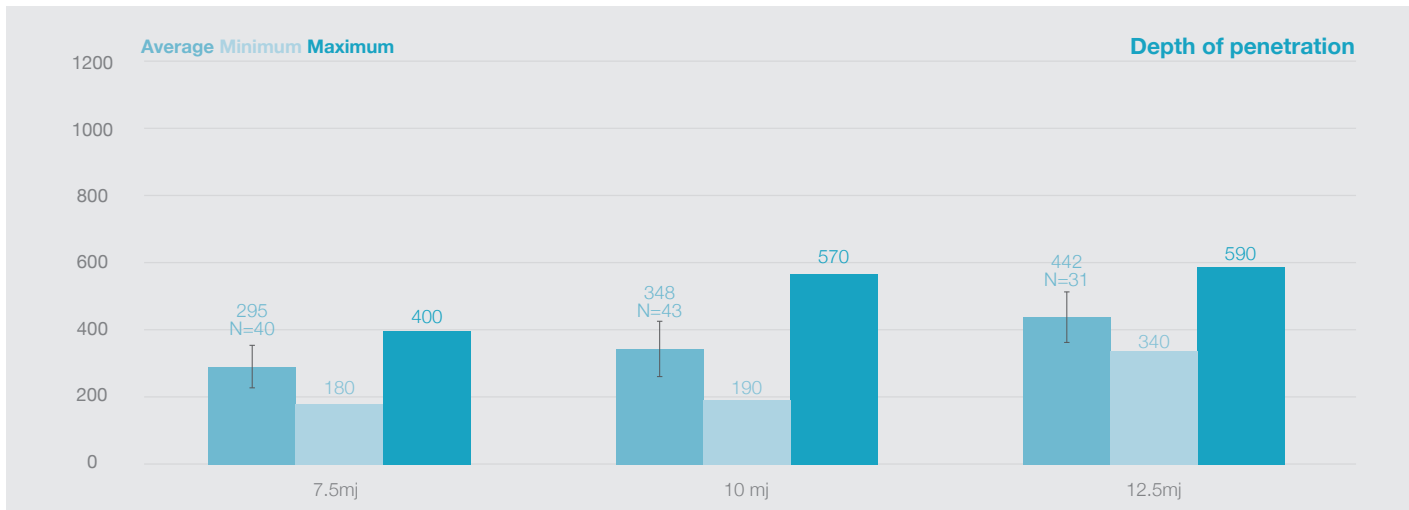
Figure 2: Total penetration depth, ablation and coagulation

Total penetration depth (ablation and coagulation) at various energy levels of the AcuPulse treatments in the vaginal wall of study porcine, using the FemTouch handpiece. Measurements done on histological slides. The left columns represent the average of measurements, whereas the other two columns represent the minimum and maximum values measured at each energy level, respectively.

The numbers of observations for each power level are indicated in the above the green columns (indicated as "N").

The photo below demonstrates the axis of penetration depth measurement, which includes both, the ablative and coagulative zones.





Power Level

In addition to the ablative effect, the collateral thermal necrosis zone is a supportive factor in tissue remodeling. Immediately after deploying the laser energy, the target tissue reaches its peak temperature, and then it begins to cool. The thermal relaxation time is the amount of time the tissue requires to cool to half of its peak temperature. When the energy deployed to the tissue is greater than the thermal relaxation time, a stacking of the laser energy and rapid heat accumulation occur. This stacking effect causes the formation of necrotic area/coagulation zone.

The coagulation area around the ablative part can reach 50-100 micron in the vaginal tissue when using the CO₂ laser, and can further induce tissue effect when compared to the 20-50 micron of collateral damage caused by the Er:YAG laser, due to its shallow penetration.

Another consequence of residual thermal damage during laser resurfacing on the skin is immediate shrinkage due to denaturation of type I collagen. With heat accumulation, type I collagen undergoes a helix-coil transition that forcefully shortens the fibers

by approximately 15%-25% during CO₂ lasing, and only 1%-2% shrinkage when using Er:YAG. It seems plausible that like the immediate shrinkage of the skin which “tighten” the face and reduce wrinkles, the same effect can potentially cause a more firm and tight vaginal tissue, which in turn can serve as a strong supportive structure for the urinary sphincter.

The alternative Er:YAG treatment has developed a technology that controls the energy and pulse width, prolonging the pulse duration, yielding non ablative pulse with thermal penetration of up to 100 microns in depth. The new pulses presented are in the range of a few hundred milliseconds for each pulse and triggering a prolonged procedure. The use of CO₂ laser energy to the vaginal canal and the vestibule area, will combine the advantages of ablative and thermal effects in an efficient and timely manner.

The fractional scanner of the CO₂ laser is fast to deploy the exact amount of energy, and the depth of penetration is controllable, and can be adjusted to clinical status and to the desired tissue/ clinical effect.

CO₂ Laser Fractional Treatment for Patient with Stress Urinary Incontinence- Initial Treatment Experience

Our group recently treated a small cohort of women with the CO₂ Laser (FemTouch™ from Lumenis) (Figure 3). FemTouch™ delivers low continuous wave CO₂ energy levels in a fractional pattern along the vaginal lining.

Uniform delivery of the fractional pattern is achieved through a unique scanner designed to evenly and homogeneously scan microbeams of 210µm each in a controlled and uniform manner.

Figure 3



AcuPulse System

Controlled small ablation/coagulation zones are created in the lamina propria using energy levels from 7.5 to 12.5mJ. The restriction of these parameters allow to provide effective vaginal remodeling process while limiting penetration depth to up to 600µm to ensure fibromuscular layer safety. The fractional scanning pattern enables a quicker vaginal tissue healing.

To complement the intra-vaginal treatment, an optional external treatment of the introitus and vaginal vestibule is possible using the AcuScan 120 Microscanner

Following a 60 minute training session on the use of the laser, 4 urologists who specialize in female pelvic medicine and reconstructive surgery provided in office treatment to a total of 9 patients. Nine patients received one treatment and two patients received 2 treatments for a total of 11 laser treatments as of the writing of this white paper. Our goal is to complete 3 treatments in 12 patients.

Patients with symptoms of GSM and SUI were evaluated with a pelvic exam including a vaginal pH and a cough stress test. Patients reporting either symptoms of GSM and/or SUI were offered treatment and a negative stress test or a normal vaginal pH did not exclude treatment.

Patients were asked to fill out a series of validated questionnaires as part of our standard office practice in treating patients with SUI and GSM. Validated questionnaires included International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF), Female Sexual Function Index (FSFI), Incontinence-Quality of Life (I-QOL).

Subjective assessments of vaginal atrophy and pain assessment during treatment were also recorded.

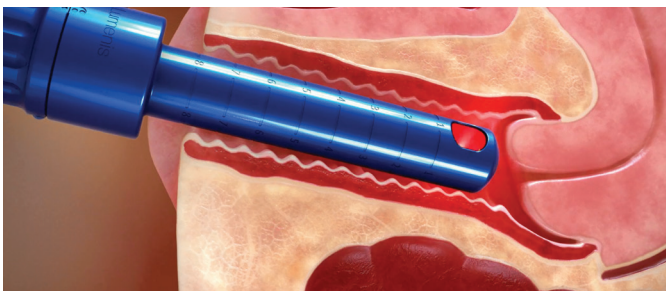
Median age of patients treated was 59 years (Range 34-88). Patients had the following primary and/or secondary diagnosis: GSM (9), SUI (9), Lichen Sclerosis (1), UTI (2). Mean pH was 5.6 (Range 4.5-7). The procedure was performed with topical lidocaine/prilocaine (EMLA) anesthetic to the vulva in 6 treatments and no topical anesthetic was used in 5 treatments. Use or non-use of topical anesthetic was based on physician and patient discretion.

Following vaginal probe insertion into the vagina, although exact time was not recorded, treatments took less than 5 minutes (Figure 4). 10 mJ of energy was used in 11 treatments and density of treatment was set at 10% in 8 treatments and 5% in the remaining 3 treatments. Treatment was well tolerated in most patients and insertion and movement of the probe into the vagina was reported as causing very minor discomfort.

On treatment pain assessment, on a scale of 0-10 average pain on insertion was 0.8 (range 0-2.5), movement of the probe was 0.91 (0-5), and vaginal lasing 0.09 (0-1). One patient that did not have EMLA cream have a 5/10 pain report due to the laser hitting the outside of the vagina. No other patients reported pain on the vulvar area. No complications after treatment were reported and the two patients that had a second treatment did not report any adverse events.

Overall, following a short clinician training session, treatments were easily performed in the office setting with minimal discomfort to patients. While longer follow up and outcome data are obviously imperative prior to recommending CO₂ laser treatment for SUI, the procedure appears to be well tolerated in our small cohort of women undergoing treatment.

Figure 4:
FemTouch™ vaginal probe



FemTouch™ intended use:

The Lumenis AcuPulse system and the FemTouch™ is cleared by the United States Food and Drug Administration (FDA) for a wide range of indications including, but not limited to, ablation, coagulation, incision, excision, and vaporization of soft tissue in medical specialties such as gynecology, genitourinary, and general surgery.

Conclusion

Minimally invasive Lumenis CO₂ laser treatment offers a unique therapeutic option for women with SUI. Histologic changes are evident on basic science studies and vaginal laser treatment appears safe and well tolerated. We strongly believe that further research and future clinical studies including well designed randomized controlled trials will demonstrate the desired clinical outcomes in addition to the safety which is already a proven factor. The potential of advancing SUI treatment to a safe, minimally invasive, expeditious, durable and effective treatment option using CO₂ laser therapy is an exciting area deserving further study.

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