

Mechanisms of Action of the CO₂RE Fractional CO₂ Laser on Vaginal and Vulvar Tissue and Effects on Female Genitourinary and Sexual Health

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Background

Changes in genitourinary anatomy and physiology can adversely affect female sexual health and quality of life over a woman's lifetime. Common medical conditions due to childbirth or age-related changes include Vaginal Relaxation Syndrome (VRS), Stress Urinary Incontinence (SUI), and Genitourinary Syndrome of Menopause also known as Vulvar and Vaginal Atrophy (VVA). Vaginal laxity, mild to moderate SUI and symptoms of increased dryness, itching, burning and dyspareunia result in discomfort and problems with intimacy and sexual satisfaction for many women.^{1,2} Findings from the REVIVE (Real Women's Views on Treatment Options for Menopausal Vaginal Changes) study reported that these symptoms affected sexual satisfaction in 59% of women responding, and in nearly one-fourth (23%) of respondents, these symptoms affected general temperament and general life enjoyment.³

An optimal treatment option is lacking for women with these medical conditions. Pelvic floor exercises or electro-stimulation are often prescribed to improve vaginal relaxation syndrome but are not uniformly successful.⁴ Surgical options carry an inherent downtime and associated risks.⁵ Topical treatments and hormones are also therapeutic options, but are often considered inconvenient or insufficient for relief of symptoms. Moreover, there is a subset of women who prefer not to use hormonal therapy, and in circumstances such as in cancer survivors, hormonal therapy may not be an advisable option.^{2,6,7}

Understanding these issues and offering solutions for these symptoms are important for the maintenance of sexual health and general well-being.^{8,9} This paper presents information that supports a therapeutic approach

for tissue remodeling of the vaginal canal, introitus and labia using CO₂ laser technology, which is considered the gold standard in tissue rejuvenation.¹⁰⁻¹⁵

MECHANISMS OF ACTION

Laxity, as seen in Vaginal Relaxation Syndrome (VRS) and symptoms of Stress Urinary Incontinence (SUI) can be responsive to structural improvements in the vaginal tissue. Other symptoms more consistent with the Genitourinary Syndrome of Menopause such as mucosal thinning and dryness respond via a different mechanism, both further described below.

Carbon dioxide (CO₂) lasers reach all of the various temperature thresholds necessary for optimal ablation and coagulation of tissue. Both of these mechanisms play an important role in rejuvenation and tissue remodeling.¹⁰⁻¹⁴ Ablation occurs when water is instantly heated above 100°C and vaporization of tissues occurs.¹¹ This effect improves epidermal texture and pigmentation and zones of coagulation beyond the ablation zones are produced¹¹, where temperatures that induce collagen denaturation (65-67°C) and subsequent remodeling occur.¹⁵ CO₂ lasers have long been shown to regenerate and remodel collagen through heat-induced collagen contraction.¹⁰⁻¹⁴ Histologic changes induced by CO₂ laser pulses in human skin have been extensively studied.¹⁰⁻¹³ Neocollagenesis persists at 6 months after the procedure and new collagen formation has been documented up to one year after treatment.¹² Fractional techniques provide a further means by which tissue is coagulated and collagen is generated with the added benefit of low risk and minimal downtime.¹⁶

Compared to erbium lasers, which cause tissue contraction as a normal part of the wound healing response, CO₂ lasers stimulate collagen via heat-induced collagen contraction and subsequent stimulation. There is an increased risk of scarring seen in wound contracture with erbium lasers as compared to heat-induced collagen formation.¹³

Histology specific to vaginal tissue after CO₂ laser treatment demonstrates fibroblasts that are found during the proliferative phase, and subsequent histology reveals collagen remodeling and new deposition.¹⁷ Dermal remodeling with new collagen deposition improves the tissue quality of the vaginal canal, and symptoms of relaxation syndrome are improved when there is generalized tissue rejuvenation. SUI symptoms are also reported to be improved when this deposition is significant enough to improve the tissue structure of the anterior vaginal wall under the mid-portion of the urethra.^{18,19} Additionally, there is general structural improvement in the connective tissue with new active fibroblasts, collagen and ground substance and the presence of typical blood capillaries representing healthy vascularization.²⁰

Dermal remodeling and thickening via heat-induced coagulation and stimulation is an important characteristic of CO₂ lasers but ablation is also a significant component necessary to optimally rejuvenate tissue. For general rejuvenation of the labia, particularly dyschromia, ablation is necessary. Moreover, thinning of the epithelial lining of the vagina and lower GU tract⁶ improves after treatment with CO₂ laser, where there is an improvement in lubrication and a return to a more acidic and healthy vaginal pH.²⁰ Zerbinati, et al.²⁰ observed that the CO₂ laser is capable of restoring the pH of the vaginal mucosa by liberating glycogen and acidic mucins from the epithelium. Symptoms of dryness and itching, dysuria and recurrent infections can be alleviated by increasing the glycogen, which allows a rebalancing of lactobacilli that keep pathogenic bacteria at bay.²⁰

The CO₂RE laser not only treats multiple levels of tissue, but also arrives at the various temperature thresholds required to ablate, coagulate and stimulate tissue by heat. Additionally, its agility and versatility make it a highly useful tool for comprehensive treatment of the vaginal region. The device easily moves from the surgical mode that can be used for incision and excision of tissue to a fully ablative or fractional mode. The fractional mode has the highly desirable ability to simultaneously treat superficially and deeply in the same rapid pass without the need for changing hand pieces. In the Fusion Mode,

rejuvenation is accomplished by simultaneously remodeling tissue and treating dyschromia. CO₂RE gives physicians the ability to treat both superficial and deep skin layers simultaneously with precision control over the intensity, pattern and depth of ablation.

CO₂ LASER EFFECTS ON VAGINAL TISSUE – PRIOR STUDIES

There are multiple published studies to date reporting on the effects of a CO₂ laser on the vaginal mucosa^{17,20,22} with subsequent improvement in symptoms of vaginal atrophy^{21,23} and stress urinary incontinence.¹⁸

Gaspar, et al.²² demonstrated that treatment with a fractional CO₂ laser improved vaginal tissue in all layers of the vaginal wall. Biopsies showed improvement in all three layers of the vaginal tissue versus only the epithelium as shown with estrogen.²²

Salvatore, et al.¹⁷ corroborated these findings by showing remodeling of vaginal connective tissue including collagen and fibroblasts by biopsy. In this study, five postmenopausal women with symptoms of vulvovaginal atrophy were treated with a CO₂ laser. Biopsies of treated and control tissue were taken and examined under light and electron microscopy. Treated tissue demonstrated areas of ablation, fibroblast activation, changes in collagen and elastin fibers and presence of mucopolysaccharides in the lamina propria relative to control, which demonstrated a flattened epithelium, loss of dermal papillae and absence of fibroblasts.¹⁷ In another histological study, Zerbinati, et al.²⁰ demonstrated new collagen and extracellular matrix molecules in vaginal mucosa after a single treatment with fractional CO₂ at 30 and 60 days post treatment.

In addition to demonstrated histological and microscopic improvements, numerous studies have reported improvement in clinical symptoms and patient satisfaction after undergoing treatment with a CO₂ laser. Other studies of post-menopausal women report significant improvement in symptoms such as vaginal dryness, burning, itching, and dyspareunia. These improvements led to improved sexual function and subsequent improvement of quality of life. Changes in the mucosa were measured using the Vaginal Health Index scale, and symptoms and satisfaction were measured using the Vaginal Atrophy Scale and a 5-point Likert Scale. In these combined studies, over 100 patients were treated and reported over 90% satisfaction rate for the procedure based upon improvements in symptoms, improvement of sexual satisfaction and quality of life.^{21,23}

The CO₂ laser has been shown to be safe and effective in the treatment of a variety of important vulvovaginal atrophy symptoms and is a rapid and comfortable alternative to existing treatment options.

CO₂RE INTIMA



Figure 1 CO₂RE System and Main Screen

The CO₂RE laser system consists of a radiofrequency excited Coherent GEM 30A laser tube optically coupled to a 2-axis scanner and a beam relay incorporated into an articulated arm that allows for easy manipulation of the delivery end relative to the treated tissue region. This architecture enables a very high degree of flexibility of spatial geometry and laser energy delivered to the tissue. For treatment of both the vaginal canal and external regions, the Deep Mode is used for deeper tissue remodeling. Deep Mode consists of a user-controlled array of 3 to 64 micro-beams, each of which has a diameter of 150 μ m. Each of the micro-beams can be set to deliver 30-70mJ of energy, which correlates to fluences of 170-396 (30 – 80 mJ / 170 – 453 J/cm² outside the USA). The exact ablation and coagulation depth depends upon the local water content in the tissue being treated. Typical values for mucosal tissue penetration, in the treatment fluence range administered by a single pulse, are from 500-700 μ m.

Of importance, CO₂RE's system architecture incorporates an in-board scanner inside the device, so the hand pieces are light, easily maneuverable and not obstructed by a bulky scanner. The fractional mode is unique in its ability to simultaneously treat superficially and deeply in the same rapid pass without the need for changing hand pieces. In Fusion Mode, rejuvenation is accomplished by remodeling tissue and treating dyschromia. The device easily moves from the surgical mode that can be used for incision and excision of tissue to a fully ablative or fractional mode.

CO₂RE Intima Uniquely Treats All 3 Intimate Areas: Internal, External and Introitus



Figure 2. (Handpieces from left to right): External to treat dyschromia and pigmentation and to remodel vulvar and labial tissue, Internal to remodel vaginal tissue, and Surgical for incision and excision of tissue

CO₂RE Histologic Data

In a clinical study (non-published results), nine subjects previously scheduled for abdominal surgery received treatment with fractional CO₂ on the abdomen at a predetermined time prior to surgery. Treatment was performed using a variety of different parameters. Biopsies were taken at various times after treatment, and morphological and morphometric analyses were performed in the ablative and coagulative tissue areas for comparison at the end of the study. Histologic evaluation (Figures 3a-3c) showed 800-900 micron diameter zones of ablation and coagulation confined to the uppermost layer of the skin in the mode with the greatest fractional skin coverage (Light Mode 30-50%), while ablation to deeper levels of up to 900 microns with a limited diameter of 150-200 microns were seen with higher energy settings and minimal fractional skin coverage of 1-5% (Deep Mode).

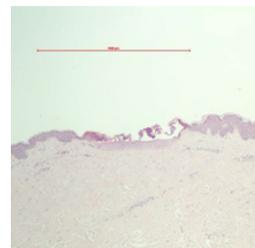


Figure 3a: CO₂RE Deep Mode at 50 mJ

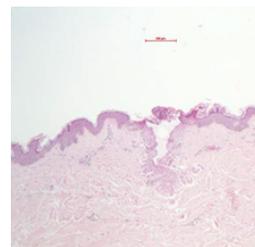


Figure 3b: CO₂RE Mid Mode at 60mJ

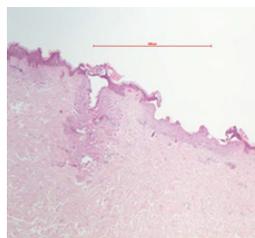


Figure 3c: CO₂RE Fusion Mode at 60 mJ

CO₂RE Intima Procedure and Clinical Findings

The CO₂RE Intima procedure is rapid and well-tolerated. Women who meet criteria for treatment can undergo the procedure with a minimum of disruption to their routine. After cleaning the treatment area, a small amount of Johnson's Baby Oil is applied to the tip of the probe and if necessary, introitus. The probe is gently inserted until it abuts the end of the canal. Energy, using the Deep Mode, is then delivered to the anterior vaginal wall at the twelve o'clock or zero-degree position. The length of the vaginal wall is treated at 1 cm intervals, as marked on the hand piece (Figure 4a) until the window appears at the introitus. The probe is not removed, but rather turned 45-90 degrees (Figure 4b) and reinserted. The next section of the vaginal wall is then treated in the same fashion.

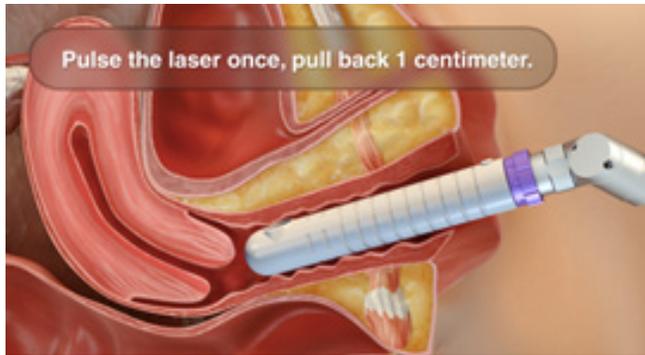


Figure 4a



Figure 4b

Once the desired coverage is achieved in the vaginal canal, the probe is then removed and the hand piece is changed to the external hand piece in order to treat the desired portions of the external mucosa and the labia.

Effect of CO₂RE Intima on the vaginal canal before and after treatment:

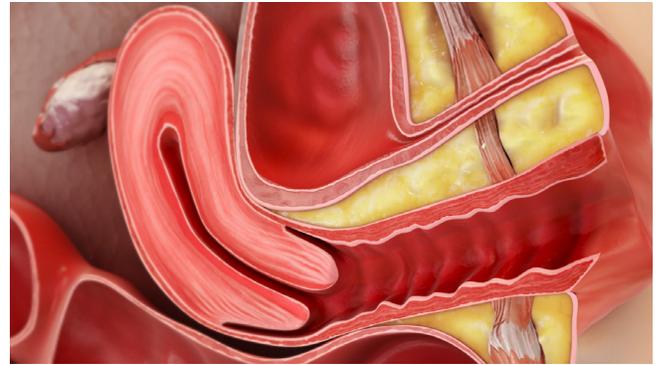


Figure 5a. Before

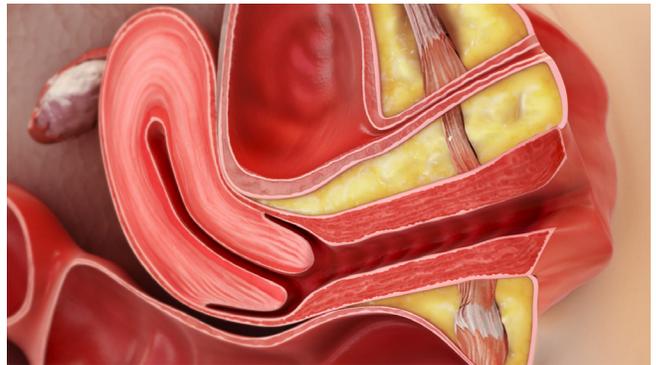


Figure 5b. After

Use of CO₂RE Intima on the labial skin:



Figure 6

CO₂RE Intima histologic data:

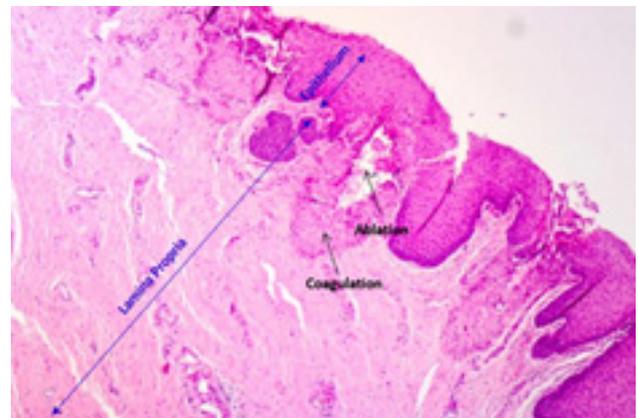


Figure 6

CO₂RE Intima Clinical Study

In a study of premenopausal women (mean age 45± 7 years) with complaints of vaginal laxity, 21 women were treated up to three times with the CO₂RE CO₂ laser system. The procedure was an in-office procedure requiring no anesthetic. In each case the length and circumference area of the vaginal canal were treated with up to two passes. The introitus was treated with a single pass over the mucosal surface.

Sexual function, satisfaction and improvement were evaluated by a subject questionnaire, based upon a 5-point Likert scale at baseline and at follow-up up to 12 weeks post final treatment. The Questionnaire for Urinary Incontinence Diagnosis (QUID) was administered to record symptoms at baseline, and at 8 and 12 weeks post last treatment. A 10-mm visual analog scale was used to measure discomfort associated with the treatment. The

Vaginal Health Index (VHI) was used by the investigator to assess changes in vaginal elasticity, fluid volume, pH level, epithelial integrity and moisture.

Subjects reported an improvement of their symptoms after being treated with the CO₂RE fractional laser. Following the 2nd treatment, based on their symptom improvement, 92% reported satisfaction with the treatment and would recommend the procedure, 75% reported improvement in overall vaginal rejuvenation and 73% of subjects reported an improvement in sexual gratification. Most patients (96%) reported that both internal and external treatment phases were accompanied by mild to no pain. There was a trend towards continued improvement with subsequent sessions, and there were no significant adverse events. The CO₂RE Intima treatment is associated with improvement of sexual function, sexual satisfaction, stress urinary incontinence and overall vaginal rejuvenation in premenopausal women.

Table 1: CO₂ Technology is the Gold Standard for Rejuvenation.

TECHNOLOGY	MECHANISM	PROCEDURAL TIME	VERSATILITY	RESULTS
Radiofrequency	Transmucosal heating of the tissue to 40-42°C. Promotes prolonged edema.	Up to 30 minutes per area.	No capability to treat pigment.	Collagen contracture. Maintenance periods treatment every 6 months. No long term results.
Erbium	Collagen contracture from wound healing response.	15-20 minutes.	Very shallow impact. Requires more pulses.	Superficial collagen contracture. Can target collagen and pigment.
CO ₂ with CO ₂ RE	Ablation above 100°C. Collagen partial denaturation (65-67°C). Heat induced collagen contraction/ elastin generation. ^{17,20,22}	10-15 minutes for full procedure.	Highly versatile. Multiple levels of impact –shallow and deep.	Collagen contracture. Collagen remodeling up to 1 year after treatment. Pigmentation and skin textural improvements.

CONCLUSION

CO₂ laser treatment has been well studied over many years for its effects on human tissue, and it remains the current gold-standard for tissue rejuvenation. More recently, this technology has shown to be highly effective in ameliorating numerous troublesome genitourinary

symptoms for women. The CO₂RE laser system with the CO₂RE Intima module is exceptionally versatile and comfortable to use in the treatment of a spectrum of genitourinary pathology involving the skin and soft tissues leading to improvement in women's intimate wellness.

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