Pelvic Floor Disorders: Epidemiology and Pathophysiology and New Treatment Options

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Abstract

The female pelvic floor is composed of the musculature, soft tissues, and connective tissues providing structural support for the bowel, bladder, uterus, and other pelvic organs. Disorders affecting one or more of these organs, broadly referred to as pelvic floor disorders (PFDs), are a common occurrence following pregnancy, childbirth—in particular vaginal deliveries—and menopause. The weakening of the pelvic floor or relaxation of the vaginal muscles, also referred to as vaginal relaxation syndrome (VRS), is one of the most common PFDs. VRS causes a loss of voluntary muscle control and decreased vaginal sensation, impacting urinary control and sexual function. Distention of the vaginal wall musculature leads to a cascade of cellular changes that ultimately weaken impact protein and collagen metabolism, thus resulting in patient morbidity. Another common consequence associated with aging, especially after menopause, is vaginal atrophy (VA), when estrogen deprivation accelerates the process of deterioration of vaginal tissue, leading to vaginal dryness and irritation, among other conditions. While the health implications of these problems are significant, they also negatively impact self-esteem and quality of life for women.

Current treatment options for VRS and VA range from non-invasive approaches such as pelvic floor muscle exercises (PFME), topical creams, and medications to more invasive approaches such as laser treatments and surgery, each with associated drawbacks. Because PFDs are rooted in muscle and soft tissue changes and damage, modalities that have been used successfully to treat musculoskeletal and other soft-tissue injuries—including low-level light therapy (LLLT), heat, and therapeutic vibration technology—are now being used to address these symptoms. More specifically, LLLT promotes tissue healing at the cellular level by acting on cellular structures responsible for energy production and upregulating transcription factors. The application of heat has a twofold effect of improving blood flow/microcirculation and metabolism while also causing denaturing of proteins, which can result in tightening of the extracellular matrix upon recombination. Vibration induces changes at the cellular level via the mechanical perturbation of tissues, which increases fibroblastic activity and hormone activity.

vSculpt is a class II OTC medical device made by Joylux, Inc. approved by Health Canada and currently under 510(k) review in the U.S. with the Food and Drug Administration (FDA)[1]. It uniquely combines these three modalities (LLT, heat and vibration) to provide a new treatment option for women suffering from VRS and VA. The vSculpt device, inserted into the vagina and designed for self-use, has been shown in an early pilot study using quality-of-life questionnaires (QoL) to improve the quality of life for women in the areas of vaginal muscle tone and tightness, decreased bladder leakage, and improved vaginal lubrication and sexual function. A larger clinical trial (results to be released October 2016) measuring both objective and subjective clinical endpoints positively supports the conclusion that vSculpt has the potential to be transformative for women with VRS and VA, offering a simple yet effective non-invasive treatment option.

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Joylux makes no claims regarding vSculpt safety or effectiveness in the United States while it is being reviewed by the FDA [1]

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Introduction

As a common consequence of pregnancy and childbirth (particularly vaginal deliveries) and aging, women often experience weakening or relaxation of the pelvic floor and vaginal musculature leading to vaginal relaxation syndrome (VRS). The resulting condition can include loss of voluntary muscle control and decreased vaginal sensation, impacting urinary control, sexual function, and other issues affecting a women's genitourinary health, with both physical and psychological impact [1-3]. With age, especially menopause, vaginal atrophy (VA) occurs when there is a deprivation of estrogen causing a deterioration of the vaginal tissues [4], the primary symptom being vaginal dryness and irritation. This lack of lubrication can adversely affect sexual intercourse and decrease pleasure during sexual arousal [2, 3]. Collectively, these conditions significantly impact a woman's self-esteem and can have a substantial negative effect on quality of life [3, 5].

Treatment for VRS- and VA-related symptoms includes a wide range of options from simple exercises and topical treatments or medications to more invasive medical procedures and surgeries. These options, while varied, have drawbacks as they either are associated with poor effectiveness, require significant amount of time and patient compliance, are cost prohibitive, or are considered invasive with numerous side effects.

The most commonly prescribed conservative treatment, pelvic floor muscle exercises (PFME)—commonly known as Kegel exercises—are largely ineffective for several reasons. When performed properly, these exercises can help to increase the strength and stability of the pelvic floor musculature [6, 7]; however, in many cases, women do not perform these exercises correctly on their own, failing to accurately isolate and contract the levator muscles that are key to success [6, 7]. Physiotherapists who specialize in pelvic floor disorders can help patients isolate the appropriate muscles. However, women still need to perform the high number of PFMEs required to have a positive impact, independent of their time with the physiotherapists, which is a challenge [6-9]. Even in patients who do perform the requisite amount of exercises, while muscle strength and stability may increase, these exercises fundamentally do not aid in tissue restoration and do not address vaginal lubrication or sensation concerns. Other conservative treatments such as dilators, topical and oral applications such as estrogen agents and medications, or electrical modalities such as electrical stimulation have shown minimal effectiveness in improving muscle tone or tissue regeneration and also come with numerous side effects [10-13].

In serious or extreme cases, surgical options such as pelvic mesh implants are available, although surgeries are generally considered the "last resort" for patients for whom conservative treatments have failed. Indeed, the American College of Obstetricians and Gynecologists (ACOG) has recommended that nonsurgical treatment options for conditions such as urinary incontinence should take precedence over surgical treatments [14]. Despite its minimal effectiveness, ACOG recommends behavioral therapy (including PFME or the use of pessaries) prior to investigating surgical options, based largely on the potential disadvantages of surgical treatment, including complications associated with general anaesthetic and the potentially difficult recovery associated with this type of surgery, in addition to the high cost.

More recently, non- or minimally invasive energy-based procedures that correct and restore the structure of the vagina and surrounding tissues have become a viable treatment option to address VRS and VA. These modalities include CO_2 laser-based and radio-frequency (RF)-based technologies and erbium:yttrium-aluminum-garnet (Er:YAG) lasers (Table 1). By using these energy sources to heat the connective tissues of the vaginal wall, they induce collagen contraction, neocollagenesis, vascularization, and growth factor infiltration, which act to regenerate the elasticity and moisture of the vaginal mucosa. While clinical studies and patient feedback have shown encouraging results, the need for in-office treatments and the high cost to patients ($1000 to $3000 per treatment) present significant barriers to their widespread adoption.

Given the drawbacks of the aforementioned options, there is a need for a simple, effective, and affordable treatment option that addresses both the musculature and tissue symptomatology. The purpose of this review is to provide a summary of the currently available literature, with a focus on the epidemiology and pathophysiology of VRS and VA, and to investigate possible new treatment modalities to help common PFD conditions.

Table 1 - Laser and Radiofrequency-Based Devices for Vaginal Rejuvenation

FemiLift Alma Lasers (Buffalo Grove, IL) Fractional CO2 laser
MonaLisa Touch, Cynosure (Westford, MA) Fractional CO2 laser
IntimaLase, Fotona (Dallax, TX) 2,940-nm nonablative Er:YAG
Petit Lady, Lutronic (Burlington, MA) 2,940-nm Er:YAG
ThermiVa, ThermiAesthetics (Southlake, TX) Temperature-controlled radiofrequency
ReVive, Viora (Jersey City, NJ) Bipolar radiofrequency
Venus Fiore, VenusConcept (Toronto, CA) Multipolar-radiofrequency
Viveve System, Viveve Medical (Sunnyvale, CA) Patented radiofrequency
Protégé Intima, BTL Aesthetics, (Framingham, MA) Focused radiofrequency
Pelleve, Ellman International (Hicksville, NY) Monopolar radiofrequency

Epidemiology

VRS is a common condition associated with childbirth and aging. Vaginal childbirth has been shown to be associated with a 4- to 7-fold increase in pelvic floor disorders [15], although the exact incidence of such disorders is largely unknown, as not all women are symptomatic and not all seek treatment [16]. While it has been conservatively estimated that up to one-third of adult women in the United States are affected by pelvic floor disorders [17-20], with subsequent negative effects on quality of life, it is believed that up to 50% of women experience urinary incontinence at some point in their lifetime, but the condition remains underreported to medical practitioners [21]. A large review of over 149,000 women reported an 11% risk of undergoing a surgical procedure for pelvic floor disorders or incontinence by the age of 80 and also found that multiple surgeries were required in 29% of women in this cohort [22]. Serious events associated with VRS such as pelvic organ prolapse are estimated to occur in 4% of the female population [23], while the lifetime risk of surgery for pelvic organ prolapse is up to 13% [24].

VA commonly occurs in the majority of menopausal women, but not all women will be symptomatic. Symptoms may also occur in perimenopausal women, who may not necessarily have signs of VA. Studies have shown that vaginal dryness impacts 27% to 55% of women, with quality-of-life questionnaires reporting higher rates of vaginal dryness (over 50%) than clinical observations (around 33%) [25-27], which suggests that most women don't seek treatment for these issues.

While the symptoms experienced with both VRS and VA are not life threatening, they can exert a significant negative impact on quality of life. For instance, *Nilsson et al.* noted that 38% experience sexual dysfunction due to urinary incontinence [28], and *Stenberg et al.* noted that 32% of women complaining of vaginal dryness lose interest in sexual relations [25]. Additionally, women pull away from daily activities, such as exercise, to avoid the embarrassment of accidental leakage.

Pathophysiology

VRS results broadly from distention of the vaginal wall, due to trauma associated with vaginal childbirth or as a consequence of the aging process. This distention leads to a cascade of cellular changes that ultimately weaken the musculature and impact protein and collagen metabolism, thus resulting in patient morbidity.

Vaginal wall distention results in disruption of the normal structure and metabolic processes in the musculature and exerts its effects at the cellular level, the most pronounced of which is its effect on the expression of matrix metalloproteinases (MMPs), bone marrow cells, and elastase enzymes, expressed predominantly in connective tissue [29]. The increased expression of MMP-2 and MMP-9 associated with vaginal wall distention hastens the destruction of elastin, a protein important to maintaining the spring-like characteristics of collagen and connective tissue and whose destruction is caused by the release of MMPs. One of the key features of collagen as a connective tissue is its ability to return to its original shape following stretching. Elastin damage reduces this ability to rebound from stretching and is a key pathophysiological event in VRS.

The vaginal tissue structures—the mucosal walls and muscle tissue itself—are composed of a network of cells and extracellular matrix (ECM) that constitute the architecture of the organs themselves. The ECM is composed of fibres of multiple proteins, including collagen and elastin. Collagen protein is constructed as a triple helix, with individual chains connected via hydrogen bonds, providing an elastic, resilient property to the individual chains. These chains aggregate and form fibrils: larger collagen fibres possessing spring-like tensile properties. This spring-like quality is lost when collagen is stretched and damaged, such as in VRS. One of the ways to improve this condition requires tightening of the collagen fibres to restore their original shape and elasticity. To accomplish this, the ECM of protein fibres and the fibres themselves must be tightened. Energy-based technologies that heat the vaginal tissue to accomplish ECM tightening have shown encouraging results; this mechanism of action is discussed further in the review.

Estrogen receptors have also been identified in the pelvic floor musculature and tissue and are susceptible to the estrogen deprivation that can occur in menopause [30]. As a result of this deprivation, vaginal wall connective tissue components—collagen, elastin, and smooth muscle—all degenerate [31]. The vaginal epithelium then becomes less cellular and thinner, and glycogen production, which is responsible for vaginal secretion, gradually declines and then comes to a complete halt [32]. Blood flow to the vagina is also reduced, which is associated with decreased fluid secretion during sexual arousal, thus increasing susceptibility to trauma and pain during intercourse. These changes produce a variety of symptoms, most notably vaginal dryness.

Viable Treatment Modalities

Modalities such as laser and light therapy, heat and cold therapies, and therapeutic vibration are staples of musculoskeletal treatment, being routinely used to treat a wide range of injuries; including sports injuries, repetitive strain injuries, chronic strains, and sprains. These modalities have proven themselves effective at decreasing inflammation and pain, and encouraging healing [33-38]. Based on their success in these fields, these modalities have been evaluated for use in other injuries rooted in soft tissue damage. PFDs are a prime candidate for the application of these modalities, as the pathophysiology underlying this condition mirrors that of other musculoskeletal and soft tissue conditions [39, 40].

The Effect of Low-level Light Therapy on Tissue

Photobiomodulation—the process whereby the application of light energy modifies the metabolic activities of tissue cells—is an important and increasingly utilized concept in health care, with applications in a wide variety of conditions and injuries. Low-level light therapy (LLLT) as a treatment modality has been used extensively in rehabilitation, based on its ability to induce healing in damaged tissue by affecting processes at the cellular level [38]. With the additional benefits of being non-invasive and painless, non-coherent light-emitting diodes (LEDs) have been increasingly used to stimulate cellular function in recent years. They have been the subject of ongoing research in the field of dermatology, from skin rejuvenation to acne and hair regrowth, and with more serious diseases from neurological conditions such as traumatic brain injury, stroke, spinal cord injury, degenerative central nervous system disease, acute human stroke patients, and severe wound healing [33].

LLLT has become an increasingly common and effective treatment for soft tissue injuries and repetitive strain injuries. Central to the use of LLLT in treating these injuries is its ability to decrease both pain and inflammation while also promoting healing. This contention is supported by a number of recent systematic reviews and meta-analyses that have demonstrated the clinical effectiveness of LLLT in addressing these conditions. *Huang et al.* [36] evaluated seven clinical trials examining the effectiveness of LLLT for treatment of chronic low back pain and found a significant decrease in reported pain scores across all studies when compared with placebo groups. Similarly, a comprehensive review of passive physical modalities in the treatment of motor vehicle accident injuries found LLLT to be an effective method of treatment, noting specific improvements over placebo in subacromial impingement syndrome [41] and extremity injury [42]. Finally, *Enwemeka et al.* [34] noted significant improvements in pain level (d=+1.11; n=9) and tissue repair (d=+1.81; n=46) in a meta-analysis of 34 clinical trials, observing positive effect sizes for collagen formation (d=+2.78), rate of healing (d=+1.57), tensile strength (d=+2.13), and time needed for wound closure (d=+0.76), reflecting the value of LLLT as an effective treatment modality.

While the precise biochemical mechanism responsible for the healing potential of LLLT is not fully understood, the body of anecdotal and basic science evidence continues to grow [33]. There has also been a level of skepticism around the use of LEDs versus lasers, as LEDs are also used as low-power indicator lights for electronic devices. But as *Karu et al.* concludes, to date there is vast statistical material that has been amassed proving that light has a positive effect, and there is no significant difference in cell stimulation regardless of whether the light used was generated by a laser or an LED [43] provided the dosimetry parameters of the LED (wavelength, power density, energy, and treatment time) are optimized for therapeutic use. Lasers are used to cut, burn, or coagulate tissue to induce a healing response in the tissue, whereas LLLT from LEDs conversely triggers the upregulation of cellular function, allowing cells to accelerate their natural healing response. And because the light is diffused and does not cut, burn, or coagulate tissue like lasers do, the LLLT delivered through LEDs is associated with no known adverse effects [35, 37].

What is universally believed is that light-energy from LEDs at the right dosimetry parameters produces photochemical reactions at the cellular level, specifically cell membranes, cellular organelles, and enzymes. Evidence indicates that LLLT acts on the mitochondria [44] to increase adenosine triphosphate (ATP) production [45], in addition to the induction of various transcription factors [46]. Ultimately, LLLT causes increases in protein synthesis that triggers increased cell proliferation and migration, as well as modulation of growth factors, inflammatory mediators, and increased tissue oxygenation [33]. This combination of cellular effects is the cornerstone of the ability of LLLT to induce healing and repair at the cellular level.

Regarding connective tissue, LLLT appears to also affect fibroblasts by stimulating their proliferation, migration, and collagen synthesis. Light in the deep red spectrum, including some near-infrared portions, also prevents apoptosis, modulates inflammatory and antioxidant responses, and stimulates angiogenesis and tissue repair.

The Effect of Heat on Connective Tissue

The application of heat has a twofold effect on connective tissue. On a macro-tissue level, heat increases blood flow and metabolic rate, while on a micro-tissue level, heat can cause dimensional changes in the collagen molecule itself [47].

The application of heat is a mainstay in the treatment of musculoskeletal disorders and is used extensively in the treatment of a wide variety of musculoskeletal injuries [48-51]. While cold is often used in the more acute stages of injury to minimize inflammation and to decrease pain, heat is often incorporated in the later stages, once the inflammatory process has diminished and the healing process has begun. For heat to induce physiological changes and be effective as a healing modality, the connective tissue temperature must be raised to 40° to 42°C [52]. The key effects of heat application to connective tissue remain the increase in blood flow, microcirculation, and increased metabolism, factors that are central to the healing process. But at the micro-tissue level, the application of heat at the target temperature of 40° to 42°C takes advantage of the highly heat soluble nature of collagen bonds [53], allowing the elevation of tissue temperature to be used to denature these bonds and increase tissue extensibility [54]. The predominant effect of heat at the micro-tissue level is the denaturing of proteins. Denaturing refers to the process by which the normal structure of a protein is destroyed via chemical, physical, or other means. Tightening the ECM is commonly accomplished by denaturing the fibres, resulting in their separation and reformation into the native orientation and structure. This process is critical to healing of connective tissue, specifically collagen, which is structured as random coils of collagen fibrils when at body temperature [55]. When exposed to temperatures slightly above body temperature, however, the random coil configuration changes to a more linear configuration, reflecting the denatured collagen protein. The properties of reformation and tightening are directly related to the maximum temperature to which the proteins are exposed. This is an important consideration, as the ability of collagen to denature at low temperatures (40° to 42°C) allows for it to denature and reconfigure locally, imparting elasticity and strength upon the collagen fibres.

The Effect of Vibration on Tissue

Vibration has wide-ranging effects on the human body. Whole-body vibration as a treatment modality has been proposed for conditions ranging from low bone density (the hallmark of osteoporosis) to obesity [56-62]. The common theme with these applications is the effect that the mechanical stimuli associated with vibration has on tissues, specifically at the cellular level. Manipulation of these properties has seen whole-body vibration therapy used to improve muscle strength, balance, and flexibility [63]. Connective tissue is no exception to this cellular effect, making vibration therapy a key consideration when addressing the pathophysiology of VRS.

The key effects of vibration therapy on connective tissue center around its effects on a variety of cell types, most importantly fibroblasts, which are integral participants in the process of remodelling the ECM [64-68]. Two ECM glycoproteins, tenascin and collagen XII, are specifically expressed in areas of high mechanical strain. Tenascin appears around healing wounds and is part of the control response involving another protein important in collagen binding, fibronectin [69]. Vibration therapy takes advantage of the body's reaction to mechanical stress, a state in which higher levels of tenascin and collagen XII are produced by fibroblasts attached to strained collagen, as compared with relaxed collagen.

Vibration has also been shown to have a number of other effects on various tissues. It is known to affect the production of proteoglycans, important primary proteins found in connective tissue and cultured chondrocytes [70]. As well, in female athletes preconditioned with low-magnitude vibration (8-10 Hz) [63], myofibril formation and collagen type I expression have been shown to increase significantly [71]. Increases in collagen type I gene expression by a factor of 3-4 and significant increases in B-actin expression have been noted [71]. Expression of myoD, a master regulator protein in the early and terminal differential stages of myogenesis, has also been observed to increase by a factor of 7 when cells are exposed to vibration [71]. These alterations were paralleled by changes to the muscular structure itself; with myotube number, length, area, and fusion rate all increasing by similar orders of magnitude when cells were exposed to vibration.

vSculpt as a Treatment for PFDs

This body of clinical evidence supports the conclusion that these modalities—LLLT, heat, and vibration—can be used for the treatment of PFDs. As such, vSculpt is a new OTC medical device uniquely combining these modalities to promote vaginal muscle and tissue regeneration and repair.

vSculpt incorporates therapeutic LED lights that generate gentle heat and emits light energy in a spectrum range (662 to 855nm) sufficient to prevent apoptosis and cell death while stimulating collagen synthesis and fibroblast proliferation and migration, modulating inflammatory and antioxidant responses and stimulating angiogenesis; upregulation of muscle, nerve and connective tissue cells, and tissue repair; and increases blood flow and micro-circulation. While vibration acts as mechanical stimuli on the tissue to improve muscle tone, it also induces a pleasure response that makes the therapy comfortable, ensuring women stay compliant with their therapy.

vSculpt addresses the key processes required for musculature and connective tissue healing with modalities that have been clinically proven to be efficacious, offering a new and innovative treatment option for women suffering from VRS and VA.

Early Clinical Results

The vSculpt device has been the subject of a pilot study that has shown positive results (data on file). Twenty-four women aged 30-55 used vSculpt over the course of 60 days and completed the clinically validated Female Sexual Function Index (FSFI) QoL questionnaire and a Joylux questionnaire at days 1, 7, 30, and 60. Primary outcomes included perceived vaginal tightness, bladder leakage, vaginal lubrication, and intercourse-associated pain. At study's end, significant improvements were noted in all outcomes. Eighty-percent (80%) of study subjects reported that their bladder leakage decreased after 30 days and 90% of subjects after 60 days (p<0.001). Perceived vaginal tightness similarly improved, with 80% of subjects reporting improvements after 30 days and 95% reporting improvements after 60 days (p<0.001). Vaginal dryness and intercourse-associated pain also improved significantly, with 91% and 89% (respectively) of

women reporting improvements after 60 days of use. Importantly, no adverse events or complications were noted during the pilot study or follow-up period. Building on the findings from this pilot study, a larger clinical study of 50 women was designed to further investigate the safety and efficacy of the device with both subjective and objective end-points. The results of the study will be released in October 2016.

Conclusion

Decreased vaginal tissue and muscular function is essentially a result of damage to the vagina at a nerve, muscular, cellular, and connective tissue level caused primarily by pregnancy and aging.

While a wide variety of treatments are available to address the symptoms of VRS and VA, the general lack of a simple, effective, and affordable treatment leaves a large gap in the treatment options available for women suffering from these difficult conditions. Given the effectiveness of LLLT, heat, and vibration in inducing changes at the cellular level and promoting tissue healing with other health conditions, there is considerable promise in manipulating these characteristics to provide a treatment option for PFDs in general. vSculpt provides an opportunity for a home-use device that is simple to use, effective in providing both relief and healing, and is affordable for the patient. The early clinical results support an ability to improve quality of life, the primary treatment goal of the vSculpt device. While the larger clinical study results have not yet been released, early indications are that vSculpt is a worthwhile non-invasive treatment option for women suffering from VRS and VA.

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