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Minimal invasive procedures for the treatment of genitourinary syndrome of menopause (GSM). Un update

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Abstract

Genitourinary syndrome of menopause (GSM) is a new term for a condition more renowned as atrophic vaginitis. It is used to describe a variety of menopausal symptoms and signs that are related to the physical changes of the vulva, vagina and lower urinary tract. The etiology of GSM is secondary to decreased levels of endogenous estrogens and represents a common but underreported condition. In this update we present novel minimal invasive procedures that may benefit GSM symptoms making particular focus on platelet-rich plasma (PRP) treatment, hyaluronic acid (HA) treatment and energy-based devices (CO₂ laser, YAG laser, radiofrequency device and high intensity focused ultrasounds).

Currently, PRP has becoming popular as a non-operative treatment option for GSM symptoms. The principle underlying PRP treatment has to do with its ability to reproduce natural mechanisms of cell regeneration through the sequential secretion of numerous growth factors. Moreover, HA has been widely used as an important ingredient in topical hydrating and lubricating gels or injected for conditions such as dyspareunia. Lately, it has also been used as a new tool to treat age-related fat lysis of the female genitalia and especially the labia majora. The Energy based devices have been recently suggested for the management of GSM. They utilize technologies such as laser, electromagnetic waves and high intensity focused ultrasounds to focus energy in the vaginal wall heating the targeted tissue at various depths without causing any pain or needing a recovery time. These minimal invasive procedures appear to be promising options for the treatment of GSM symptoms. However, further studies are necessary to evaluate more thoroughly the effectiveness and safety of these procedure and assess medium and long term results.

Key words: GSM, Laser, Hyaluronic acid, PRP, Dyspareunia, Vaginal atrophy.

Introduction

Genitourinary syndrome of menopause (GSM) is a new term for a condition more renowned as atrophic vaginitis. It is used to describe a variety of menopausal symptoms and signs that are related to the physical changes of the vulva, vagina and lower urinary tract¹. The GSM includes genital (dryness, burning, irritation), sexual (lack of lubrication, discomfort, dyspareunia) and urinary symptoms (urgency, dysuria, recurrent urinary tract infections)¹.

The etiology of GSM is secondary to decreased levels of endogenous estrogens² and represents a common and underreported condition due to sexual embarrassment or general disregard due to associating it as a liability of natural aging². The syndrome or its features manifest in approximately 15% of premenopausal³ and 40-54% of postmenopausal women⁴.

Clinicians play a major role in recognizing the signs of GSM because many women are reluctant to report their symptoms. GSM is most commonly diagnosed when the patient presents with dyspareunia⁵. In fact when the vulvo-vaginal epithelium is inadequately lubricated, ulceration and fissures may develop during intercourse, causing dyspareunia secondary to vaginal dryness. Vaginismus, or painful spasm of vaginal muscles, can also occur as a physiological response when there is anxiety toward expected sexual pain⁵.

The symptoms of GSM are particularly bothersome and usually require intervention, as vaginal health represents an essential component of active and healthy aging in women at midlife and beyond. In the literature, various hormonal products or vaginal lubricants or moisturizers are used in order to relieve patient's symptoms⁵. In this update we present novel minimal invasive procedures that may benefit GSM symptoms making particular focus on platelet-rich plasma (PRP) treatment, hyaluronic acid (HA) treatment and energy-based devices (CO₂ laser,

YAG laser, radiofrequency device and high intensity focused ultrasounds).

Platelet-rich plasma (PRP) treatment

PRP is an autologous solution of human plasma that has an increased content of platelets (4-7 times the baseline concentration)⁶. The principle underlying PRP treatment has to do with its ability to reproduce natural mechanisms of cell regeneration through the sequential secretion of numerous growth factors (platelet-derived growth factors, transforming growth factors b, epithelial growth factors, vascular endothelial growthfactor, insulin-like growth factor, basic fibroblast growth factors), which modulate cell proliferation, differentiation, angiogenesis and chemotaxis⁷⁻⁹.

The PRP preparations can be classified according to the preparation method and the content of the PRP sample. Preparations vary in terms of centrifugation speed, centrifugation time, and anticoagulant use, while the content varies depending on the predominant constituent (e.g., platelets, leukocytes, or growth factors)¹⁰⁻¹¹.

Currently, PRP has becoming popular as a non-operative treatment option for a broad spectrum of gynecological disorders. Based on the experience of using PRP to improve smoothness and to decrease wrinkles in the facial area¹²⁻¹³, aesthetic practitioners have also used PRP for the regeneration of the vaginal mucosa and skin in patients with vaginal atrophy and symptoms of dyspareunia. Following PRP injection, vaginal vascularity seems to increase with a subsequent improvement of sexual function. In addition, the mucosa becomes thicker and firmer, making the vagina look much more youthful¹⁴⁻¹⁵.

A few pilot studies concerning GSM treatment using PRP have reported promising findings¹⁵⁻¹⁷. Kim et al¹⁵ reported the use of autologous lipofilling mixed with PRP in a 67 year-old patient with vaginal atrophy. A total of 40 cc of autologous fat mixed with

PRP was transferred to labia majora. Lipofilling with PRP relieved symptoms, restored contour of the labia majora and achieved remission of lichen sclerosus on labia minora. Regarding use of PRP in sexual function improvement Runels et al¹⁷ injected PRF in clitoris and vagina of 11 women aged between 24-64 with female orgasmic disorder, hypoactive sexual arousal disorder, anorgasmia or dyspareunia. 71% of the study population improved their status from being “distressed” to being “not distressed” after the procedure, while two patients (18%) showed no change in their levels of distress.

In conclusion, PRP is an innovative, affordable and easily performed therapeutic modality, which has been recently studied in women with various urogenital disorders. Although the specific mechanisms of action of PRP have not been completely elucidated, various studies have shown that the high concentration of growth factors in PRP may potentially initiate inflammatory reactions and promote the healing process¹⁰⁻¹¹. Efficacy appears promising and the risks of PRP therapy seem to be minimal. However, evidence is based on a few low-quality pilot studies¹⁵⁻¹⁷, case reports and anecdotal series, including only a small number of patients and with a short-term follow-up. Randomized controlled studies based on validated objective and patients reported outcomes are urgently required to confirm its efficacy and safety.

Hyaluronic Acid (HA) treatment

HA is a high-molecular-weight anionic polymer. It is a member of the non-sulfated glycosaminoglycan superfamily, and its structure is based on the linear repetition of disaccharide sequences¹⁸. It is naturally present in many tissues and plays important physiologic roles in living organisms, including maintenance of the viscoelasticity of liquid connective tissues and control of tissue hydration, especially in the dermis, mucous membranes, and submucosal tissue layers¹⁸.

In gynecology, HA has been widely used as an important ingredient in topical hydrating and lubricating gels or injected for conditions such as dyspareunia. Lately, it has also been used as a new tool to treat age-related fat lysis of the female genitalia and especially the labia majora¹⁹⁻²⁰. The labia majora are anatomic structures primarily dedicated to protection and shock absorption and therefore labia majora fat is different from facial fat. Thus injected HA gel characteristics should be adapted to this specific environment to prevent product migration after the treatment¹⁸. In Europe, only one product (Desirial Plus, Vivacy) has been clinically tested and received approval for this very specific indication.

In the literature there are several studies suggesting that HA may be useful in the treatment of GSM symptoms. However, these studies are small and lack rigor. Aguilar et al¹⁹ presented a case of a 39 years old woman who had vaginal laxity resistant to physical therapy, a retractile episiotomy scar and a slightly atrophic vaginal mucosa. She was treated with injection of purified fat cells in the posterior vaginal wall and PRP-HA solution in the perineum focusing in the episiotomy. During the follow-up period the authors observed an improvement of the patients sexual life and vulvoperineal rejuvenation. Moreover, Hersant et al¹⁶ studied the efficacy of PRP combined with hyaluronic acid for the treatment of vulvovaginal atrophy in postmenopausal women with history of breast cancer. All participants (20 women) showed improvement in the clinical symptoms of vaginal dryness and dyspareunia. Improvement in hydration and vaginal epithelial integrity was reported. No adverse events were reported. The authors concluded that the injection of PRP combined with hyaluronic acid is a promising method to improve the trophicity and hydration of vaginal mucosa in postmenopausal breast cancer survivors with contraindications to hormone therapies.

Energy Based Devices

Energy based devices have been recently suggested for the management of GSM²¹⁻²⁶. They utilize technologies such as laser, electromagnetic waves [Radiofrequency (RF)] and high intensity focused ultrasounds (HIFU) to focus energy in the vaginal wall heating the targeted tissue at various depths without causing any pain or needing a recovery time²¹. The principle of these treatments is the induction of neocollagenesis, vascularization, lubrication and tightness of vaginal structures²¹. However, there is an FDA warning regarding all these devices because they have not yet obtained an FDA approval for vaginal rejuvenation and there is ongoing research on this field²⁷.

Lasers

Lasers were the first to come out with many published studies in PubMed evaluating their safety and efficacy using objective and subjective outcomes²⁵⁻⁴⁷. There are 2 types of laser-devices; the CO₂ and Er:YAG devices²¹. These 2 laser types differ in wavelength, fluence, duration of the laser pulse, spot size and penetration depth²¹. The standard treatment protocols are 3 laser-sessions at monthly intervals for both laser types. For CO₂-laser this standard protocol may be extended by an additional 4th or even a 5th treatment³⁵. Nevertheless, all studies, regardless of laser type, consistently suggest that a significant improvement in all GSM symptoms and clinical signs is present following laser treatments²⁵⁻⁴⁷. Specifically, dyspareunia, vaginal dryness, itching, burning, dysuria, frequency, urgency and incontinence could be significantly decreased as soon as 1-month after the first laser application⁴⁵⁻⁴⁷. This positive impact of laser treatments was further reflected by improvements in women's quality of life and sexual function^{30,35,38-42,45-47}. It is essential that all aspects of sexual function (desire, arousal, satisfaction, orgasm and lubrication), as assessed by validated patient reported outcomes,

were significantly improved^{30, 35,38-42,45-47}. Specifically, it has been found that following 3, 4 or 5 CO₂ laser-treatments normal sexual function resumed in 41%, 69% and 84% of women respectively³⁵. Moreover, lasers' positive results were maintained for a long-term (up to 36-months)^{30,32,39-41}. In fact, 1-year after the last laser-session, improvements in dyspareunia, vaginal dryness and all aspects of sexual function were the same as 1-month after the last laser session³⁰. The authors suggested that 1-month after the last laser-therapy may be indicative of the GSM symptoms at 12-months and the time point to decide whether treatments' extension should be offered [30]. Randomized controlled trials suggested that CO₂-laser had a similar efficacy as vaginal estrogens in improving all GSM symptoms and a better efficacy than promestriene or lubricants in improving vaginal health^{28,29,33,34}.

Cytological, microbiological and histopathological studies further confirmed the efficacy of laser-treatments indicating that the "placebo effect" is probably not the mode of lasers' action^{37,38,42,48-51}. The pathophysiological changes of the vaginal mucosa resembled to those at premenopausal status. The international Society for the Study of Women's Sexual Health and the North American Menopause Society have suggested that the increased parabasal cells on maturation index and pH values of the vaginal fluid >4.5 are supportive findings of the GSM diagnosis¹. Studies evaluating these 2 aspects following CO₂-laser treatments, found that the vaginal maturation value increased significantly with a profound decrease of parabasal cells, while pH of the vaginal fluid reached values <4.5^{37,38,42}. In accordance, CO₂-laser treatments proved to be beneficial for the vaginal microenvironment, as lactobacilli increased significantly and uropathogens decreased significantly, resulting in a significant increase of women with normal vaginal flora⁴⁸. Moreover, authors of histopathological studies stated that there was a restoration of the vaginal

thick squamous stratified epithelium with a significant storage of glycogen in the epithelial cells and a high degree of glycogen-rich shedding cells at the epithelial surface^{21,49-51}. In addition, they observed active fibroblasts, collagen and ground substance molecules as well as newly-formed papillae of connective tissue and blood capillaries penetrating the papillae providing all the necessary metabolic support^{21,49-51}.

Radiofrequency (RF) devices

RF devices emit within a frequency range of 3kHz to 24GHz generating an electric field that induces collisions and motion among charged and polar atoms and molecules^{21,26}. Energy is transferred to the tissue as heat^{21,26}. RF devices for vulvovaginal application include temperature-controlled devices, cryogen-cooled monopolar devices, multipolar radio frequency-pulse electromagnetic fields devices and focused radio-frequency devices. The mechanism of action and treatments protocols between these RF types differ substantially. For example, the temperature-controlled devices produce a transmucosal heating of the tissue to 40-47^o promoting tightening of the vaginal mucosa at 460 kHz^{21,26}. Three treatments are suggested at 4-6 weeks intervals up to 30 minutes time per area with a maintenance every 6 months^{21,26}. The cryogen-cooled monopolar RF reverse thermal gradient and cools the surface mucosa allowing a high RF energy at 6MHz promoting neocollagenesis^{21,26}. In this RF type of device, one treatment with an annually maintenance is adequate for clinical results to be observed²⁶. The multipolar RF and pulsed electromagnetic fields produce a non-thermal release of tissue growth factors (FGF2) to trigger new collagen synthesis^{26,52}. Only one treatment is suggested but with unknown maintenance time²⁶. The focused RF device requires 2-4 treatments at 2-3 weeks intervals annually with results to be obtained after 4 weeks of treatment²⁶.

Regardless the type of RF device, studies have consistently reported that dyspareunia, vaginal dryness, sexual function (especially arousal and orgasm) and satisfaction, frequency, urgency, incontinence and vulvovaginal tightening may improve significantly following RF treatments^{21,26,53-57}. However, only 6 studies including 120 participants have been published on the field; one of them was randomized placebo-controlled trial. All but 2 studies had a short-term duration; 1 study presented results at 6-months and 1 study at 12-months duration suggesting a sustained positive efficacy.

High intensity focused ultrasound (HIFU)

HIFU bases its action on a focused thermal effect at a certain depth producing cavitation, apoptosis and thermal coagulative microdamage caused by a 60-70^oC temperature. This is a technique originally used in oncology for tumor removal⁵⁸. This action is determined by the concentration of energy emitted by a round and concave ultrasound transducer of 20mm in diameter that directs convergent ultrasonic waves to a specific focal depth according to the position of the transducer crystal. These convergent mechanical waves produce the molecular vibration of the water, which raises the temperature of the tissue and produces its physical modifications⁵⁸.

Manufacturers advocate that HIFU produces a better rejuvenation effect than laser and RF due to its capability to perform a deeper penetration depth into fibromascular layer up to adventitia, while lasers may reach up to lamina propria and RF up to fibromascular layers⁵⁸. Currently there are no published studies evaluating its safety and efficacy in postmenopausal women with GSM.

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