Vulvo-vaginal atrophy as a main symptom of the Genito Urinary Syndrome of Menopause (GSM) is a consequence of aging, particularly after menopause as a result of follicular ovarian follicle depletion and consequently low estrogen levels. Anatomical structures derived from the urogenital sinus, such as the distal urethra trigone and vestibule, are the most affected areas because of the high concentrations of alpha- and beta-estrogen receptors.

The most common symptoms associated with vulvo-vaginal atrophy are dyspareunia, vaginal dryness, irritation, recurrent urinary tract infection and urinary incontinence, which negatively affect the patient’s quality of life and sexuality.

The purpose of this pilot study was to evaluate a protocol with topical growth factors that seeks to activate collagen and elastin at a molecular level, and thus restore all vaginal functions such as secretion, absorption, elasticity, lubrication and vaginal epithelium thickness.
At the end of the reproductive years in women, as a consequence of a lack of estrogen, many ultrastructural modifications of the genital tract lead to the Genito Urinary Syndrome of Menopause (GSM), which affects between 20 and 45% of women. GSM is related to a wide range of uro-gynecological symptoms, such as thickening of collagen fibrils and disorganization of total collagen content, mainly due to decreased collagen I synthesis and increased fibril fragmentation. In addition, aging is associated with increased levels of matrix metalloproteinases, which can break down collagen and elastin fibers, combined with impaired transforming growth factor (TGF-β) signaling, which may reduce collagen deposition.

The main symptoms of GSM are lack of lubrication, itching, a burning sensation, pain, and urinary incontinence, which can have emotional and physical effects on patients and their partners through unsatisfactory sexual relationships (Fig. 1). Restorative treatments are procedures aimed to restore normal function and metabolism to connective tissue. The most important restorative treatment is bio-stimulation, which consists of a series of procedures that biologically activate fibroblast anabolic functions, and particularly enhance the production of type III collagen, elastin and hyaluronic acid from their precursors.

Bio-stimulation is not the same as bio-restructuration, which is the variation of the components of the affected derma to achieve aesthetic improvement, albeit while damaging the physiology of the connective tissue.

Many stimuli can promote bio-stimulation and, as a consequence, elastin fibers, collagen formation, and re-organization of ground matrix, including thermal, biochemical, magnetic, ultrasonic, and pulsed electrical fields (Fig. 2). Of these, the most studied has been the thermal effect of a carbon dioxide laser applied intravaginally, which produces outstanding improvements in vaginal health following collagen and ground matrix remodeling due to the induction of heat shock proteins. The most important pathway for events leading to vaginal epithelial proliferation is the induction of growth factors.

To date, there have been no reports on the role of topical growth factors in patients suffering from GSM. Previous reports have indicated that topically applied growth factors and cytokines can promote skin rejuvenation. Growth factors known to directly affect collagen biosynthesis include platelet-derived growth factor, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), granulocyte-colony stimulating factor, keratinocyte growth factor, and hepatocyte growth factor. Cytokines that affect collagen biosynthesis include TGF-β, interleukin (IL)-6, and IL-8. The application of growth factors to the vaginal mucosa on a regular basis may stimulate re-epithelialization to the same extent as hormone replacement therapy.

However, as signaling proteins, growth factors work at the cell-transcription level to up-regulate sex steroid receptors. They can also induce cellular proliferation, differentiation, and apoptosis without the side effects sometimes reported by patients using topical estrogen therapy (Fig. 3).

Animal models have been used to document the effects of human growth factor cocktails on atrophic vaginal mucosa. Histologic examinations show the restoration of epithelial tissues to a normal state, without stimulation by estrogens.

**MATERIALS AND METHODS**

A pilot study was conducted from April 2018 to June 2018 at the primary Urogynecology Unit Hospital Universitario San Jorge, Pereira, Colombia. Women aged 53 to 66 years, who had attended the Urogynecology unit for at least one year, were invited to participate...
in this study that was approved by the regional ethic review board.

Informed consent was obtained and a written authorization was included in the subjects’ medical records according to the Declaration of Helsinki, the Belmont report, CIOMS rules, GCP/ICH and resolution 008430 of the Colombian government established on 4 October 1993.

This study included 10 postmenopausal women who had exhibited genito urinary symptoms related to Genito Urinary Syndrome of Menopause (GSM) within the previous 24 months, such as a burning sensation, pain, heaviness, and/or dryness, as evaluated by the Gloria Bachman Vaginal Health Index (VHI). The exclusion criteria were non-adequately classified patients, previous surgery, recurrent lower urinary tract infection, BMI > 35, cognitive psychiatric disorders, inability to contract the pelvic floor muscles, and pelvic organ prolapse greater than 2, according to the POP-Q Classification System International Continence Society (ICS). Sexual and quality of life (QOL) impact was evaluated by the Female Sexual Function Index (FSFI).

Each subject was given thrice-weekly applications of growth factors (Recombinant human growth factors, Skin Gen International, Inc., Toronto, Canada) to the vagina and vulva for 12 weeks. Biopsies of the vagina were obtained before and after 12 weeks of growth factor treatment. The vaginal samples were subjected to basic and special histological studies performed by a blinded pathologist to identify trophic changes after treatment. The pathologist used both Hematoxylin and Eosin (H&E) and modified Masson’s trichrome staining.

**Primary Outcome**
- Clinical changes related to vaginal atrophy as evaluated by clinical examination, and changes in the VHI and FSFI scores.

**Secondary Outcomes**
- Cosmetic improvement of the vulvar and perineal area as evaluated by a Vulvar Symptoms Questionnaire (VSQ).
- Treatment satisfaction as evaluated using a visual analogue scale (VAS) from the baseline conditions to the end of treatment.

**Data Analysis**
Statistical analysis was performed using SPSS 11.5.1 (SPSS Inc., Chicago, IL, USA).
All 10 subjects completed the protocol (Table I). Important clinical and histological changes were seen during the 12-week course of treatment. All of the subjects who were treated with topical growth factors showed improvements according to scores on the visual analogue scale (VAS) and vaginal health index (VHI). All patients reported high satisfaction with the results regarding symptoms related to GSM as well as cosmetic improvement in the labia majora and perineal area. No side effects were reported by any of the subjects (Table II).

Upon clinical examination at the end of the treatment period, the quality and trophism of both the vaginal mucosa (Fig. 4) and the vulvar skin and perineal area (Fig. 5) showed dramatic changes. The histological studies showed an important recovery of vaginal tissue (epithelium and stroma) in the treated areas (Figs. 6, 7).

The present results with the application of topical growth factors suggest that this treatment is safe and tolerable and can offer patients an important means to counteract vaginal atrophy in GSM. Future studies should include a longer follow-up and a larger population to corroborate our findings.

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