JOURNAL OF CLINICAL CASE STUDIES, REVIEWS & REPORTS

Research Article

Volume 2 | issue 2

Management of the Genitourinary Syndrome of Menopause One Decade After Its Description

Victor Manuel Vargas Hernandez

Department of Gynecologic Oncologic, Reproductive Medicine, Academia Mexicana de Cirugía, Academia Nacional de Medicina de México

***Corresponding Author:** Victor Manuel Vargas Hernandez, Obstetrics and Gynaecology, Department of Director of Women's Health Clinic, Insurgentes Sur 605-1403, Nápoles 03810, Mexico. Tel No: 55746647, Cel No: 5552179782.

Submitted: 12 Feb 2024 **Accepted:** 17 Feb 2024 **Published:** 23 Feb 2024

Citation: *Victor Manuel Vargas Hernandez (2024). Management of the Genitourinary Syndrome of Menopause One Decade After Its Description. J of Clin Case Stu, Reviews & Reports 2(2), 1-13.*

Abstract

Background: *genitourinary syndrome of menopause (GSM), term includes all symptoms and signs caused by changes in the bladder, urethra, vagina and vulva; such as dryness, burning sensation or discomfort; sexual symptoms, such as pain due to decreased lubrication and urinary symptoms such as dysuria and recurrent urinary tract infections or urinary urgency due to progressively decreasing estrogen levels chronically and requiring treatment.*

Methods: *A review of the evidence was carried out, with a search in PubMed between January 2020 and 2023 Including 71 items in PubMed/MEDLINE, Cochrane Library, EMBASE, Google Academic, using the words dyspareunia, dryness, hormonal therapy, non-hormonal therapy and alternatives. management for GSM. A total of 67 articles in English were reviewed.*

Results: *Management is guided by the patient's symptoms; initial therapy is with non-hormonal vaginal moisturizers and lubricants, low-dose vaginal estrogen, dehydroepiandrosterone or prasterone or testosterone or ospemifene are indicated; Even in patients with breast cancer, the risk of recurrence is not increased.*

Conclusions: *Initial therapy for GSM is non-hormonal vaginal moisturizers and lubricants; If they do not respond, hormonal therapy with vaginal estrogen is indicated.*

Keywords: Atrophy, Hormonal Therapy, Cancer, Non-Hormonal Serm Management, Laser, Menopause

Background

Vulvovaginal atrophy (VVA) is the result of the loss of estrogen and is associated with vulvovaginal symptoms (dryness, burning, dyspareunia mainly), urinary frequency and recurrent urinary infections also occur; after menopause. In 2014, the new term genitourinary syndrome of menopause (GSM) was introduced, more descriptive and broad of genitarian, urinary and sexual alterations, add articles table 1; covers all VVA and bladder-urethral symptoms due to estrogen deficiency and Figures 1 and 2, table 2; add that it requires long-term treatment, not only to relieve symptoms, but to restore the effects of urogenital atrophy due to estrogen deficiency, which causes sexual dysfunction, postcoital hemorrhage, and recurrent urinary tract infections [1,2].

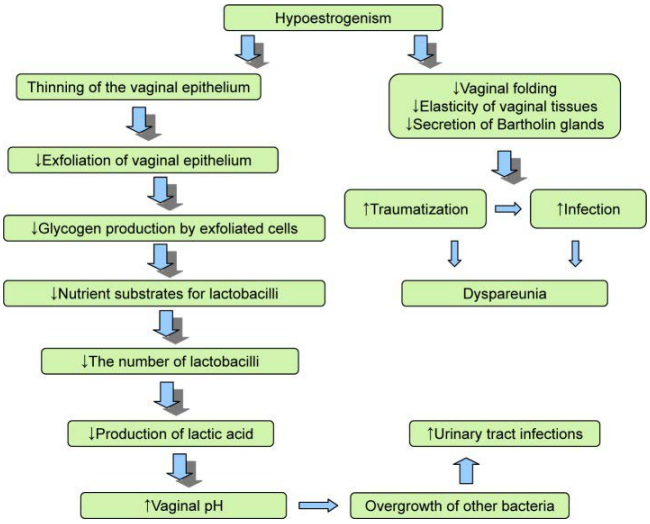

Figure 1: Cascading effects of the VVA mechanism. The vaginal epithelium is a stratified squamous epithelium, which until menopause is moist and thick with rugae. At menopause, with declining levels of estrogen, the vaginal epithelium thins. Fewer epithelial cells result in less exfoliation of cells into the vagina. As epithelial cells exfoliate and die, they release glycogen, which is hydrolyzed to glucose. Glucose, in turn, is broken down into lactic acid by the action of lactobacillus, a normal vaginal commensal organism. Without this cascade, the pH in the vagina rises, resulting in a loss of lactobacilli and an overgrowth of other bacteria, these bacteria can cause symptomatic vaginal infections and inflammation. After menopause, the elasticity of the vagina is reduced and connective tissue increases.A decline in estrogen level causes a decrease in vaginal blood flow and a decrease in vaginal lubrication. These changes can be reversed by the use of estrogens.

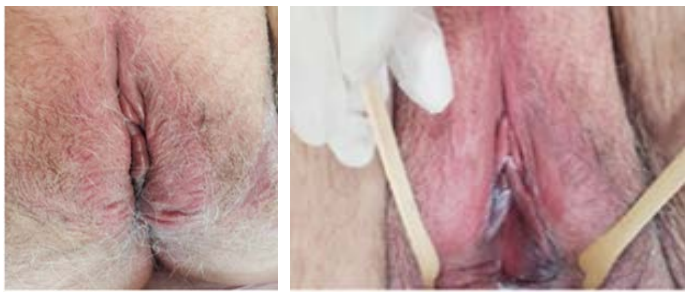

Figure 2: Vulvar During Menopause

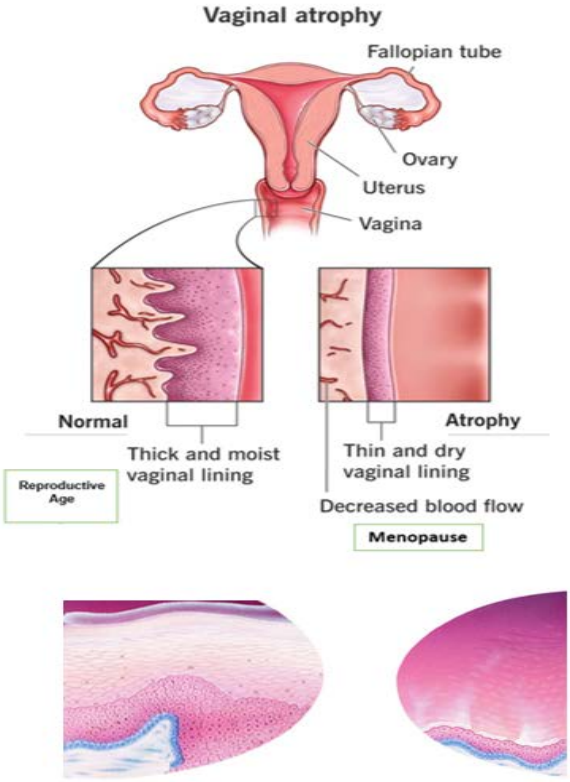

Figure 3: Atrophic genital epithelium in menopause and mature genital epithelium in reproductive age. A typical vaginal lining consists of healthy tissue that is thick and moist. With vaginal atrophy, this tissue becomes dry and thin with less blood flow to the area.

Management of Genitourinary Syndrome of Menopause

Treatment options include hormonal and non-hormonal interventions, the main indication for the treatment of GSM is to relieve vulvovaginal symptoms; Although, many patients do not seek medical attention for these problems (due to embarrassment, cultural, religious or social beliefs, or lack of knowledge about safe and effective treatments, many doctors do not ask their menopausal patients about these symptoms [3-5]. GSM negatively impacts quality of life and affects 15 to 55% of postmenopausal women; although, the real prevalence is higher, because the majority of women do not seek medical help [1-4,5]. First line are usually non-hormonal vaginal moisturizers and lubricants, lifestyle modifications and laser add If first line therapies do not provide adequate symptom relief, menopausal hormone therapy (MHT) with estrogen therapies (ET) is indicated or other hormonal medications for patients without contraindications for their use [6-8]. The majority of patients with GSM achieve adequate symptom relief with vaginal ET, but there are other therapeutic alternatives, such as physical therapy or vaginal dilators, for refractory symptoms or if hormonal therapy is contraindicated [9-12]. Add The vaginal microbiota is a dynamic variable system of a variety of bacteria, the balance of which provides vaginal homeostasis. The production of lactic acid, as a result of bacteria, ensures the maintenance of the optimal low pH of the vaginal fluid, thus protecting against infections of the urogenital tract. The low pH of vaginal fluid is also maintained by active proton transport by the vaginal epithelium formed due

to anaerobic glucose metabolism mine look figure 1-3, until you find one that meets your needs at an appropriate cost [1-6]. Vaginal moisturizers are designed to be used routinely, generally two or three days a week, not only during sexual activity, and lubricants are used only at the time of sexual activity, these are water-based, and are usually bioadhesive. Hyaluronic acid is often used as a key ingredient in vaginal or oil-based moisturizers.

Moisturizers such as preservative-free lubricants are effective as vaginal ET, for vaginal dryness and restoration of normal vaginal pH [13,14]. The use of a vaginal moisturizer, lubricant, and regular sexual intercourse help in treatment; Women are recommended to avoid systemic MHT use; but vaginal ET is more effective; There are a variety of different vaginal estrogen compounds, doses, and routes of administration, including estriol cream and pessary, estradiol tablets, vaginal ring, and conjugated equine estrogens (CEE) cream. The choice between different treatments with local estrogens depends on the severity of the symptoms and the patient's preference.

In postmenopausal breast cancer (BC) survivors with VVA, a gel with added lactic acid (pH 4.0) decreased vaginal irritation, dryness, and dyspareunia compared to a gel without lactic acid (pH 7.2) the patient should be evaluated for other etiologies of vaginitis [1-6]. In persistent symptoms, vaginal ET is a common second-line treatment for GSM that does not respond adequately to moisturizers and lubricants. Some GSM urinary tract symptoms improve with vaginal ETs, including frequent urinary tract infections, urinary frequency and urgency without infection, but urinary incontinence usually requires other modes of treatment; Vaginal dehydroepiandrosterone (DHEA) or oral testosterone and ospemifene are available for the treatment of GSM. or laser surgery; This safety and effectiveness is uncertain [7].

Prasterone is an inactive precursor that is converted to estrogens and androgens in vaginal tissue; it has positive effects on VVA through activation of vaginal androgen and estrogen receptors. Intravaginal administration of 6.5mg of prasterone is effective for postmenopausal women affected by GMS.

Low-dose vaginal ET is the most effective treatment for moderate to severe VVA symptoms unresponsive to non-hormonal intervention leads to restoration of normal vaginal acidic pH and microflora, thickening of epithelium, increased vaginal secretions, decreased vaginal dryness and dyspareunia, with benefits for the urinary tract, including reduced incidence of urinary tract infections and overactive bladder symptoms [15-18]. Plasma estradiol levels from vaginal ET absorption have not been sensitive enough to measure low serum estradiol levels in menopausal patients when measuring compounds other than estradiol, a higher level of absorption with initial ET is due to the greater absorption of estrogens through the thin atrophic vaginal epithelium. In patients using the low-dose vaginal ring, it releases higher doses of estradiol during the first 24 hours of use. Low-dose vaginal ET is the option for some patients with estrogen-sensitive cancers; for example: endometrial cancer (EC), breast cancer (BC) that fail non-hormonal treatments; but it requires discussion of shared risks and benefits of the patient and doctor [19,20]. There are no data to support abstention from coital activity for a specific period of time after vaginal TE use [14]. Exposure of a male partner to vaginal TE cream during sexual intercourse is rarely clinically significant [1-6,19,20]. vaginal estrogen cream, tablet, capsule, ring preparations are conjugated estrogens (cream) and estradiol (cream, tablet, capsule and ring); others available in creams or estriol suppositories, inserts and rings were equally effective in relieving VVA symptoms. The vaginal ET preparations with the lowest systemic absorption are the standard regimens of 4mcg or 10mcg estradiol tablets or capsules and the 7.5mcg/day estradiol ring [21,22].

Low-dose vaginal ET is defined as ≤ 50mcg of estradiol or ≤ 0.3mg of conjugated estrogens (in ≤ 0.5g of cream). Other doses are considered higher dose preparations of conjugated estrogen cream (≥ 0.625mg in 1g of cream) and vaginal estradiol cream (>1g). The silastic ring impregnated with estradiol locally to the vagina [23-26]. The ring is designed to release 7.5mcg of estradiol into the vagina daily for a period of 90 days, at which time the patient or doctor replaces it with a new ring [26]. Serum estradiol levels with use of the low-dose ring, 7.5mcg/day, are 5 to 10pg/mL serum estradiol [9,22,24-28]. The other vaginal ring releases much higher doses of estradiol (50 to 100mcg per day) and is considered systemic rather than local vaginal ET; in postmenopausal patients who initially received 0.5g of conjugated estrogen daily intravaginally, where superficial cells are reported in cytology similar to normal premenopausal patients. Conjugated equine estrogens (0.625 mg/1 g of cream; doses range between 0.5 and 2 g of cream; equivalent to 0.3 to 1.25 mg of conjugated estrogens [21-28].

The recommended regimens for VVA are: ET of 0.5 to 2g of cream administered intravaginally in a continuous (twice a week) or cyclical regimen (daily for 21 days and then rest for 7 days). Estradiol (100mcg estradiol/1 g cream), doses vary from 0.5 to 4g cream. This is equivalent to 50 to 400mcg of estradiol; 200mcg of estradiol cream results in a serum estradiol level of 40pg/mL [29,30]. Using 0.5g of estradiol cream, 2 to 4g of intravaginal cream daily for one to two weeks, maximum doses of various forms of vaginal creams indicated produce premenopausal plasma levels of estradiol (premenopausal estradiol ranges between 40 and 600pg/mL , depending on the phase of the menstrual cycle). Estriol is the 16-hydroxylated metabolite of estradiol; in vulvar and vaginal tissues, estriol is a weak estrogen agonist and does not require opposing progestin: for patients with GSM, low-dose vaginal ET, a progestin (progestogen or progesterone) is generally not indicated to protect against hyperplasia endometrial (HE) or EC [31,32]. Use the 10mcg estradiol insert daily for two weeks and then twice a week for 52 weeks [19,31-33]. The duration of higher-dose vaginal ET or systemic ET should be guided by the risks and benefits. The preference for vaginal ET is based on its superior efficacy for GSM symptoms and the risks of systemic menopausal hormone therapy (MHT): there are alternative hormonal medications other than estrogen that are used to treat GSM. Vaginal Dehydroepiandrosterone (DHEA) may result in less estrogen exposure, but there appears to be an increase in serum estrogen levels even with this formulation, improving libido. Oral ospemifene, a selective estrogen receptor modulator (SERM), option for patients who prefer oral medications or who cannot insert a vaginal medication. Some doctors prescribe vaginal testosterone with the simultaneous goal of treating loss of libido [1-6].

Disadvantages of ospemifene compared to vaginal ETs are the

need for daily use and systemic side effects; vasomotor symptoms (VMS), potential risk of venous thromboembolism (VTE). The safety of ospemifene has not been demonstrated in patients with a history or high risk of BC or in patients at high risk of VTE. Ospemifene is effective in the treatment of dyspareunia and vaginal dryness in menopausal patients with VVA compared to placebo. VMSs are the most common adverse effect of ospemifene. Ospemifene causes an increase in endometrial thickness (0.4 to 0.7mm in 12 weeks); after one year of use, no cases of atypical HE or EC have been found [34-37]. Thrombotic adverse effects are a potential risk with SERMs.

Vaginal DHEA (or prasterone), a treatment option for dyspareunia associated with GSM, is effective, but is associated with a slight increase in circulating levels of DHEA, testosterone, estrone, and its effectiveness has not been directly compared. With vaginal ET, prasterone 6.5 mg (0.5% formulation) is approved for use as a daily vaginal suppository for the treatment of dyspareunia in VVA due to menopause. The mechanism of action of prasterone in the vagina is the local aromatization of androstenedione and testosterone to estrone and estradiol through a process of intracrinology [19,31-34].

Disadvantages of ospemifene compared to vaginal ETs are the need for daily use and systemic side effects; vasomotor symptoms (VMS), potential risk of venous thromboembolism (VTE). The safety of ospemifene has not been demonstrated in patients with a history or high risk of BC or in patients at high risk of VTE. Ospemifene is effective in the treatment of dyspareunia and vaginal dryness in menopausal patients with VVA compared to placebo. VMSs are the most common adverse effect of ospemifene. Ospemifene causes an increase in endometrial thickness (0.4 to 0.7mm in 12 weeks); after one year of use, no cases of atypical HE or EC have been found [34-37]. Thrombotic adverse effects are a potential risk with SERMs. Vaginal testosterone can stimulate the vaginal mucosa and improve symptoms of VVA, its use for GSM in patients on aromatase inhibitor (AI) therapy, its safety is unknown. 60% of postmenopausal women with CM report symptoms of GSM [1-6,38].

Management of these women, particularly those with estrogen receptor (ER)-positive CM, poses a challenge. These women often experience profound GSM symptoms, but treatment options are limited. Women at high risk for breast cancer or those with ER-positive breast cancers who are taking tamoxifen with persistent or severe symptoms that do not respond to non-hormonal therapies may be offered low-dose vaginal estrogen therapies, provided that have factors indicating a low risk of recurrence.

Estetrol (E4), 15mg once daily, an effective dose to relieve vasomotor symptoms of menopause, also has a beneficial effect on vaginal cytology and maturation, vaginal dryness, vaginal pain with sexual activity, as well as on quality of life, in particular on the somatovegetative and psychological symptoms that are commonly observed with estrogen deprivation in postmenopausal women.

Lasers and other energy-based devices; For example, fractional microablative CO2 laser, erbium:YAG (Er:YAG) laser, temperature-controlled radiofrequency (RF) laser, for the treatment of VVA, their safety and effectiveness are uncertain; The beneficial effects are reported to result from vaginal tissue remodeling, the optimal inclusion or exclusion criteria, number of treatment and maintenance therapy are not yet known [39-41].

Other proposed alternative and complementary therapies are oral vitamin D and the components of local vitamin E, they are phytoestrogens, they could serve as an additive to hormonal or alternative therapy in women with contraindications to estrogen, efficacy data are limited and/ or discordant [41,42-47]. Oral and vaginal probiotics alter the vaginal microbiota (VM), and their supplementation in postmenopausal women represents a feasible and safe strategy to control menopause-related disease. In particular, those that include Lactobacillus ssp. casei, helveticus, rhamnosus and reuteri, could have beneficial pleiotropic effects on health and are beneficial for GSM, but their validation is needed [48-49].

For symptoms refractory to hormone therapy, evaluation for other etiologies is warranted or those who do not respond to other therapies or who have contraindications to MHT are evaluated and treated with pelvic physical therapy; vaginal dilators are a component of pelvic physical therapy. They improve vaginal function, they are effective after MHT, they improve elasticity within the vagina and introitus [50]. For asymptomatic patients who do not need correction, treatment is not necessary unless urinary flow is impeded.

The treatments used in the management of breast cancer are responsible for the development of GSM. In fact, it has been observed that around 70% of CM survivors present symptoms attributable to a GSM condition due to the hypoestrogenism they experience. Guidelines for BC risk reduction suggest hormonal therapies that inevitably lead to early infertility and premature ovarian failure, which precede the early onset of secondary menopausal symptoms [13].

Chemotherapy has a gonadotoxic effect, causing the destruction of ovarian follicles. Endocrine therapy used in the treatment of breast cancer causes inhibitory effects on both ovarian and endometrial functions [12]. Premenopausal women undergoing treatment will inevitably suffer suppression of ovarian and endometrial function with subsequent manifestations of transient or permanent chemotherapy-induced amenorrhea. In particular, patients on AI treatment will be at increased risk of developing GSM.

On the other hand, young women with a positive pathogenic mutation for BRCA 1 and 2 who agree to undergo preventive bilateral salpingo-oophorectomy will inevitably develop early surgically induced menopause and a form of secondary permanent amenorrhea. First-line treatment for vulvovaginal atrophy, as well as for BC survivors, it is represented by non-hormonal therapies [18]. The group of non-hormonal therapies includes numerous categories of drugs and others that can play an optimal role in the treatment of dyspareunia and in general for vaginal well-being, we have: moisturizing creams and lubricants; Hyaluronic acid; Polynucleotides; Phtoestrogens; Vasodilators; Mechanical (dilators and sexual activity); Vaginal vitamin D and E; Vaginal/oral probiotics; Laser radiofrequency. In patients with BC reported moderate or severe VVA symptoms in 58% of patients taking aromatase inhibitors (AIs) and 32% with tamox-

ifen, non-hormonal options, lubricants or moisturizers are the first-line therapy there is not enough safety of MHT for GSM in women with BC in patients with SERM-treated BC, who have completed a full course of adjuvant Hormotherapy (Ht) or for those with hormone receptor-negative BC [14,22,51,52-54]. Treatment of GSM in BC remains an area of unmet need, vaginal ET is not recommended in those taking AI, because it is absorbed in small quantities and elevates blood levels within the normal postmenopausal period and potentially stimulate occult cells of the BC.

The safety of intravaginal dehydroepiandrosterone and oral ospemifene after BC has not been established. In women with isolated pain in the vulvar vestibule with penetration, topical lidocaine provides relief and 4% aqueous lidocaine versus saline applied with a cotton ball in the vestibule for 3 minutes before vaginal penetration in dyspareunia of postmenopausal survivors of CM with severe GSM for 4 weeks, reduced 88% versus 33% with saline ($P = 0.007$) and can be considered a safe treatment option for painful sexual intercourse in BC. Olive oil, vaginal exercise and moisturizer; improves quality of life, sexual function and dyspareunia ($P < 0.001$). The use of natural oils (for example, olive and coconut) for lubrication are associated with infections in the vagina, another alternative is autologous platelet-rich plasma (A-PRP), improving the vaginal mucosa after 6 months. of treatment according to the Vaginal Health Index (10.7 to 20.75; $P < 0.0001$).

The Efficacy of Platelet Concentrate Injection Combined with Hyaluronic Acid for the Treatment of VVA Atrophy in Postmenopausal Women with a History of BC. In addition to the use of vaginal moisturizers and lubricants, the regular use of vaginal dilators for symptomatic VVA reduces dyspareunia by improving vaginal elasticity, the use of vaginal dilators of graduated sizes (either by themselves or with their partners) to promote stretching of vaginal tissues. Vibratory stimulation, applied either to the vagina or directly to the clitoris, has also been studied as a modality to reduce pain from vaginal penetration; lower pelvic floor therapy reduces pain with vaginal penetration; In education about therapy with vaginal dilators, there are multiple options to treat dyspareunia and daily well-being, these compounds do not reverse atrophy, nor improve the characteristics of the vaginal epithelium, the improvement is temporary and short-term. Lubricants and moisturizers, mainly based on water, silicone or vegetable oil. Water-based agents have fewer side effects compared to oil-based products, 85% described effectiveness with follow-up of 30 days or less; there is a low risk of possible side effects from non-hormonal therapies used for climacteric symptoms Oral and vaginal probiotics to change the vaginal microbiota could possibly be beneficial for the treatment of GSM symptoms, capsules including Lactobacillus, for maintenance of the vaginal microbiota in women with breast cancer during chemotherapy proved to be useful. The quality of life (Qol) evaluation was good. Figure 4,5, table 3,4

Table 3: Management of Genitourinary Syndrome of Menopause

The use of topical estrogens is recommended for treatment
Lubricants, vaginal moisturizers, ospemifene, and vaginal DHEA are non-estrogen therapies. available for treatment, but laser therapy could be considered an additional therapy option
For menopausal women with overactive bladder symptoms, it is a combination treatment of antimuscarinics and topical ETs.

Table 4: Treatment Options for Management of Genitourinary Syndrome of Menopause in Specific Patient Populations

Individualize treatment, taking into account risk of recurrence, severity of symptoms, effect on QoL, and personal preferences
Moisturizers and lubricants, pelvic floor physical therapy, and dilator therapy are firstline treatments
Involve treating oncologist in decision making when considering the use of local hormone therapies 1
Ospemifene, an oral SERM, has not been studied in women at risk for breast cancer and is not FDA approved for use in women with or at high risk for breast cancer without indication for use of compounded vaginal testosterone or estriol is not recommended
Laser therapy may be considered in wome who prefer a nonhormonal approach; women must be counseled regarding lack of longterm safety and efficacy data
Women at high risk for breast cancer 2
Local hormone therapies are a reasonable option for women who have failed nonhormonal treatment
Observational data do not suggest increased risk of breast cancer with systemic or local estrogen therapies beyond baseline risk
Women with ER positive breast cancers on tamoxifen
Tamoxifen is a SERM that acts as an ER antagonist in breast tissue; small transient elevations in serum hormone levels noted with local hormone therapies in women on tamoxifen are less concerning than in women on AIs
Women with persistent, severe symptoms who have failed nonhormonal treatments and who have factors suggesting a low risk of recurrence may be candidates for local hormone therapy
Women with ER positive breast cancers on AI
AIs block conversion of androgen to estrogen, resulting in undetectable serum estradiol levels; transient elevations in estradiol levels may be of concern GSM symptoms are often more severe

Women with severe symptoms who have failed nonhormonal treatments may still be candidates for local hormone therapies after review with the woman's oncologist vs consider switching to tamoxifen
Women with triple negative breast cancers
Theoretically, the use of local hormone therapy in women with a history of triplenegative disease is reasonable, but data are lacking
Women with metastatic disease
QoL, comfort, and intimacy may be a priority for many women with metastatic disease
Use of local hormone therapy in women with metastatic disease and probable extended survival may be viewed differently than in women with limited
survival when QOL may be a priority

1Local hormone therapies are vaginal estrogen and intravaginal DHEA (prasterone).
2Lifetime risk > 20%, carriers of the BRCA mutation, atypical ductal hyperplasia, lobular carcinoma in situ, or ductal carcinoma in situ. AI: Aromatase
inhibitor; ER: Estrogen receptor; GSM: Genitourinary syndrome of menopause; QoL: Quality of life; SERM: Selective estrogen-receptor modulator

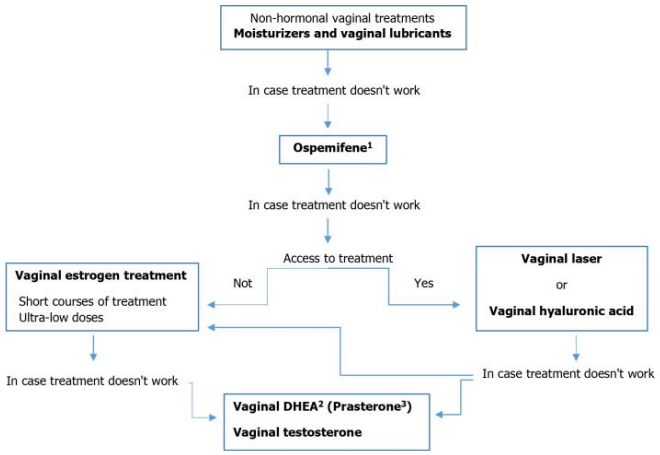

Figure 4: Treatment of Genitourinary Syndrome of Menopause in Women Undergoing Adjuvant Treatment for Breast Cancer. 1 Dehydroepiandrosterone; 2 Prasterone label Includes a Warning Against This Use in Breast Cancer Survivors.

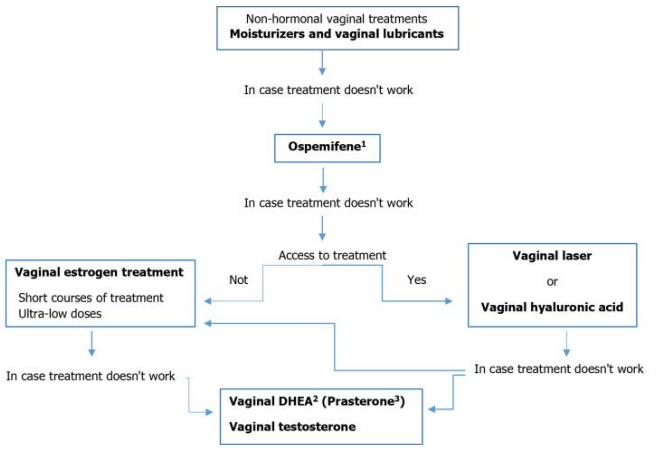

Figure 5: Treatment of Genitourinary Syndrome of Menopause in Women who have Completed Their Adjuvant Treatment for Breast Cancer. 1 Food and Drug Administration Does Not Recommend Ospemifene for Women at Risk or With History of Breast Cancer or Those with Known or Suspected Estrogendependent Neoplasia;

2 Dehydroepiandrosterone; 3 Prasterone label includes a warning against this use in breast cancer survivors.

Low-dose vaginal ET or vaginal DHEA (prasterone) in postmenopausal patients with early-stage (non-metastatic) estrogen receptor-positive (ER+) invasive BC [51]. BC patients treated with tamoxifen, who received vaginal ET (17%) compared with those who did not, had similar rates of BC recurrence during the median of 9.8 years of follow-up; Vaginal ET was not associated with increased mortality in BC survivors obtain the same type of benefits as other patients when treated with vaginal ET [52-54]. There are limited data on the use of vaginal ET in patients with hormone receptor-positive early BC receiving AI; In BC patients treated with AI, those who received vaginal ET (23%) compared to those who did not receive vaginal ET had higher rates of BC recurrence; hazard ratio (HR) 1.39, 95% CI: 1.04-1.85) during a mean of 9.8 years of follow-up [39,51]. Vaginal ET was not associated with increased mortality; these patients may have had a higher risk of recurrence compared with tamoxifen (or neither). Testosterone therapy should not increase serum estrogen levels [39]; vaginal testosterone resulted in both transient and persistent elevations of serum estradiol levels (12% of patients in both groups); VVA and sexual dysfunction improve in all patients [39]. Vaginal therapy with DHEA (prasterone) in patients with BC (97%) 60% were with AI [52]. Estradiol increased slightly with DHEA 6.5mg/day (average 3.6pg/mL to 4pg/mL) but not with 3.25mg/day; other therapies for GSM in BC survivors, the use of estriol instead of estradiol for BC patients, as its metabolic clearance is faster [53]. Fractional CO2 laser therapy in BC survivors and improve GSM symptoms; although, no increased risk of BC recurrence within 5 years was found in women with a personal history of BC with vaginal ET for GSM [48-50]. The risk of BC recurrence was comparable with vaginal TE and those who did not receive any estrogen receptor (hazard ratio 1.03, 95% CI 0.91–1.18) and ER+ (hazard ratio 0.94, 95% CI 0.77– 1.15) [54-58].

Currently, there is a need for a safe and effective solution for the treatment of GSM. Hyaluronic acid (HA) is a key extracellular matrix molecule present in various tissues, including the vaginal mucosa. It is a polysaccharide of the glucosamino-glycan family

that plays an important role in maintaining water balance and regulating inflammation, immune response, scar formation and angiogenesis [20,21]. Synthetic HA preparations are available in the form of local gels and have a "medical device" status; The effects of HA on GSM have been evaluated with promising results, most subjective evaluation of symptom response with its topical administration, HA is an endogenous molecule and its effects are better if injected into the layers superficial epithelial cells. The cross-linked HA Gel that is administered by injection into the vaginal mucosa to restore hydration, elasticity, tone and sensitivity to the vulvovaginal area is injected directly into the tissues that need it. It contributes to reducing dehydration in the vaginal mucosa and strengthens the quality of the tissues; a more elastic gel that is capable of reshaping the outer lips (labia majora) after volume loss (atrophy).

As well as an improvement from an aesthetic point of view, the inner lips (labia minors) are better protected indirectly: the efficacy and safety of hyaluronic acid-based vaginal pessaries for the treatment of GSM in postmenopausal women, a hyaluronate-based pessary , a non-sterile glyceride-based solid preparation containing 0.2% of a colorless, odorless, transparent, aqueous moisturizing gel and a moisturizing suppository, both hormone-free and made without parabens, every 3 days for 3 months, was effective to improve GSM signs. Figure 6.

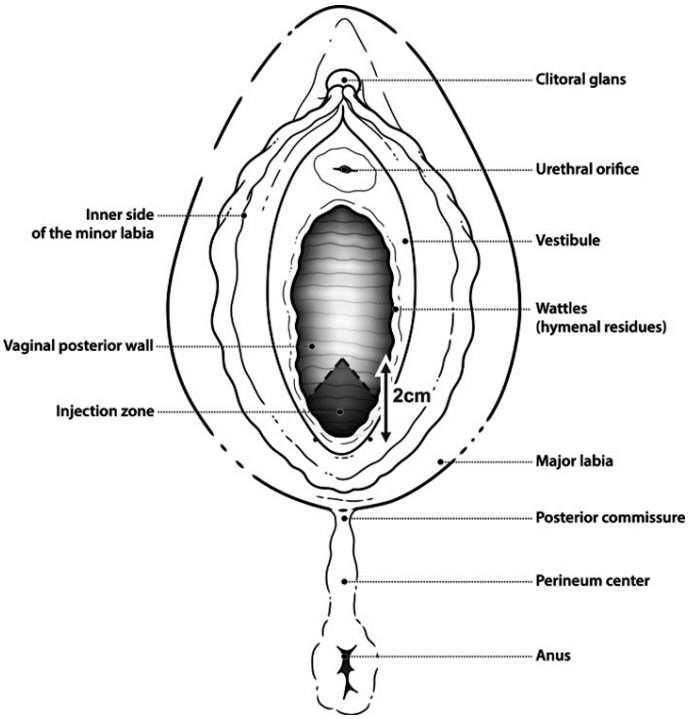

Figure 6: Diagram Showing Ha Gel Injection Sites. Hyaluronic Acid Infiltration of the Labia Majora is Able to Provide a Significant Rejuvenation with A Simple Outpatient Procedure. We Achieved Significant Improvements with one Infiltration in All Cases. the Treatment is Repeatable, has Virtually no Complications and it is Reversible.

The aqueous extract of Triticum vulgare increases the healing of wounds and ulcers in both cutaneous and non-cutaneous tissues, since it stimulates tissue reparative processes, incites chemotaxis and fibroblast maturation, in addition to increasing the fibroblast index, because it encourages synthesis of mRNA and DNA in fibroblasts and lymphocytes; which results in an early synthesis of granulation tissue, optimizing the re-epithelialization processes, the positive effect of its intravaginal use was observed, in addition to favoring the score of the Female Sexual Function Index (IFSF); becoming a non-hormonal alternative. Its use is associated with a significant improvement in both genitourinary and sexual symptoms.

Discussion

Around the world, populations are aging. Today, women spend 40% of their lives in the postmenopausal state GSM progresses chronically and requires treatment with long-term care because symptoms recur if treatment is interrupted. 50 to 70% of postmenopausal women have symptomatic GSM to at least some degree; However, GSM remains extremely underdiagnosed despite its high prevalence.

GSM is a condition that affects quality of life, it occurs in more than half of postmenopausal women, or women who suffer from other hypoestrogenic states, such as the puerperium, premature ovarian failure and treatment with antiestrogens. The most common complaints are dyspareunia and vaginal dryness, burning, itching, discharge, urinary discomfort or bleeding during intercourse. This condition is prevalent, effective treatment is unsatisfactory. Lifestyle modifications and hormonal or non-hormonal treatments, such as lubricants, moisturizers, and non-pharmacological therapies. Lubricants and moisturizers are the first options, vaginal moisturizers containing hyaluronic acid (HA) are one of the effective non-hormonal strategies to treat GSM symptoms.

Women should be advised to choose a product that has an optimal balance in terms of pH and osmolality so that it is physiologically more similar to natural vaginal secretions. The World Health Organization (WHO) has proposed a guide on the recommended osmolality and pH of lubricants. Moisturizers and lubricants are useful for women who have a true contraindication to estrogen, such as breast cancer patients taking aromatase inhibitors (66). Objective diagnosis is confirmed by precise pelvic examination, including gentle inspection of the vulva, vestibule, vagina, and urethra to recognize signs of GSM (Table 5) and scoring on validated scales (67). The Vaginal Health Index Score is a clinical evaluation that evaluates 5 parameters (vaginal elasticity, vaginal secretions, pH, epithelial mucosa, vaginal hydration), obtaining a final score that defines the degree of atrophy in the genitourinary tract by assigning a unique score for each parameter.

Table 5: Components Used for The Development of the New Terminology

ANATOMICAL	DESCRIPTION	PROBLEMS	PHASE OF LIFE
Vagina	Vulvo-vaginal	Atrophy	Middle age
Genital	Vulva	Alterations	Aging
Lips	Gynecological	Changes	Menopause
Vestibule	Reproductive	Condition	Perimenopause
Urethra	Urogenital	Postmenopausal	Disease
Urogenital	Bladder	Disorder	
	Genitourinary	Deficiency	
	Urinary	Dysfunction	
		Syndrome	
		Vaginitis	

The total score ranges from 5 to 25, with lower scores corresponding to greater urogenital atrophy [68]. Vulva Health Index evaluates labia, urethra, clitoris, introitus, elasticity and pain during intercourse; The total score ranges from 0 to 24, with higher scores corresponding to greater vulvar atrophy. If the vulvar health index is greater than 8 or a score of 3 (severe) in any category, vulvar atrophy is suggested [69]. In severe cases, tissues are easily traumatized and irritated by touching or inserting the speculum [70]. Organ prolapses or pelvic floor hypertonicity with secondary vaginismus may also occur, such as vulvovaginal signs that require differential diagnosis by performing colposcopy or performing bacteriological analyzes [11].

In general, GSM is a clinical diagnosis and few laboratory tests to support the evidence, the evaluation of vaginal pH and vaginal maturation index (VMI) are the most used [41]. With the VMI it identifies the relative proportion of parabasal, intermediate and superficial vaginal epithelial cells; suggests hypoestrogenism and atrophy when there is a predominance of parabasal cells, the change to a greater number of superficial cells is the main endpoint of any treatment [71]. Even vaginal pH alone is a simple procedure, influenced by infections and intimate products, which reflects the hormonal environment and its effects on the vaginal epithelium, it was consistently correlated with parabasal and superficial cells, visual vaginal epithelial changes, symptoms of dryness and dyspareunia [71].

Subjective assessment (MBS) and objective assessments (measurement of vaginal ripening index and vaginal pH) should be combined. Although a high rate of subjective symptoms is associated with the clinical diagnosis of GSM in more than 90% of cases [65-71].

Objective signs and subjective symptoms have a different prevalence distribution in the years after menopause and are not strictly associated, visible and self-reported vaginal dryness are correlated, along with pH > 5, mucosal paleness and thinning of the wrinkles are important objective signs for diagnosis, the presence of other vulvar and urinary signs is relevant for severity and its impact on daily life [65-71].

Visual vaginal, vulvar and pelvic evaluation by the doctor is a useful measure to diagnose GSM and evaluate response to treatment and identify women at risk of vaginal dryness and dyspareunia, engage in conversations about sexual health. Performing colposcopy or performing bacteriological analyzes [8-12]. In general, GSM is a clinical diagnosis and few laboratory tests to support the evidence, evaluation of vaginal pH and vaginal maturation index (VMI) are the most used. With the VMI it identifies the relative proportion of parabasal, intermediate and superficial vaginal epithelial cells; suggests hypoestrogenism and atrophy when there is a predominance of parabasal cells, the change to a greater number of superficial cells is the main endpoint of any treatment. Even vaginal pH alone is a simple procedure, influenced by infections and intimate products, which reflects the hormonal environment and its effects on the vaginal epithelium, it was consistently correlated with parabasal and superficial cells, visual vaginal epithelial changes, symptoms of dryness and dyspareunia.

Subjective assessment (MBS) and objective assessments (measurement of vaginal ripening index and vaginal pH) should be combined. Although a high rate of subjective symptoms is associated with the clinical diagnosis of GSM in more than 90% of cases, objective signs and subjective symptoms have a different prevalence distribution in the years after menopause and are not strictly associated with vaginal dryness. Visible and self-reported are correlated, along with pH > 5, pale mucous membranes and thinning of wrinkles are important objective signs for diagnosis, the presence of other vulvar and urinary signs are relevant to severity and its impact on daily life; table 6,7.

Table 6: Genitourinary Syndrome of Menopause (GSM)

SYMPTOMS	SIGNS
Genital dryness	Decreased humidity
Decreased Lubrication during intercourse	Decreased elasticity
Discomfort or pain during intercourse	Resorption of the labia minora
Post-coital hemorrhage	Paleness, erythema
Decreased desire or arousal or orgasm	Loss of vaginal roughness
Irritation, burning or itching of the vagina or vulva	Tissue fragility, fissures, petechiae
Urinary frequency or urgency	Loss of hymen Resorption of the labia minora remnants
	Prominence of the urethral meatus
	Retraction of the introitus
	Recurrent urinary tract infection

Table 7: Genitourinary Syndrome of Menopause Correlation of Symptoms and Signs

SYMPTOMS	SIGNS
Supporting findings:	pH > 5, > parabasal cells < superficial
Genital dryness	Decreased moisture
Decreased lubrication with sexual activity	Decreased elasticity
Discomfort or pain with sexual activity	Fused labia minora
Post-coital hemorrhage	Paleness/erythema
Decreased arousal orgasm, and sexual desire	Loss of vaginal ridges
Irritation, burning, itching vulva or vagina	Fragility of tissues, fissures or petechiae
Dysuria	Urethral eversion or prolapse
Frequency or urgency urinary tract of the	Loss of the remains of the hymen, urethral meatus protrusion
Recurrent infections of the lower urinary tract	Retraction of the introitus

Visual vaginal, vulvar and pelvic evaluation by the doctor is a useful measure to diagnose GSM and evaluate response to treatment and identify women at risk of vaginal dryness and dyspareunia, engage in conversations about sexual health. Figure 6-9, table Checklist for diagnosing GSM in routine clinical practice.

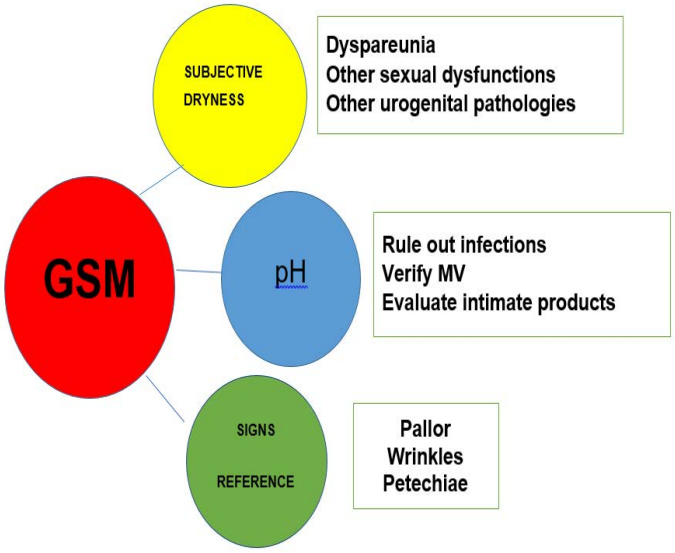

Figure 6: How to make the GSM diagnosis

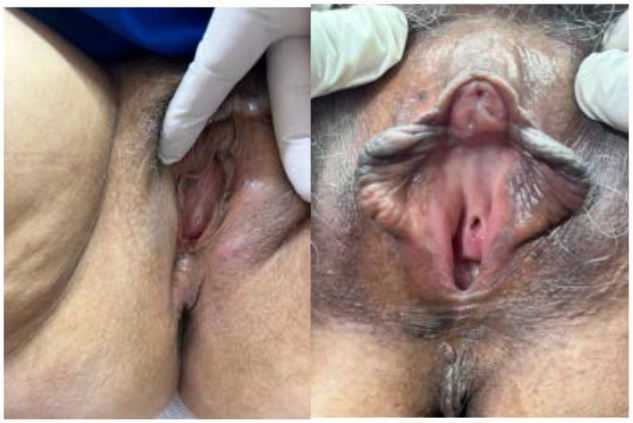

Figure 7: Menopausal Patients with Data of Urogenital Atrophy Are Presented (A,B)

A B

Figure 8: 59-Year-Old Woman Under Prolonged Local Et, Application of Estrogen Cream (A), Effect of Estrogen Therapy (B)

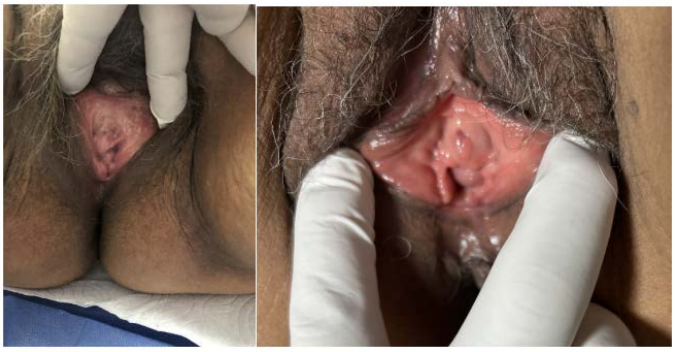

Figure 9: A. Genital Atrophy; B. Genitals with Estrogen Therapy.

The principle of this treatment is to relieve symptoms by normalizing the physiological environment of the urogenital organs [1-8]. They help recover normal vaginal flora, increase the amount of vaginal discharge, improving the division of the vaginal epithelium, induce the proliferation of capillaries and improve the maturation rate of the vaginal epithelium. All types of topical estrogen medications; (cream, vaginal tablet and vaginal ring) are effective in reducing the symptoms and signs of VVA, because there is a potential risk of increasing the level of blood estrogen even to the slightest degree, in women with BC, especially those who use a AI to reduce the level of estrogen, requires specialized management [56].

There are no clinical data to ensure the safety of endometrium for long-term application of more than 1 year, the duration of use of low-dose vaginal estrogen should be limited to less than 1 year and thereafter should be used in conjunction with evaluation of the endometrium [1-6,58]. The vaginal agents ospemifene and dehydroepiandrosterone (DHEA) are non-estrogen medications that improve symptoms of vaginal atrophy and dyspareunia. Ospemifene, a selective estrogen receptor modulator (SERM), is more effective than a lubricant in reducing dyspareunia by treating moderate or severe vaginal atrophy in menopausal women, it is considered for women who are not suitable for treatment with vaginal estrogens. Vaginal DHEA is approved as a medication for the treatment of GSM because it reduces vaginal dryness and dyspareunia, as well as vaginal acidity by recovering thickness, epithelial cells and increasing the amount of vaginal discharge [59]. There is potential for vitamin D to support the urogenital and sexual health of women during the menopausal transition and postmenopausal periods [60].

Recently, carbon dioxide laser therapy has been shown to improve sexual function and relieve symptoms such as dyspareunia, itching, burning sensation and dryness by improving the amount of glycogen in vaginal epithelial cells and promoting tissue remodeling; vaginal connectives for GSM. It is expected to become an appropriate treatment; There is concern because there has been chronic pain, burning sensation and dyspareunia after receiving laser therapy, the safety and effectiveness of laser therapy requires future investigation [61].

Pelvic floor muscle training, vaginal ring insertion and topical estrogen treatment improve vaginal epithelial cell function and accelerate connective tissue growth. Vaginal estrogen reduces urinary urgency or frequency, overactive bladder, and urinary incontinence by reducing contraction of the bladder muscles by increasing blood flow around the bladder, bladder neck, and urethra. On the contrary, systemic ET increases the occurrence of urgency urinary incontinence and stress urinary incontinence. In women with existing symptoms of urinary incontinence, treatment worsens symptoms, leading to a reduced quality of life [62]. The use of autologous fat, called 360 vaginal beautifications, in the labia majora augmentation and vaginal tightening appears to be a safe technique due to use of autologous tissue transfers and to be associated with high satisfaction rate and an advantage of being more minimally invasive than surgical labia majora augmentation and vaginal tightening [63].

To treat the symptoms of an overactive bladder, lifestyle changes and bladder training are very important and are recommended as primary treatment methods. Systemic ET shows a similar effect to placebo in treating symptoms of nocturia and urinary frequency, but is more effective than placebo in treating symptoms. Combined administration of vaginal estrogen and antimuscarinic drug is more suitable, and topical estrogen is considered to play an important role in the treatment of overactive bladder, combined therapy of an antimuscarinic drug and topical estrogen is the main drug treatment for women menopausal women with overactive bladder symptoms [63].

Topical ET was shown to be effective in preventing recurrent urinary tract infections by restoring microbiological changes that occur within the vagina after menopause and by reducing vaginal acidity, but systemic ET was not effective in preventing recurrence of infections. urinary table 6,7 [1-6,10]. Postmenopausal women with a wide variety of pelvic floor disorders are often advised to incorporate vaginal dilators to allow penetrative intercourse with less pain [64].

Key Points for Clinical Practice in Gsm Vva

The increased frequency and clinical importance of the effects of VVA are not adequately diagnosed or treated.
Diagnosis is essential for better treatment and follow-up.
Vaginal pH is useful but a fresh smear is superior to diagnose VVA
Non-hormonal therapy is suitable in the short term, only low-dose vaginal ET is the standard reference for VVA.
In the presence of associated general menopausal symptoms or health risks and in the absence of contraindications, systemic MHT is appropriate, at the safest and lowest doses of estrogen, reducing the potential risk of complications.
Newer hormone therapies, such as DHEA and ospemifene, are effective and safe. DHEA mainly when they have sexual dysfunction. Long-term safety studies are still required for complications such as BC and thromboembolism.
When there is an absolute contraindication to ET, non-hormonal therapies are the first line, such as hyaluronic acid or vitamin D. If it is insufficient, an ultra-low dose of estriol applied locally with or without lactobacilli is safe, DHEA or ospemifene are safe.
Estetrol (E4) is a promising new drug with a good safety profile, but endometrial proliferation must be monitored.
Radiofrequency or laser wave therapies have not yet been proven effective and safe.

Conclusion

Hormonal therapy is the most effective treatment for GSM, which is not relieved by non-hormonal therapies, although the risks of MHT differ for women, depending on type, dose, duration of use, route of administration, timing of administration At baseline and if a progestin is needed, treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic evaluation and reassessment, approved therapies are low-dose vaginal ET, vaginal DHEA, or oral ospemifene.

Conflict of Interest

The author has no financial involvement in any organization or entity with or financial conflict with the subject matter or materials discussed in this article.

References

1. The NAMS 2020 GSM Position Statement Editorial Panel (2020) The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause 27: 976-992.
2. Mili N, Paschou SA, Armeni A, Georgopoulos N, Goulis DG, et al. (2021) Genitourinary syndrome of menopause: a systematic review on prevalence and treatment. Menopause. 28: 706-716.
3. Gloria Bachmann, JoAnn V Pinkerton (2023) Genitourinary syndrome of menopause (vulvovaginal atrophy): Treatment. Literature review current through: This topic last updated: Nov https://www.uptodate.com/contents/genitourinary-syndrome-of-menopause.
4. Gloria Bachmann, JoAnn V Pinkerton (2023) Genitourinary syndrome of menopause (vulvovaginal atrophy): Treatment. Literature review current through https://medilib.ir/uptodate/show/5464 .
5. Rostami-Moez M, Masoumi SZ, Otogara M, Farahani F, Alimohammadi S, et al. (2023) Examining the Health-Related Needs of Females during Menopause: A Systematic Review Study. J Menopausal Med 29: 1-20.
6. Da Silva AS, Baines G, Araklitis G, Robinson D, Cardozo L (2021) Modern management of genitourinary syndrome of menopause. Fac Rev 10: 25.
7. Elizabeth J Cathcart-Rake, Kathryn J Ruddy (2022) Vaginal Estrogen Therapy for the Genitourinary Symptoms of Menopause: Caution or Reassurance? J Natl Cancer Inst 114: 1315-1316.
8. Lubián López DM (2022) Management of genitourinary syndrome of menopause in breast cancer survivors: An update. World J Clin Oncol 13: 71-100.
9. Academic Committee of the (2020) Korean Society of Menopause, Sa Ra Lee, Moon Kyoung Cho, Yeon Jean Cho, Sungwook Chun, Seung-Hwa Hong, Kyu Ri Hwang, et al. The 2020 Menopausal Hormone Therapy Guidelines. J Menopausal Med 26: 69-98.
10. Djapardy V, Panay N (2022) Alternative and non-hormonal treatments to symptoms of menopause. Best Pract Res Clin Obstet Gynaecol 81: 45-60.
11. Genazzani AR, Monteleone P, Giannini A, Simoncini T (2021) Hormone therapy in the postmenopausal years: considering benefits and risks in clinical practice. Hum Reprod Update 27: 1115-1150.
12. Liu M, Juravic M, Mazza G, Krychman ML (2021) Vaginal Dilators: Issues and Answers. Sex Med Rev 9: 212-220.
13. The 2023 (2023) nonhormone therapy position statement of The North American Menopause Society Menopause 30: 573-590.
14. Fosdick MG, Chheda PR, Tran PM, Wolff A, Peralta R, et al. (2021) Suppression of human T cell activation by derivatives of glycerol monolaurate. Sci Rep 11: 8943osdick.
15. Claudia Pignatti Frederice, Ticiana Aparecida Alves de Mira, Helymar Costa Machado, Luiz Gustavo Oliveira Brito, Cássia RT Juliato (2022) Effect of Vaginal Stretching and Photobiomodulation Therapy on Sexual Function in Women with Pelvic Floor Myofascial Pain - A Randomized Clinical Trial, The Journal of Sexual Medicine 19: 98-105.
16. Yen-Pin Lin, Wei-Chun Chen, Chao-Min Cheng, Ching-Ju Shen (2021) Vaginal pH Value for Clinical Diagnosis and Treatment of Common Vaginitis. Diagnostics (Basel) 11: 1996. doi: 10.3390/diagnostics11111996.
17. Anne R Cappola, Richard J Auchus, Ghada El-Hajj Fuleihan, David J Handelsman, Rita R Kalyani, et al. (2023)

Hormones and Aging: An Endocrine Society Scientific Statement. J Clin Endocrinol Metab 108: 1835-1874.
18. Caroline M Mitchell, Joseph C Larson, Carolyn J Crandall, Shalender Bhasin, Andrea Z LaCroix, et al. (2022) Association of Vaginal Estradiol Tablet with Serum Estrogen Levels in Women Who Are Postmenopausal: Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 5: e2241743.
19. Shim S, Park KM, Chung YJ, Kim MR (2021) Updates on Therapeutic Alternatives for Genitourinary Syndrome of Menopause: Hormonal and Non-Hormonal Managements. J Menopausal Med 27: 1-7.
20. Berreni N, Salerno J, Chevalier T, Alonso S, Mares P (2021) Evaluation of the effect of multipoint intra-mucosal vaginal injection of a specific cross-linked hyaluronic acid for vulvovaginal atrophy: a prospective bi-centric pilot study. BMC Womens Health 21: 322. doi:10.1186/s12905-021-01435-w
21. Johnston S, Bouchard C, Fortier M, Wolfman W (2021) Guideline No. 422b: Menopause and Genitourinary Health. J Obstet Gynaecol Can 43: 1301-1307.e1. doi:10.1016/j.jogc.2021.09.001.
22. Lubián López DM (2022) Management of genitourinary syndrome of menopause in breast cancer survivors: An update. World J Clin Oncol 13: 71-100.
23. Jang YC, Leung CY, Huang HL (2022) Comparison of Severity of Genitourinary Syndrome of Menopause Symptoms After Carbon Dioxide Laser vs Vaginal Estrogen Therapy: A Systematic Review and Meta-analysis. JAMA Netw Open 5: e2232563.
24. Long J, Zidan G, Seyfoddin A, Tong S, Brownfoot FC, et al. (2022) An estriol-eluting pessary to treat pelvic organ prolapse. Sci Rep 12: 20021.
25. Alvisi S, Ceccarani C, Foschi C, Baldassarre M, Lami A, et al. (2023) Effect of ospemifene on vaginal microbiome in postmenopausal women with vulvovaginal atrophy. Menopause. 30: 361-369.
26. Apiwat Jongjakapun, Woraluk Somboonporn, Teerayut Temtanakitpaisan (2023) Effectiveness of vaginal estriol with lactobacilli on urinary symptoms in postmenopausal women: a randomized-controlled trial. Menopause 30: 441-446.
27. Mitchell C (2023) Evaluation and treatment of vulvovaginal itching in postmenopausal women. Menopause 30: 969-971.
28. Rojas K, Spring LM, O'Riordan L, Weiss A (2023) Endocrine Therapy for Surgeons: Practical Pearls for Managing Menopausal, Bone Loss and Sexual Adverse Effects. Ann Surg Oncol 30: 5951-5961.
29. ML Hull, B Stuckey, K Hartman, N Zack, A Thurman, et al. (2023) Safety and acceptability of intravaginal rings releasing estradiol and progesterone, Climacteric 26: 465-471.
30. Garzon S, Apostolopoulos V, Stojanovska L, Ferrari F, Mathyk BA, et al. (2021) non-oestrogenic modalities to reverse urogenital aging. Prz Menopauzalny 20: 140-147.
31. Ferrante KL, Wasenda EJ, Jung CE, Adams-Piper ER, Lukacz ES (2021) Vaginal Estrogen for the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women: A Randomized Clinical Trial. Female Pelvic Med Reconstr Surg 27: 112-117.
32. Clark AL, Goetsch MF (2024) Genitourinary Syndrome of Menopause: Pathophysiology, Clinical Presentation, and Differential Diagnosis. Clin Obstet Gynecol 67: 13-26. doi: 10.1097/GRF.0000000000000845.
33. Sarmento ACA, Costa APF, Vieira-Baptista P, Giraldo PC, Eleutério J Jr, et al. (2021) Genitourinary Syndrome of Menopause: Epidemiology, Physiopathology, Clinical Manifestation and Diagnostic. Front Reprod Health 3: 779398. doi: 10.3389/frph.2021.779398.
34. The 2022 (2022) hormone therapy position statement of The North American Menopause Society. Menopause 29: 767-794.
35. Liu JH, Bernick B, Mirkin S (2022) Estradiol softgel inserts for the treatment of VVA symptoms: an expert opinion. Expert Opinion on Drug Delivery 17: 1573-1581.
36. Gerald Gartlehner, Sheila V Patel, Shivani Reddy, Caroline Rains, Manny Schwimmer, et al. (2022) Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 328: 1747-1765.
37. Pingarron C, de Lafuente P, Ierullo AM, Poyo Torcal S, Maroto Díaz CJ, et al. (2021) Ospemifene in clinical practice for vulvo-vaginal atrophy: results at 3 months of follow-up of use. Gynecol Endocrinol 37: 562-566.
38. Robert L Reid, Denise Black, Christine Derzko, David Portman (2020) Ospemifene: A Novel Oral Therapy for Vulvovaginal Atrophy of Menopause, J Obstet Gynaecol Canada 42: 301-303.
39. Cagnacci A, Xholli A, Venier M (2020) Ospemifene in the Management of Vulvar and Vaginal Atrophy: Focus on the Assessment of Patient Acceptability and Ease of Use. Patient Prefer Adherence 14: 55-62.
40. Lilue M, Palacios S (2020) Del Carmen Pingarrón Santofimia M. Experience with ospemifene in patients with vulvar and vaginal atrophy and a history of breast cancer: case studies. Drugs Context 9: 3-4.
41. Ishrat Hussain, Vikram Sinai Talaulikar (2023) A systematic review of randomised clinical trials – The safety of vaginal hormones and selective estrogen receptor modulators for the treatment of genitourinary menopausal symptoms in breast cancer survivors. Post Reproductive Health 29: 222-231.
42. Alshiek J, Garcia B, Minassian V, Iglesia CB, Clark A, et al. (2022) Clinical Consensus Statement: Vaginal Energy-Based Devices. Urogynecology (Phila) 28: 633-648.
43. Feduniw S, Korczyńska L, Górski K, Zgliczyńska M, Bączkowska M, et al. (2022) The Effect of Vitamin E Supplementation in Postmenopausal Women-A Systematic Review. Nutrients. 15: 160. doi: 10.3390/nu15010160.
44. Li FG, Maheux-Lacroix S, Deans R, Nesbitt-Hawes E, Budden A, et al. (2021) Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Symptom Severity in Women with Postmenopausal Vaginal Symptoms: A Randomized Clinical Trial. JAMA 326: 1381-1389.
45. Paraiso MFR, Ferrando CA, Sokol ER, Rardin CR, Mat-

thews CA, et al. (2020) A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: The VeLVET Trial. Menopause 27: 50-56.
46. Mackova K, Mazzer AM, Mori Da Cunha M, Hajkova Hympanova L, Urbankova I, et al (2021) YAG laser application in the menopausal ewe model: a randomised estrogen and sham-controlled trial. BJOG 128: 1087-1096.
47. Filippini M, Porcari I, Ruffolo AF, Casiraghi A, Farinelli M, et al. (2022) CO2-Laser therapy and Genitourinary Syndrome of Menopause: A Systematic Review and Meta-Analysis. J Sex Med 19: 452-470.
48. Pessoa LLMN, Sarmento ACA, Medeiros KS, Costa APF, Gonçalves AK, et al. (2021) Efficacy and Safety of Laser Therapy for the Treatment of Genitourinary Syndrome of Menopause: A Protocol for Systematic Review and Meta-Analysis of Clinical Trials. Front Reprod Health 3: 772690.
49. Kamronrithisorn T, Manonai J, Vallibhakara SA-O, Sophonsritsuk A, Vallibhakara O (2020) Effect of Vitamin D Supplement on Vulvovaginal Atrophy of the Menopause. Nutrients 12: 2876.
50. Kim S, Seo H, Rahim MA, Lee S, Kim YS, et al. (2021) Changes in the Microbiome of Vaginal Fluid after Menopause in Korean Women. J Microbiol Biotechnol 31: 1490-1500.
51. Barrea L, Verde L, Auriemma RS, Vetrani C, Cataldi M, et al. (2023) Probiotics and Prebiotics: Any Role in Menopause-Related Diseases? Curr Nutr Rep 12: 83-97.
52. Maria Grazia Matarazzo, Giuseppe Sarpietro, Debora Fiorito, Salvatore Di Pasqua, Simona Ingrassano, et al. (2021) Intravaginal 6.5 mg prasterone administration in postmenopausal women with overactive bladder syndrome: A pilot study. Eur J Obstet Gynecol Reprod Biol 263: 67-71. Doi. https://doi.org/10.1016/j.ejogrb.2021.06.009.
53. Cold S, Cold F, Jensen MB, Cronin-Fenton D, Christiansen P, et al. (2022) Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study. J Natl Cancer Inst 114: 1347-1354.
54. Treatment of (2021) Urogenital Symptoms in Individuals with a History of Estrogen-dependent Breast Cancer. Clinical Consensus No. 2. American College of Obstetricians and Gynecologists. Obstet Gynecol 138: 950-960.
55. Carter J, Baser RE, Goldfrank DJ, Seidel B, Milli L, et al. (2021) A single-arm, prospective trial investigating the effectiveness of a non-hormonal vaginal moisturizer containing hyaluronic acid in postmenopausal cancer survivors. Support Care Cancer 29: 311-322.
56. Agrawal P, Singh SM, Able C, Dumas K, Kohn J, et al. (2023) Safety of Vaginal Estrogen Therapy for Genitourinary Syndrome of Menopause in Women with a History of Breast Cancer. Obstet Gynecol 142: 660-668.
57. Cathcart-Rake EJ, Ruddy KJ (2022) Vaginal estrogen therapy for the genitourinary symptoms of menopause: caution or reassurance? J Natl Cancer Inst 114: 1315-1316.
58. Nida Jugulytė, Guoda Žukienė, Daiva Bartkevičienė (2023) Emerging Use of Vaginal Laser to Treat Genitourinary Syndrome of Menopause for Breast Cancer Survivors: A Review. Medicina 59: 132. https://doi.org/10.3390/medicina59010132.
59. Claudia Collà Ruvolo, Olimpia Gabrielli, Carmen Formisano, Gianluigi Califano, Paolo Manna, et al. (2022) Prasterone in the treatment of mild to moderate urge incontinence: an observational study. Menopause 29: 957-962.
60. Angelica Lindén Hirschberg, Johannes Bitzer, Antonio Cano, Iuliana Ceausu, Peter Chedraui, et al. (2021) Topical estrogens and non-hormonal preparations for postmenopausal vulvovaginal atrophy: An EMAS clinical guide Maturitas 148: 55-61.
61. Costa APF, Sarmento ACA, Vieira-Baptista P, Eleutério J Jr, et al. (2021) Hormonal Approach for Postmenopausal Vulvovaginal Atrophy. Front Reprod Health 3: 783247.
62. Blumenfeld Z, Leiba R, Stam T (2023) What may be the best menopausal hormone treatment? Arch Gynecol Obstet 307: 659-662. doi: 10.1007/s00404-022-06889-3.
63. Quick AM, Zvinovski F, Hudson C, Hundley A, Evans C, et al. (2021) Patient-reported sexual function of breast cancer survivors with genitourinary syndrome of menopause after fractional CO2 laser therapy. Menopause 28: 642-649.
64. Cihantimur B, Aglamis O, Ozsular Y (2021) 360 genital fat transfer. Aesthetic Plastic Surgery 45: 2996-3002.
65. Lucia Merlino, Giulia D'Ovidio, Viviana Matys, Maria Grazia Piccioni, Maria Grazia Porpora, et al. (2023) Therapeutic choices for genitourinary syndrome of menopause (GSM) in breast cancer survivors: A systematic review and update. Pharmaceuticals (Basel) 16: 550.
66. Potter N, Panay N (2021) Vaginal lubricants and moisturizers: a review into use, efficacy, and safety. Climacteric 24: 19-24.
67. Hassanein MM, Huri HZ, Abduelkarem AR, Baig K (2023) Therapeutic Effects of Vitamin D on Vaginal, Sexual, and Urological Functions in Postmenopausal Women. Nutrients 15: 3804.
68. Mension E, Alonso I, Tortajada M, Matas I, Gómez S, et al. (2022) Vaginal laser therapy for genitourinary syndrome of menopause - systematic review. Maturitas 156: 37-59.
69. Irene Lambrinoudaki, Eleni Armeni, Dimitrios Goulis, Petra Stute, Mick van Trotsenburg, et al. (2022) Menopause, wellbeing and health: A care pathway from the European Menopause and Andropause Society EMAS Consensus statement. MATURITAS 163: 1-14.
70. Berreni N, Salerno J, Chevalier T, Alonso S, Mares P (2021) Evaluation of the effect of multipoint intra-mucosal vaginal injection of a specific cross-linked hyaluronic acid for vulvovaginal atrophy: a prospective bi-centric pilot study. BMC Womens Health 21: 322. doi:10.1186/s12905-021-01435-w
71. Víctor Manuel Vargas Hernández, Gumersindo, Gaspar Vázquez Castillo, Víctor Manuel Vargas Aguilar (2023) Avances en el tratamiento de pacientes con síndrome genitourinario de la menopausia Revista del Climaterio 1: 10-19.