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Genitourinary Syndrome of Menopause - Therapeutic Strategies for a Clinical Enigma

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Abstract

In 2014, the term Genitourinary Syndrome of Menopause (GSM) was coined to replace formerly termed Vulvovaginal atrophy to include the range of inter-related symptoms. It is frequently underestimated and mostly underreported disorder that requires careful clinical assessment of symptomatology. Other conditions mimicking this condition needs to be ruled out before establishing the diagnosis for an accurate and safe management. The etiology is by far unknown but could be due to interplay of various local and systemic hormonal and inflammatory markers. An extensive PubMed literature search was conducted by the authors to collect recent evidence published after 2015 on the diagnosis and management of GSM. In this review, we attempt to highlight the importance of addressing these concerns by the healthcare professionals and describe the existing therapeutic options.

Keywords: Sexual Health; Estrogens; Quality of Life; Dyspareunia; Atrophy; Morbidity

Abbreviations: GSM: Genitourinary Syndrome of Menopause; UTI: Urinary Tract Infections; REVIVE: Real Women's Views of Treatment Options for Menopausal Vaginal Changes; SERM: Selective Estrogen Receptor Modulators; DHEA: De Hydro Epi Androsterone.

Introduction

The Genitourinary Syndrome of Menopause (GSM) describes a constellation of urogenital & sexual symptoms arising in the menopausal women due to underlying hypoestrogenism. Previously known as vulvovaginal atrophy or urogenital atrophy, the terminology 'Genitourinary Syndrome of Menopause (GSM) was adapted by the International Society for the Study of Women's Sexual Health and the North American Menopause Society in 2014 to accurately describe the chronic and progressive sequalae of menopause.

The syndrome affects 50% of the postmenopausal women and upto 15% of women in premenopausal period. Clinical features include dryness, burning and irritation in the external genitalia; urgency, dysuria and recurrent urinary tract infections; and sexual symptoms like discomfort or dyspareunia, lack of lubrication, and impaired function [1,2]. The symptoms may cause considerable morbidity and unlike vasomotor symptoms, they do not improve over time if left untreated. The experience of the symptoms may be severely debilitating in cases of abrupt estrogen deprivation, for instance, as in surgical menopause, with significant sexual dysfunction and even poorer quality-of-life outcomes [3].

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However, GSM remains underreported and underdiagnosed due to variety of reasons. Embarrassment and reluctance to discuss sexual health with clinician, dismissal of the symptoms as a consequence to aging by women themselves, and a general lack of awareness are significant barriers to healthcare seeking behaviour in these women [4]. Further, there may be a lack of proactive assessment by clinicians for GSM as part of routine clinical review.

It is important to timely detect and ensure proper patient education regarding GSM to avoid the long-term morbidity. Treatment must be tailored based on clinical profile and severity of symtpoms [5].

Pathophysiology

Development & Premenopausal Physiology

During embryologic development in females, the urinary bladder, trigone, entire urethra, vaginal vestibule and lower fifth of vagina, is formed by the mullerian ducts, urogenital sinus and sinovaginal node (i.e, Muller tubercle). Mullerian ducts fuse to form the uterus and upper four-fifths of the vagina. The genitalia and lower urinary tract share common embryological & estrogen receptor function. They carry receptors that are dependent on endogenous estrogen levels to maintain normal physiology [6]. Though less studied, androgens too are implicated to have a role in maintenance of normal function & structure of the genitourinary tissues. Receptors for these steroids, especially estrogen, are distributed throughout the vulvovaginal tissues, pelvic floor musculature, endopelvic fascia and the lower urinary tract.

During the reproductive years, estrogen stimulation helps in the upkeep of these tissues in various ways. This includes production of adequate epithelial collagen content to maintain an appropriate mucosal thickness and elasticity, stimulation of hyaluronic acid and glycogen rich mucopolysaccharide production to help with surface moisturisation, maintenance of optimal blood flow via regional vasculature, and promotion of a healthy vaginal flora. Activated estrogen receptors encourage prolubricative and proelastic function of vaginal epithelium during sexual stimulation. Epithelial proliferation gives rise to rugosity of the vaginal mucosa which increases mechanical compliance of the vagina during sexual stimulation [7].

Thus, the vaginal epithelium, in response to estrogen is thick, elastic, rugated, and well-lubricated with secretions rich in glycogen. A healthy vaginal flora consisting of a variety of aerobic and anaerobic, gram-positive and gram-negative bacteria with predominantly lactobacilli create an acidic environment (pH 3.5-4.5) due to conversion of hydrolysed glycogen to lactic acid. This has a protective role in prevention of infection in the urogenital tract from infections by discouraging growth of pathogenic bacteria.

Postmenopausal Physiology

Declining estrogen levels due to ovarian ageing and progressive loss of receptors, has both vulvovaginal and urologic effects. Atrophy of the genital tissues occurs due to substantial loss of vascularization and dermal collagen. Vaginal epithelium characteristically appears attenuated, pale, flat and featureless due to loss of rugosity. Length and elasticity of vagina is also reduced causing frictional trauma and dyspareunia [8]. Hypoestrogenism causes alterations in vaginal microflora and cellular biochemistry appear as well. Accumulation of glycogen in the vaginal epithelial cells is hampered which leads to reduced Lactobacilli colonies. This causes change in vaginal fluid to an alkaline pH of ≥5.0, which further promotes overgrowth of skin & rectal flora (gram-negative rods, fecal flora including group B streptococci, staphylococci, coliforms, and diphtheroids) inducing inflammation, vaginal infections and UTIs [3].

GSM-related incontinence is another key cause of recurrent UTI in postmenopausal women. While incontinence in premenopausal women occurs mainly due to anatomical changes, postmenopausal hypoestrogenism decreases receptor mediated sensory threshold of bladder, and impairs the urethral closure and the Valsalva leak-point pressures causing urge symptoms. In addition, altered connective tissue integrity and urethral sphincter dysfunction contribute to stress incontinence [9,10] .

GSM-related incontinence is a key cause of recurrent UTI in postmenopausal women, signifying the importance of GSM evaluation and management to avoid the repercussions of inessential antibiotic therapy.

Epidemiology

Prevalance

Since the condition remains underreported, exact prevalence of GSM is not established. However, most menopausal women eventually develop urogenital atrophy which may be symptomatic or asymptomatic. A systematic review on GSM prevalence and treatment observed that 40-60% of the pre and postmenopausal women report GSM related concerns with many women describing upto four or five symptoms (32% & 10% respectively) [11].

Etiology

Declining estrogen levels in peri & postmenopausal phase remain the key factor in development of GSM. Duration of hypoestrogenism appears to have a direct correlation with severity of symptoms. Besides menopause, other

hypoestrogenic states may also cause GSM like symptoms. These include conditions like Primary Ovarian Insufficiency, bilateral oophorectomy, and iatrogenic causes of ovarian failure or insufficiency due to radiation, chemotherapy, complication of uterine artery embolization, antiestrogenic drugs etc. Postpartum reduction in estrogen levels, especially during lactation may also cause hypoestrogenic symptoms (Figure 1).

Clinical Evaluation

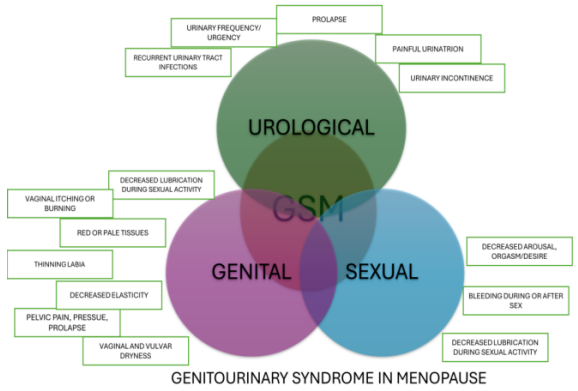

Figure 1: Symptoms of Genitourinary Syndrome in Menopause.

Clinical manifestations of GSM are summarised in Figure 1. Symptoms may be due to vulvovaginal, sexual or urinary dysfunction.

The REVIVE trial (Real Women's VIews of Treatment Options for Menopausal Vaginal Changes) survey in Europe by Nappi Re et al in 2022. Most bothersome menopausal symptom being vaginal/vulvar dryness, reported in almost 80% followed by vulvar/vaginal irritation (41%) [12]. The prevalence of vaginal dryness increased from 4% in premenopause to 25% after one year of menopause which rises to 72% in women aged older than 70 years. Spectrum may range from mild to debilitating [13]. This is predominantly related to vulvo-vaginal atrophy due to hypoestrogenism. The significance of Melbourne Women's health initiative lies in the intricate details that it provided. Similarly, Women's Health Initiative Study, around 10% of participants had never declared these symptoms. The symptoms of GSM are more prevalent in women undergoing surgical menopause, after receiving treatment for breast cancer.

There is an increased need to address these concerns through a properly framed questionnaire offered to every menopausal woman prior to their consultation. Most of these symptoms are underreported and hence these figures are an underestimation. Women essentially consider the sexual dysfunction and vulvovaginal symptoms to be a part of normal ageing due to rigid social norms. The history and physical examination must be taken in a sensitive manner. Healthcare professionals need to stay updated with the local and systemic treatments available [14].

Approach to GSM requires proactive assessment by the treating physician as many women are reluctant to discuss urogenital symptoms due to personal or socio-cultural inhibitions. Many are not aware of the available treatment options and self-treat by making lifestyle changes (e.g. abstinence from sex) to control symptoms. Clinical evaluation should include a thorough medical history and a pelvic examination. Diagnosis is clinical and laboratory testing is not usually required. Complications have been enumerated in Table 1.

History

History should include obstetric, menstrual and sexual history with a review of systems to evaluate urogenital symptoms attributable to causes other than peri or postmenopausal hypoestrogenism. Use of hygiene products which may be possible irritants should be enquired. These include perfumes, deodrants, soaps, powder, lubricants, panty liners etc. Symptoms related to vulvar pain that may be due to infection or inflammation should be discussed to rule other differentials. Psychological aspects related to appearance of symptoms should also be assessed e.g. behavioural response to symptoms and adverse impact of symptoms on daily life, sexual activity and relationship with the partner.

Pelvic Examination

Examination may reveal features which include but are not limited to vulvovaginal pallor, dryness, fissures, tissue fragility, labial fusion, retraction & narrowing of vaginal introitus, absence of vaginal rugosity, prominent urethral meatus, urethral eversion due to loss of collagen support and pelvic organ prolapse. Caution must be excised during examination, as even gentle surface contact with speculum or even examiner's hand may cause pain and bleeding. Levator muscles may go into spasm upon contact with the posterior vagina. Vagina may be narrowed and shortened. Cervix may be found flushed with the vaginal vault and fornices obliterated. Examination must be stopped if patient becomes too distressed due to pain or discomfort. Vaginoscopy may be done as an alternative [11].

Laboratory Investigations

Laboratory tests are not typically required to conclude a diagnosis. Vaginal pH may be tested using a simple pH strip by holding it against the vaginal wall. A raised pH (≥5) in absence of infection or due to semen in the setting of a recent

intercourse may suggest hypoestrogenism induced atrophy. Vaginal smear may be taken for assessment of Maturation Index, wherein the proportion of parabasal, intermediate and superficial cells is described. A progressive increase in parabasal cells and a decrease in the superficial cells are observed with increasing duration of hypoestrogenism. Microscopic evaluation of urine and vaginal discharge is pertinent if UTI or vaginitis is suspected.

Table 1: Complications of Gym		
Labial atrophy	Ischemia of vesical trigone	CSS
Vulvar atrophy and lesions	Meatal stenosis	
Atrophy of Bartholin glands	Cystocele and rectocele	
Intravaginal retraction of urethra	Urethral prolapse	
Alkaline pH (5–7)	Urethral atrophy	
Reduced vaginal and cervical secretions	Retraction of urethral meatus inside vagina associated with vaginal voiding	
Pelvic organ prolapse	Uterine prolapse	
Vaginal vault prolapse	Urethral polyp or caruncle	
Vaginal stenosis and shortening		
Introital stenosis		

Table 1: Complications of Gum.

Etiological Risk Factors for Genitourinary Syndrome of Menopause

- Non-menopause hypoestrogenism
- Bilateral oophorectomy
- Cigarette smoking
- Alcohol abuse
- Decreased frequency and sexual abstinence
- Ovarian failure
- Lack of exercise
- Absence of vaginal childbirth (Figure 2).

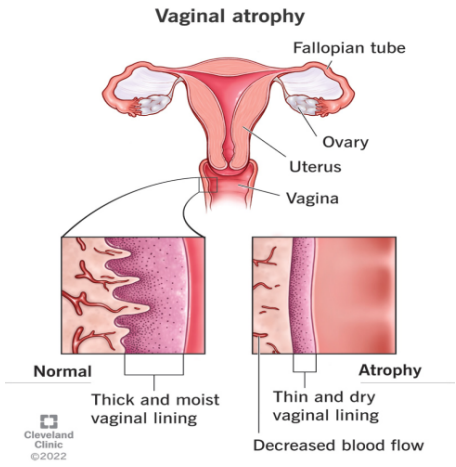

Figure 2: Vulvovaginal atrophy in patients with Genitourinary Syndrome [15].

Investigations

Apart from clinical evaluation, certain tests are required to correlate the physical findings.

Cystoscopy

- Squamous metaplasia of trigone
- Shortening of urethra
- Pale urethral mucous membrane
- Urinary sphincter dysfunction
- Reduced compliance
- Pale trigone

Laparoscopy

Atrophic uterus, fallopian tubes and ovaries
Supporting lax ligaments

Diagnostic Aid

- Vaginal cytology: increase in parabasal cells and a decrease in superficial cells along with decrease in lactobacilli concentrations and presence of leukocytes;
- Ultrasound of pelvis (TVS/TAS): An endometrial thickness of ≤5 mm indicates decreased estrogen stimulation.
- Pap test
- Vaginal swabs to rule out infections and pH testing (symptomatic pH-5 to 7)
- Magnetic Resonance imaging/Computed tomography scan- pelvic and adnexal abnormalities

Differential Diagnosis

- Infections: Bacterial vaginosis, candidiasis, trichomoniasis
- Vaginal stenosis secondary to infection
- Foreign matter/ piercings/ contact irritants, Sexual trauma
- Precancerous lesions of vulva and vagina
- Endocrine disorders- Diabetes mellitus, hypothyroidism
- Dermatological conditions- Lichen sclerosus, Lichen planus (Table 2).

Formulation	Composition	Dosages
Nonhormonal Options		
Lubricants	Water/Silicone/Polycarbophil Based	
Moisturizers	Hyaluronic Acid	5 Mg daily for 2 Weeks, then 3-5 times per week
	Polyacrylic Acid	3 g daily
	Polycarbophil-Based Vaginal Moiturizer	2.5 g three times/ week
Vaginal Suppositories	Vitamin D, E	1000 IU, 30-200 IU respectively
Lidocaine	4% Aqueous Lidocaine	Fully saturated cotton ball applied to vulva for 3 minutes
Hormonal Options		
Vaginal Cream	Conjugated Equine Estrogen	Twice weekly 0.5 g intravaginally for moderate-to-severe dyspareunia
		Dosage regimen of 1g every night for 2 weeks Or 0.5 g twice a week are commonly used
Vaginal Cream	Testosterone	300 ug Or 150 ug applied daily
		300 ug Or 150 ug applied daily for 2 weeks, then 3 times a week
Vaginal Ring	17 Beta-Estradiol	7.5 ug/D for 90 days
Vaginal Tablet	Estradiol Hemihydrate	10ug/day for 2 weeks, then 10 Ug/day 2 times a weeks
		A vaginal insert containing 4 Ug is available, although not used in included studies.
Vaginal Insert	Prasterone	One 6.5mg vaginal insert once daily

Table 2: Nonhormonal and Hormonal Treatment Options.

Treatment of GSM

Table 2 briefly describes all the available treatment options in a clinician's armamentarium for the management of GSM.

GSM is a chronic condition requiring life-long treatment. It may range from non-hormonal local moisturizers and estrogen creams for vulvovaginal symptoms related to sexual activity. Whereas for women with vulvovaginal symptoms related to sexual activity can be treated through systematic approach including non-hormonal vaginal lubricants, low dose estrogen therapies (creams, rings and tablets) and systemic estrogen. The effects can be correlated with vaginal maturation index. Nonhormonal methods should be considered first-line treatment for urogenital symptoms in individuals with a history of estrogen-dependent breast cancer. Although hormonal-based treatments may be an option for individuals with a history of breast cancer, because many nonhormonal treatments are low-cost and low-risk, an initial trial of these options can be useful. Certain herbal remedies such as Black cohosh have been extensively studied but it is still controversial whether it exerts estrogenic effects on the atrophied vagina [2]. To assess the effectiveness of treatment, a pH test and cytologic analysis may be utilized [16].

Lubricants and Moisturizers

As mentioned, the first line treatment used for vulvovaginal symptoms unrelated to sexual intercourse should be use of lubricants along with a regular use of long-acting vaginal moisturizers. Moisturizers contain poly-carbophilic based polymers and stick to vaginal walls. When combined, they

help temporarily relieve the friction-related irritation of atrophied vagina during sexual activity. While using barrier contraceptives, it is important not to use oil-based lubricants, though most water-based and silicone-based lubricants are safe to use.

Moisturizers must mimic the vaginal secretions in terms of pH, osmolality, and composition. Usually, they stay for <24-hour duration and need daily applications. Hyaluronic acid-based moisturizers may be used as an alternative to estrogen-based treatment for vulvovaginal symptoms and decrease vaginal pH to premenopausal levels but does not improve vaginal maturation index. The use of topical lidocaine may be particularly effective for dyspareunia related to introital pain.

Estrogen Therapy

Hormonal therapy is considered as first line option for moderate-to-severe symptoms or where lubricants/ moisturizers did not relieve the symptoms. It is important to rule out all risk factors and patient needs to be fully explained about the benefits and risks before prescribing. Local vaginal applications and administering systemically have been known to rapidly restore vaginal epithelium and associated vasculature thereby removing the vulvovaginal symptoms.

Although not significant, there is a theoretical risk of high estrogen levels and its proliferative effects on the endometrium. Hence, the lowest effective dose of local estrogens should be advised. According to the North American Menopause Society, low-dose vaginal estrogens decrease vaginal pH, increase the number of vaginal lactobacilli, improve vaginal and urethral cytology, and prevent frequent UTI.

Upon systemic absorption, it could lead to unwanted side effects such as breast tenderness or enlargement, vaginal bleeding, nausea and weight gain due to water retention [17].

The adverse effects due to unopposed estrogen exposure are not usually observed if used up to 6 months. A hormone-free interval followed by resumption is advisable. The common side effects of intravaginal products include vaginal secretion, vaginal spotting, and pruritus which subside after a few applications [18]. Systemic hormone therapy may precipitate stress incontinence and hence not recommended as a solo treatment. If vaginal estrogen is not an option, vaginal dehydroepiandrosterone (DHEA) or testosterone may help with dyspareunia and improve vaginal tissue health [7,19] .

Contraindications to the Use of ET

- Suspected cases of breast cancer,
- Estrogen-dependent cancers,
- Undiagnosed vaginal bleeding,
- History of thromboembolism (ie, blood clotting disorders),
- Endometrial hyperplasia or cancer,
- Hypertension,
- Hyperlipidemia,
- Liver disease,
- Hypersensitivity to active compounds in ET,
- History of stroke,
- Venothrombotic events,
- Coronary heart disease,
- Pregnancy,
- Smoking in those age >35 years,
- Migraines with neurologic symptoms, and
- Acute cholecystitis/cholangitis.

Synthetic Steroid

Tibolone, a potent synthetic steroid, has been found to have estrogenic, androgenic and progestational activities. It has been used systemically to improve the vaginal maturation index thus reducing vulvovaginal symptoms and improve sex drive. Moreover, urinary incontinence problems of nocturia and urgency were found to be minimized.

Selective Estrogen Receptor Modulators (SERM)

SERMs have been used for treatment of various gynecological conditions including as a contraceptive. Ospemifene, administered orally, was approved by the Food and Drug Administration in 2013. The drug is found to be efficacious in improving the pH and vaginal wall vasculature in women and can be used as a potential alternative in women with contraindications to starting estrogen therapy [20].

Unfortunately, it also increases the risk of thromboembolism and should be avoided in the susceptible population.

Lasofoxifene is another SERM in phase III trials and not yet marketed for the use. While raloxifene and tamoxifen have no estrogen agonist effect on the vagina, lasofoxifene and ospemifene show a positive impact on vaginal tissue in postmenopausal women. Although several studies have found that lasofoxifene resulted in significant improvements in vaginal pH and vaginal maturation index, clinical development of this SERM is on hold [21].

Tissue-Specific Estrogen Complexes- Bazedoxifene (bza) and Conjugated Estrogens (ces)

A newer therapy, tissue-specific estrogen complex, involves combining a serm with a conjugated estrogen are better tolerated and high potency similar to combined hormone replacement therapy [22] bza/ce has been in use in postmenopausal women as it is designed to prevent

the vasomotor symptoms apart from being safe for the endometrium and breast. It also alleviates the loss of bone mineral density [23].

Laser Therapies

Recently, the use of laser treatment has become an innovative treatment option for gsm. In in 2014, food and drug administration has approved the use of fractional microablative carbon-dioxide laser therapy for genitourinary surgery. The erbium lasers have been used as a novel technique in refractory symptoms of genitourinary syndrome in menopause. These can stimulate the vaginal wall epithelial growth factor along with collagen and extracellular matrix. The timed impulses spread to raise the temperature of vaginal tissue causing remodelling changes of collagen in the introitus and vaginal canal. The effect on improvement of symptoms may last 6 months following treatment. Newer techniques involving low-energy dynamic quadripolar radiofrequency (dqrf) lasers produce thickening and rearrangement of collagen and elastic fibres pe=reserving the nerves and vessels and improvement in laxity, sexual satisfaction, dysuria, and incontinence [24].

Intravaginal Dehydroepiandrosterone

Dehydroepiandrosterone is a steroid hormone intermediate in the biosynthesis pathway for androgen and estrogen synthesis. In concentration of 0.5%, dehydroepiandrosterone increased superficial cell percentage and decreased parabasal cell in the vaginal epithelium, decreased vaginal ph, and decreased sexual pain.

Oxytocin

Oxytocin, the neuropeptide released by the posterior pituitary gland, has also been studied amidst concerns over et. Treated participants reported significant reduction in their most bothersome symptom. Additionally, vaginal ph decreased with use of oxytocin and no increase in endometrial thickness was observed [25].

Homeopathic Remedies

There is no proven efficacy using these remedies. It is estimated that 10% of women prefer herbal concoctions such as black cohosh, soy foods, comfrey root. They may have an association with vaginal wall remodelling.

Some vitamins such as vitamin e and d have been used for gsm therapy; vitamin d may help generate keratinocyte proliferation and differentiation in the vaginal epithelium [19].

Lifestyle Modifications

Increased sexual activity is advised for maintaining robust vaginal muscle condition. There is a positive link between sexual activity and maintenance of vaginal elasticity and pliability as well as lubricative response to sexual stimulation. Sexual intercourse improves blood circulation to the vagina and seminal fluid also contains sexual steroids, prostaglandins, and essential fatty acids, which serve to maintain vaginal tissue. Vulvovaginal tissue stretching also helps to promote vaginal elasticity. Masturbation or sex devices are options for patients without a partner.

Stress-reduction therapy and psychological counseling may benefit women with nonorganic causes of vaginal dryness. Cessation of smoking can help relieve symptoms. Lastly, wearing looser undergarments and legwear may improve air circulation, discouraging growth of microorganisms.

Conclusion

- The gsm is a comprehensive term that includes vulvovaginal symptoms and lower urinary tract symptoms related to low estrogen levels.
- The terms vulvovaginal atrophy and atrophic vaginitis now has been replaced with genitourinary syndrome of menopause.
- It is a largely underdiagnosed condition and women show reluctance to consult and take hormone therapy owing to possible side effects and consider it a part of normal aging.
- The condition GSM may have a profound negative impact on Quality of Life of postmenopausal women, women should be made aware of their problems and treated with an appropriate effective therapy.
- Vaginal estrogens effectively relieve common vulvovaginal symptoms and have additional effects on urinary symptoms such as urinary urgency, frequency or nocturia, SUI, and recurrent UTIs.
- Non-hormonal moisturizers are also a useful alternative for minor atrophy-related symptoms and for patients at risk of estrogen-related neoplasm.

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