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Review Article

The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review

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Abstract

Objective: The objective of this consensus document is to broaden the perspective on clinical management of genitourinary syndrome of menopause to include androgens.

Methods: A modified Delphi method was used to reach consensus among the 14 international panelists representing multiple disciplines and societies.

Results: Menopause-related genitourinary symptoms affect over 50% of midlife and older women. These symptoms have a marked impact on sexual functioning, daily activities, emotional well-being, body image, and interpersonal relations. Tissues in the genitourinary system are both androgen and estrogen-dependent. The clitoris, vestibule, including minor and major vestibular glands, urethra, anterior vaginal wall, periurethral tissue, and pelvic floor are androgen-responsive. Historically, treatment of postmenopausal genitourinary symptoms involved both androgens and estrogens. This subsequently gave rise to predominantly estrogen-based therapies. More recently, double-blind, placebo-controlled clinical trials have demonstrated that local vaginal dehydroepiandrosterone improves symptoms in postmenopausal women, including moderate to severe dyspareunia. Limited data suggest that systemic testosterone treatment may improve vaginal epithelial health and blood flow. Open-label studies that have used high doses of intravaginal testosterone in the presence of aromatase inhibitor therapy for breast cancer have resulted in supraphysiological serum testosterone levels, and have been reported to lower vaginal pH, improve the vaginal maturation index, and reduce dyspareunia.

Conclusions: Vaginal dehydroepiandrosterone, hypothesized to enhance local production of both androgen and estrogen, is effective for the management of dyspareunia in menopause. Vaginal testosterone offers potential as a treatment for genitourinary syndrome of menopause, but more studies are needed.

Key Words: Androgens – Dehydroepiandrosterone – Genitourinary – Menopause – Vaginal atrophy – Vulvar atrophy.

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A consensus panel was convened jointly by the International Society for the Study of Women's Sexual Health (ISSWSH) and The North American Menopause Society (NAMS) in May, 2013 to assess the usefulness of the term vulvovaginal atrophy (VVA) to describe genitourinary symptoms in women experiencing menopause. VVA was deemed insufficient in capturing the full scope of the condition and its association with the endocrinological impact of menopause. A new term was recommended—genitourinary syndrome of menopause (GSM).[1] GSM comprises a constellation of symptoms and signs associated with decreased hormone levels that can involve the labia majora/minora, vestibule/introitus, clitoris, vagina, urethra, and bladder.[1] The goal was to have a term that was acceptable for women, clinicians, researchers, educators, the media, and the public that would improve and ease conversations about genitourinary symptoms and their treatments, and also connecting those symptoms with the absence of cyclic ovarian function/menopause.[2,3] This was deemed to be particularly important, because approved therapies for VVA/GSM do not include regulatory indications for urinary tract symptomatology. The terminology was formally endorsed by the boards of both societies in 2014 and has been endorsed by the American College of Obstetricians and Gynecology and adopted by the Endocrine Society, European Society of Menopause and Andropause, and International Menopause Society.

The GSM symptoms and signs are not limited to sexually active women and include irritation, burning, and itching of the introitus; dysuria, urinary frequency, and urgency, recurrent urinary tract infections (see Supplemental patient case 1, http://links.lww.com/MENO/A320); vaginal dryness, fissures at the posterior fourchette, labial resorption, pallor/erythema, loss of vaginal rugae, protrusion of the urethral meatus and urethral sensitivity, and also sexual symptoms of diminished lubrication, vaginal, vestibular or vulvar discomfort or pain with sex, or impaired sexual function (desire, arousal, orgasm).[4]

Such symptoms can be bothersome, cause personal distress, and reduce quality of life (QoL).[2,5] The QoL impact of GSM is comparable with such serious medical conditions as arthritis, chronic obstructive pulmonary disease, asthma, and irritable bowel syndrome.[5] Unlike vasomotor symptoms that are episodic and most commonly transient, typically decreasing in frequency and severity over time, even without treatment, GSM is chronic and progressive, increasing in severity with advancing menopausal age, and does not improve without treatment.[1,4] Traditional nonhormonal therapies for GSM include over-the-counter lubricants during sexual activity and regular use of moisturizers, neither of which re-establishes normal anatomic and physiologic losses. Local hormonal therapies for GSM include estrogens: estradiol, estriol (approved outside the United States), conjugated equine estrogens (CEEs), synthetic alternatives with estrogenic activity, and also intravaginal dehydroepiandrosterone (DHEA). It is well-documented that local estrogen therapy is underprescribed with an Australian study reporting only 4.5% of women aged 40 to 65 years being current users of vaginal estrogen therapy.[6] Similarly, only 6% of women with a mean age of 58 years are current users of vaginal estrogen therapy in the United States.[7] Between 55% and 80% of women discontinue estrogen treatment due to fear of adverse effects from use, lack of efficacy, cost, or other reasons.[4,8-11] In the United States, this also may be, in part, a result of the fact that topical estrogen therapies indicated for GSM have a boxed warning suggesting an increased risk of endometrial and breast cancer, stroke, deep vein thrombosis, pulmonary embolism, and myocardial infarction. There is an additional warning of an increased risk of probable dementia in postmenopausal women over 65 years of age. These risks not only frighten patients,[12] but have been called into question, as they are scientifically invalid.[13]

Education of both healthcare professionals (HCPs) and patients is important as it is projected that there will be more than 889 million women worldwide between the ages of 50 and 80 years by 2020, and up to one-half of them will experience GSM symptoms at some point.[5,14-16] Many women remain unaware that vulvar, vestibular, vaginal, urethral, and bladder changes can be a direct result of the menopause.[2,3] As a result, GSM is both underdiagnosed and undertreated.

It is noteworthy that historically the management of women with postmenopausal symptoms included androgens.[17] Before the advent of systemic CEE (1941 and 1942 in Canada and the United States, respectively), the management of menopausal symptoms consisted of ovarian extracts. There is a general lack of awareness amongst HCPs that androgens are physiologically important for women, including for the maintenance of genitourinary health. The 19-carbon androgen sex steroid hormones include: DHEA, androstenedione,

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androstenediol, testosterone, and 5α-dihydrotestosterone (5α-DHT). Each of these hormones is synthesized in significant amounts in women. Androgen receptors are widespread throughout the genitourinary tract (clitoris, vestibule, urethra, bladder, vagina, female prostate tissue). Human and animal studies demonstrate physiological changes in these tissues in response to both androgen deprivation (atrophy) and replacement (tissue restoration) (see ''Physiology of androgens and estrogens in genitourinary tissues'' section).

To optimize treatment outcomes in patients with GSM, a potential new treatment paradigm based on emerging scientific and clinical principles may include androgens. This review summarizes the evidence supporting the role of androgens in genitourinary health and the rationale for local androgen-based therapies for the treatment of GSM.

METHODS

The International Society for the Study of Women's Sexual Health is a not-for-profit multidisciplinary, academic, and scientific organization dedicated to supporting the highest standards of ethics and professionalism in research, education, and clinical practice of women's sexual health. The ISSWSH Executive Committee chose co-chairs for this project in July, 2017 to identify potential panelists based on their expertise. Panelists were asked to perform evidence-based literature reviews, identifying high-quality publications judged to be important and pertinent to their respective topics. Selection criteria were based upon the expertise and experience of each panellist, and not systematically defined. The panel of 14 researchers and clinicians convened in Dallas, Texas, in August, 2017 to present and discuss the current state of knowledge on GSM and the role of androgens in female genitourinary tissues. Panelists, who declared potential conflicts of interest before the meeting, were ISSWSH members and nonmembers. They deliberated on the history, pathophysiology, diagnostic process, and treatment of GSM, and were assigned to writing groups for the development of this manuscript. No industry representatives were present in the closed committee meetings, and there was no industry participation in the selection and evaluation of the evidence or in the creation of this document.

GSM—SYSTEMATIC CLASSIFICATION OF THE PROBLEM

Genitourinary syndrome of menopause is a comprehensive term that includes both symptomatic VVA and lower urinary tract symptoms related to low levels of androgens and estrogens[1] (Table 1).[4] Genitourinary structures express both estrogen and androgen receptor proteins making them vulnerable to change as hormone levels begin to decline, with changes including reduced collagen and elastin, thinning epithelium, altered function of smooth muscle, loss of elasticity and flexibility, and diminished blood supply[18] (see ''Physiology'' section).

Genitourinary syndrome of menopause includes the symptoms and signs associated with age-related and postmenopausal androgen and estrogen decline, and involves anatomical and physiological changes to the labia majora and labia minora, vestibule, clitoris, vagina, urethra, and bladder and androgen receptor-rich (prostate) tissue[19]; it includes VVA[1] (Figs. 1 and 2).[20-22]

TABLE 1. *External genital, urological, and sexual manifestations of genitourinary syndrome of*[5] *menopause*

External genital		Urological		
Signs and symptoms	Complications	Signs and symptoms	Complications	Signs and symptoms
Vagina/pelvic pain and pressure	Labial atrophy	Frequency	Ischemia of vesical trigone	Loss of libido
Dryness	Vulvar atrophy and lesions	Urgency	Meatal stenosis	Loss of arousal
Irritation/burning	Atrophy of Bartholin glands	Postvoid dribbling	Cystocele and rectocele	Lack of lubrication
Tenderness	Intravaginal retraction of urethra	Nocturia	Urethral prolapse	Dyspareunia
Pruritus vulvae	Alkaline pH (5-7)	Stress/urgency	Urethral atrophy	Dysorgasmia
Decreased turgor and elasticity	Reduced vaginal and cervical secretions	Incontinence	Retraction of urethral meatus	Pelvic pain
Suprapubic pain	Pelvic organ prolapse	Dysuria	Inside vagina associated with vaginal voiding	Bleeding or spotting during intercourse
Leukorrhea	Vaginal vault prolapse	Hematuria	Uterine prolapse	
Ecchymosis	Vaginal stenosis and shortening	Recurrent urinary tract infection	Urethral polyp or caruncle	
Erythema	Introital stenosis			
Thinning/graying pubic hair				
Thinning/pallor of vaginal epithelium				
Pale vaginal mucous membrane				
Fusion of labia minora				
Labial shrinking				
Leukoplakic patches on vaginal mucosa				
Presence of petechiae				
Fewer vaginal rugae				
Increased vaginal friability				

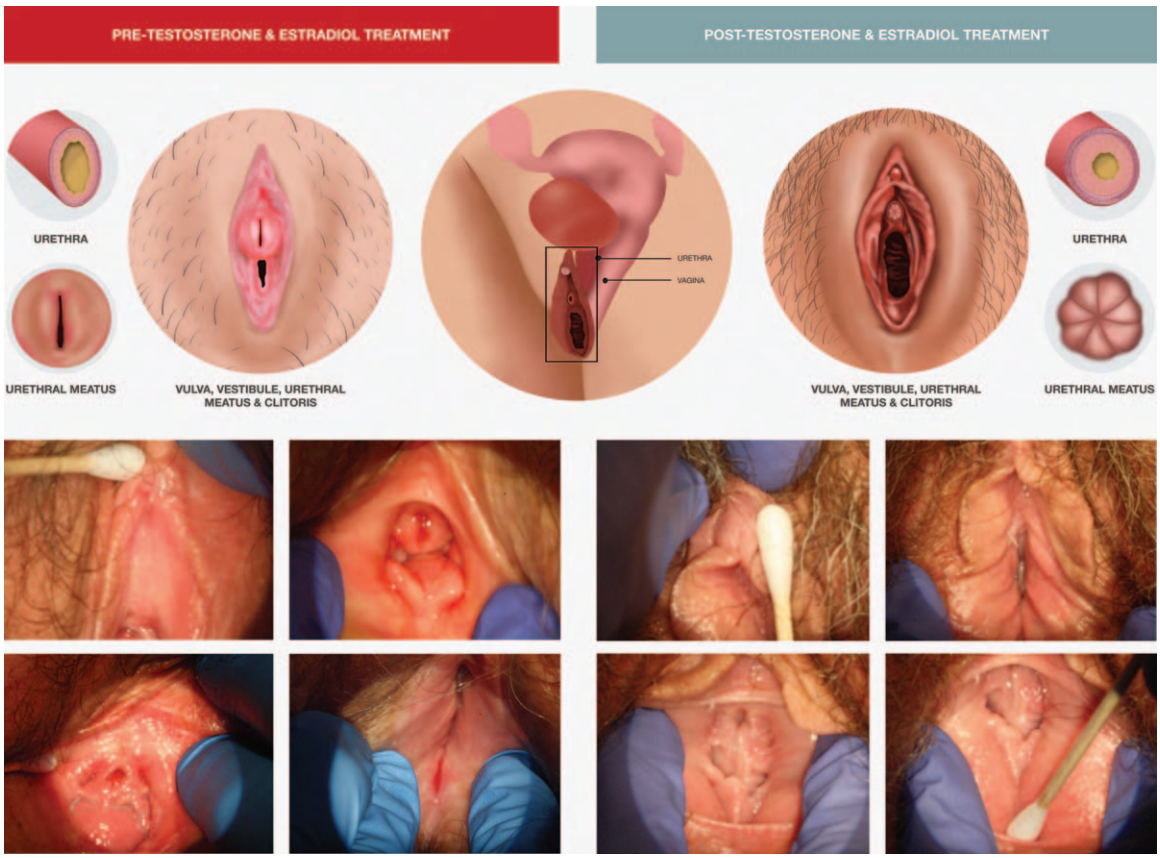

FIG. 1. External genitourinary anatomy of menopausal women with GSM showing the vulva, vestibule, urethral meatus, and clitoris before and after both systemic and local testosterone and estradiol treatment. The three-dimensional drawing in the center illustrates the external and internal genitourinary organs. Enlarged external views of region denoted in the box are shown on either side. Pretreatment illustrations and photographs (left): the urethra shows thinning of all layers (inner epithelial lining, spongy submucosa, smooth muscle layer, and outer fibroelastic connective tissue layer). Distally, the urethral meatus is prominent with a vertical urethral meatus taking up more than half of the introitus, with eversion of the epithelium. The vulva is flattened with sparse hair, with resorption of the labia minora, atrophy of the clitoral glans, and phimosis of the prepuce. The vestibule reveals pallor, erythema, and decreased moisture, and the introitus is stenotic and may reveal fissures. Post-treatment illustrations and photographs (right): the urethra, urethral meatus, vulva, vestibule, and clitoris all return to pre-GSM state. Photos contributed by I. Goldstein MD, San Diego Sexual Medicine, San Diego, CA. GSM, genitourinary syndrome of menopause.

Women may present with some or many of the symptoms of GSM.[1] GSM is highly variable, presenting with all or few of the signs and symptoms of this condition, but should not be attributable to another diagnosis, such as vaginal candidiasis or lichen planus. Discussions should include nonhormonal and hormonal therapies, with shared decision-making based upon the patient's preferences and medical considerations, including a discussion of the benefits and risks of each available treatment.[23]

EPIDEMIOLOGY AND RISK FACTORS

Incidence and prevalence

Recent Internet surveys[3,24] of women of various ages (lowest age 40) suggest that vaginal dryness ranges from 55% to 85%, dyspareunia from 29% to 59%, and vaginal itching/irritation from 26% to 77% (Fig. 1).[3] The prevalence of urinary symptoms has not been as well-quantified; however, the prevalence of new urinary incontinence has been estimated as 17% in an Australian study.[25] The Day-to-Day Impact of Vaginal Aging (DIVA) questionnaire[26] and Vulvovaginal Symptom Questionnaire (VSQ)[27] provide objective means to assess patient symptoms.

Time course

The Stages of Reproductive Aging + 10 Workshop suggests that most VVA symptoms are likely to emerge 3 to 6 years after menses ceases, although some women complain of vaginal dryness and urinary symptoms during the menopause transition.[28] In a well-characterized longitudinal study, during 7 years of the menopause transition, bothersome vaginal dryness increased linearly and affected 50% of Australian women by 3 years postmenopause.[29] An in-depth focus group of postmenopausal women reporting genitourinary symptoms suggested that these symptoms have a marked impact not only on sexual functioning but also everyday activities, emotional well-being, body image, and interpersonal relations.[5,30]

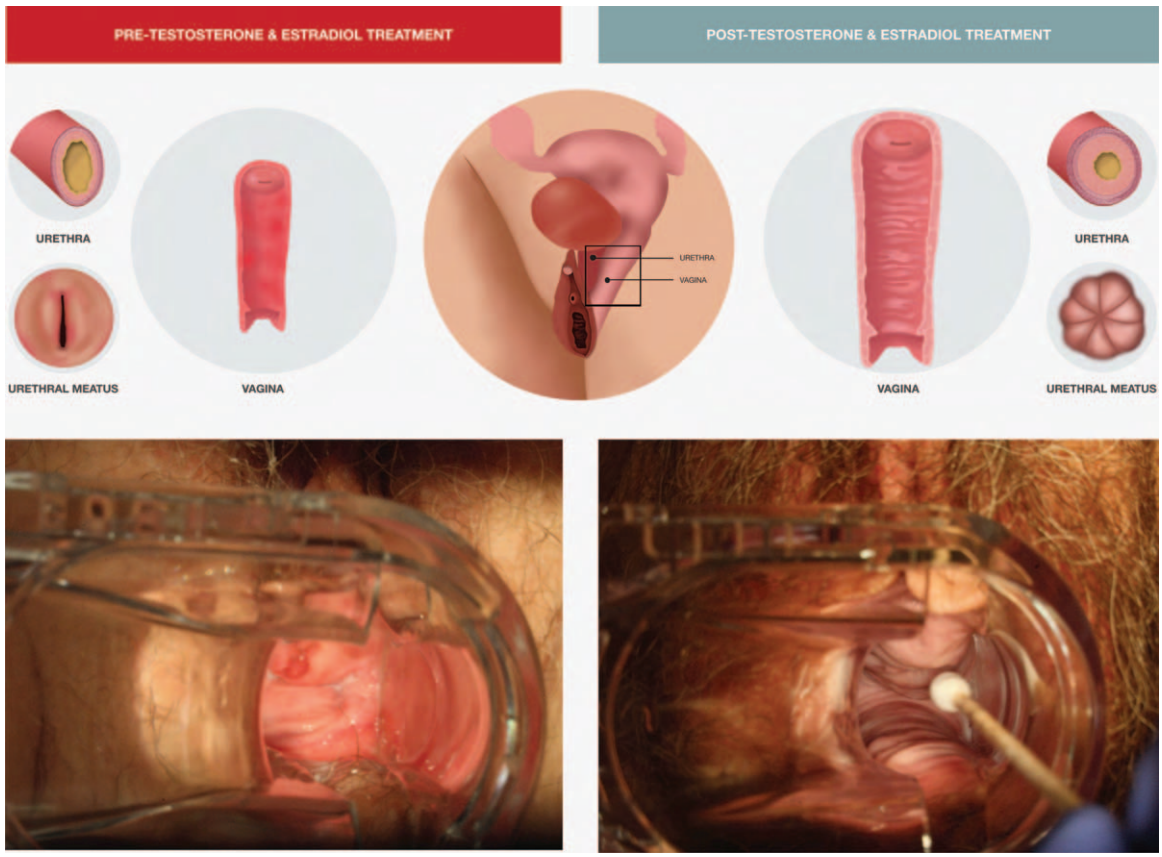

FIG. 2. Internal genitourinary anatomy of menopausal women with GSM showing the vagina before and after both systemic and local testosterone and estradiol treatment. The three-dimensional drawing in the center illustrates the external and internal genitourinary organs. Enlarged internal views of region denoted in the box are shown on either side. Pretreatment illustrations and photographs (left): the urethra shows thinning of all layers (inner epithelial lining, spongy submucosa, smooth muscle layer, and outer fibroelastic connective tissue layer). Distally the urethral meatus is prominent with a vertical urethral meatus taking up more than half of the introitus, with eversion of the epithelium. The vagina may be shortened and narrowed, and the vaginal surface may appear thin, pale, dry, less elastic, and smoother with fewer rugae. Post-treatment illustrations and photographs (right): the urethra, urethral meatus, and vagina all return to pre-GSM state. Photos contributed by I. Goldstein MD, San Diego Sexual Medicine, San Diego, CA. GSM, genitourinary syndrome of menopause.

Risk factors

Some demographic factors have been identified as associated with increased risk for symptoms. In the Women's Health Initiative observational study, Hispanic ethnicity, obesity, and diabetes (see Supplemental patient case 2, http://links.lww.com/MENO/A320) correlated with ≥two urogenital symptoms at enrollment.[31] In a US cohort study of women (average age 64 years with >70% at least 10 years beyond the menopause), vaginal dryness was associated with younger age, nonwhite race, diabetes, and lower body mass index.[32] A Kaiser Permanente study revealed that depression and urinary incontinence magnify the impact of vulvovaginal symptoms on women's QoL (activities of daily living, emotional well-being, sexual functioning, and self-image and body concept).[33] Treatment of breast cancer (see Supplemental patient case 3, http://links.lww.com/MENO/A320) increases GSM risk in several ways: ovarian insufficiency secondary to chemotherapy, selective estrogen receptor modulator therapy (usually tamoxifen), and aromatase inhibitor therapies.[34,35] As these agents are now recommended for up to 10 years of adjuvant therapy, this clinical challenge continuously grows.[36] Women with ovarian insufficiency (surgical, autoimmune, genetic, medically induced), hypoestrogenic amenorrhea (postpartum, hypothalamic amenorrhea, hyperprolactinemia), and women with ultralow-dose oral contraceptives (see Supplemental patient case 4, http://links.lww.com/MENO/A320) are also at risk.

PHYSIOLOGY OF ANDROGENS AND ESTROGENS IN GENITOURINARY TISSUES

In addition to estrogens, androgens may play a more important role for the maintenance of genitourinary tissue structure and function, than traditionally appreciated (Fig. 3).[1,37] While this perspective on the role of sex steroid hormones in genitourinary tissues is based predominantly on data from animal studies, several lines of evidence corroborate the potential importance of androgens and estrogens in human genitourinary physiology. Expression of androgen receptors (ARs) and estrogen receptors (ERs) in human genitourinary tissues has been reported by multiple

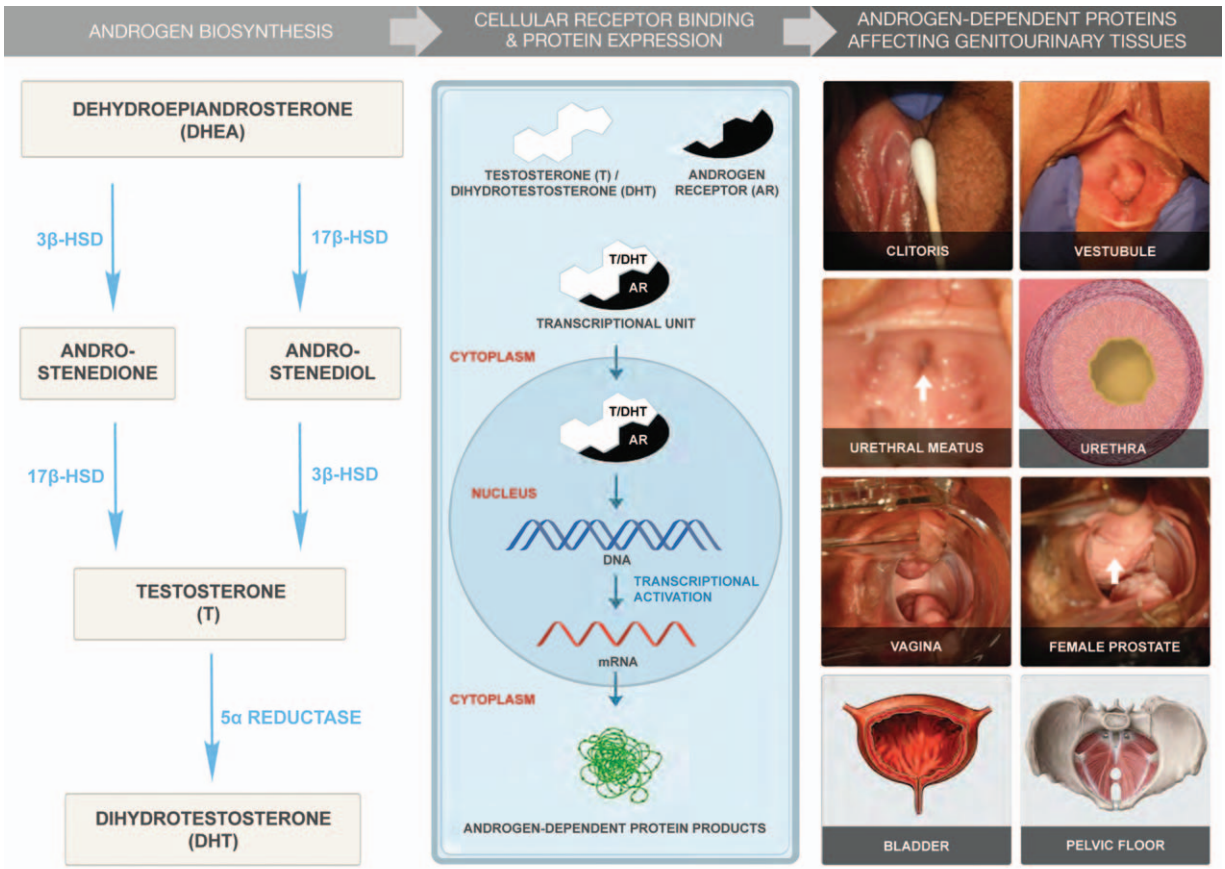

FIG. 3. Androgen biosynthesis is depicted in the left panel; cellular receptor binding and protein expression is depicted in the center panel; photographs and illustrations of androgen dependent genitourinary tissues of menopausal women with GSM after both systemic and local testosterone treatment are depicted in the right panel. Photos contributed by I. Goldstein MD, San Diego Sexual Medicine, San Diego, CA. GSM, genitourinary syndrome of menopause; HSD, hydroxysteroid dehydrogenase.

investigators utilizing immunohistochemical, western blotting, and mRNA expression techniques.[38] Biochemical, histological, and in vivo functional effects in response to decreased hormone levels and/or hormonal supplementation in patients also provide supportive information that is consistent with preclinical data. It is noteworthy that in healthy premenopausal women, the production of androgens is significantly greater than that of estrogens, and that androgens are necessary precursors for the biosynthesis of estrogens.[39,40]

Vagina

Estrogen receptors are present in the epithelium, and also in stromal and muscle cells of the human vagina.[41,42] Estrogen stimulates cell proliferation and thickening of the human vaginal epithelium.[43] More recent studies confirm that epithelia throughout the lower urinary tract of women exhibit increased proliferation in response to estrogen.[44] Androgens may also independently influence vaginal health.[45] AR protein immunoreactivity and mRNA have been detected throughout the human vagina (mucosa, submucosa, stroma, smooth muscle, and vascular endothelium).[46-49] While some effects of testosterone may be due to its conversion to estradiol by aromatase, testosterone appears to have direct effects on genitourinary tissues.[50] Androgens and estrogens regulate vaginal mucin production in epithelial cells and influence neurotransmitter content or nerve density in the vagina.[38] Sex steroid hormones may also regulate AR and ER expression in genitourinary tissues, and these biochemical alterations may further provide mechanistic understanding to the changes that occur with fluctuating hormone levels.[38]

Bladder/urethra/prostate

The responsiveness of the bladder, urethra, and female prostatic tissue[19] to sex steroid hormones in women is supported by several correlational lines of evidence. Vascular resistance has been shown to be greater in the bladder neck of menopausal women than premenopausal women, and systemic estradiol and progesterone therapy increased blood flow to the bladder neck in menopausal women with stress urinary incontinence.[51] In addition, ultrasound assessment of normal-weight premenopausal women with and without polycystic ovary syndrome suggested a positive correlation between circulating testosterone levels and the volume of urethrovaginal tissue.[52] While the full clinical significance of these

observations remains unclear, in genitourinary tissue of women (vaginal punch biopsies near external urethral meatus), estradiol levels were positively correlated and testosterone levels were negatively correlated with markers of collagen turnover.[53]

Clitoris/vulva/labia

Positive immunostaining for ER and AR has been demonstrated in the epidermis and dermis of human vulvar tissue, but ER was less prevalent and AR was more prevalent when compared with the vagina.[42,46,54] The clitoris continues to be androgen-dependent through menopause, and clitoral hypertrophy is considered one of the most sensitive markers for excess androgen production in women.[55,56] Yet, even in this androgen-sensitive organ, estrogen is functionally important. In healthy eumenorrheic premenopausal women, basal clitoral volume and blood flow varied during the menstrual cycle. In the absence of sexual arousal, estradiol levels were positively correlated with clitoral volume and negatively correlated with vascular resistance.[57] Thus, both estradiol and testosterone are necessary for maintenance of molecular signaling pathways important for vascular responsiveness of the clitoris during sexual arousal.[58]

Hormone receptor polymorphisms may influence susceptibility to certain clinically significant conditions, as hormone levels decline with age and with menopause. For example, in a small study of premenopausal women taking combined hormonal contraceptives, those who developed vestibulodynia were more likely to have longer cytosine-adenine-guanine (CAG) repeats in the AR gene—a genetic characteristic associated with decreased responsiveness to androgens in target tissues.[59] Such relationships may persist after menopause.

DIAGNOSIS OF GSM

Genitourinary syndrome of menopause is primarily a clinical diagnosis, based upon a detailed patient history and physical examination. Because many women are reluctant to discuss symptoms with an HCP, a respectful and culturally sensitive approach to taking a history and performing a physical examination are particularly important.[24] The diagnosis of GSM can be confirmed by objective outcomes: a vaginal pH ($\geq$5.0), a decreased content of superficial cells, and an increased proportion of parabasal cells (see below: ''Laboratory evaluation''). Assessment of these endpoints is commonly reserved for research, although historically, the maturation index was used for laboratory confirmation of clinical findings. The role of blood tests (ie, hormonal concentrations) in the diagnosis of GSM is controversial.

Clinical history

A menstrual and medication history should be taken to assess menopausal status, and the potential impact of pharmacologic agents on hormonally responsive, mucus membrane-like tissues. A complete review of systems should be performed, as genitourinary symptoms may be due to other etiologies (Table 1). The clinician should elicit symptoms that may be associated with infection or inflammatory conditions, and also use of products that may be topical irritants or result in allergic reactions (eg, perfumes, powders, soaps, lubricants). A pertinent sexual history should be taken to evaluate whether the symptoms are associated with sexual activity or are always present, and specifically whether the woman is having pain with foreplay or penetration. Follow-up questions as to associated alterations in desire, arousal, and/or orgasm are likewise important. QoL issues should also be assessed including personal or interpersonal ''bother'' or distress that are associated with the symptoms, and ultimately the impact of these symptoms on daily activities (sitting, urination, choice of clothing, etc), sexual activity, and partner relationships.[60]

The physical examination

To verify the diagnosis of GSM, menopausal women with symptoms should undergo a comprehensive physical examination of the genitourinary system[1] (Table 1). It can be useful to have a patient hold a mirror, or take a photo during the examination to establish a common nomenclature between patient and examiner, and to show the patient her own findings, making her an active participant in her care and helping her to self-monitor her progress during treatment.

Evaluation of the external genitalia may include evidence of thinning or absent pubic hair, diminished elasticity and turgor of the vulvar skin, introital narrowing and decreased moisture, and fusion or resorption of the labia minora. In severe cases, the labia majora may also be partially fused particularly at the superior or inferior borders. Loss of the labial fat pad can give the labia majora a flattened or even pendulous appearance, making the labia minora appear less distinct and the clitoris appear protuberant.[61,62] While erythema is a nonspecific finding in atrophic tissue, focal painful erythema in the androgen-dependent vestibule, particularly near the ostia of the Bartholin's glands (4:00 and 8:00 o'clock) or greater vestibular glands, and the Skene's glands (1:00 and 11:00 o'clock) or lesser vestibular glands, is often suggestive of hormonally associated vestibulodynia. Patients with vestibulodynia (see Supplemental patient cases 2-6, http://links.lww.com/MENO/A320) will frequently complain of penetrative dyspareunia and experience allodynia with the cotton swab palpation of the vulvar vestibule.[63] During examination of the interlabial sulci and periclitoral area, the examiner might note hypopigmentation, microfissures, and/or plaque-like tissue. Physical examination can be improved by magnification (ie, vulvoscopy), and biopsy to differentiate GSM from other dermatological conditions of the vulva such as lichen sclerosus, lichen planus, or lichen simplex chronicus.[63,64]

During evaluation of the urethral meatus, a common finding of GSM is the urethral caruncle, which presents as prominent and often erythematous tissue (see Supplemental patient cases 3, 5, 6, http://links.lww.com/MENO/A320). Urethral prolapse, a telescoping appearance, and/or urethral polyps can also occur as signs of GSM.[61]

When using the speculum to examine the vagina, it may be necessary to use a small speculum, as even gentle contact can cause pain and bleeding due to tissue thinning and/or introital stenosis. If the speculum examination cannot be completed, it should be delayed until hormonal intervention has been given adequate time to alter the introitus, or in rare cases, until it can be completed under anesthesia (Table 1). Rotating the speculum blades 90 degrees allows visualization of the anterior and posterior vaginal walls where pathology can be missed.

Upon completion of the internal vaginal/pelvic examination, the examining fingers should be turned posteriorly to assess the pelvic floor musculature, especially in women who have irritative or obstructive urinary symptoms. The levator ani muscles are palpated for hypertonicity, tenderness, weakness, and trigger points, which can provide evidence of overactive or underactive pelvic floor musculature. The examiner should also place 1 to 2 fingers against the lateral vaginal walls, palpating as the woman attempts to squeeze and relax the skeletal muscles. In the case of pelvic floor dysfunction, which can be caused or exacerbated by steroid hormone deficiency, birth trauma, primary muscular disorders, and so on, this maneuver often yields poor, and/or uncoordinated muscle recruitment and/or pain (see Supplemental patient case 6, http://links.lww.com/MENO/A320). This digital examination of both the posterior and lateral aspects of the vagina is an essential part of a comprehensive examination of the postmenopausal woman because while pelvic floor muscle dysfunction can be associated with GSM, treatment of GSM and pelvic floor muscle dysfunction can differ.[63]

Laboratory evaluation

A clinical diagnosis of hormonal deficiency can be supported by several laboratory studies. Such studies are not typically required to make the diagnosis. They include the following:

- Vaginal pH: Measurement of pH of the vaginal vault secretions is a clinically helpful laboratory test. The pH of a healthy vagina ranges from 3.5 to 5.0. Vaginal pH may reach levels of 5.5 or higher in women with GSM, and can be considered an indicator of vaginal atrophy due to hormonal deficiency.[62]
- Microscopic examination: Microscopic evaluation of a vaginal smear allows the clinician to identify status of vaginal epithelial health. The wet smear of a woman with GSM shows an abundance of small, rounded parabasal epithelial cells and a deficiency of larger, superficial cells. In addition, the lactobacillus-dominated flora are replaced by a mixed flora of gram-negative rods and gram-positive cocci. If a large number of polymorphonuclear leukocytes are present, the underlying cause of the vaginal symptoms may be inflammation or infection.[65]
- Serum hormone levels: Hormone levels should only be measured when clinically indicated, such as when primary ovarian insufficiency is suspected (follicle stimulating hormone and estradiol), or to explore other causes of amenorrhea such as hyperprolactinemia or pituitary insufficiency.[66] Although the components of GSM are a consequence of sex steroid deficiency, no laboratory blood tests will either confirm or negate the diagnosis, because there is no cut-off serum concentration for any sex steroid below which most women will experience symptoms of GSM. Some women experience substantial symptoms of GSM even when they are using systemic hormone therapy (particularly the lower doses currently recommended for oral therapies), and may require concurrent local treatment, while other women may be asymptomatic with very low serum sex steroid levels.

TREATMENT OF GSM

History of GSM therapy

Since the early 1900s, clinicians advanced the use of extracts from animal ovaries (organotherapy) for aging women.[17,67] Because the ovaries produce both androgens and estrogens, prescribing extracts possibly provided androgens, and also estrogen for treatment of menopausal symptoms.[68] However, the potential androgen component of ovarian extract therapies was not highlighted, and most attention was focused on estrogens as the most effective therapy relief of symptoms associated with estrogen insufficiency (ie, hot flashes, night sweats, disturbed sleep). Over the ensuing years, many estrogen preparations in various delivery systems became available, starting with oral CEE in 1941. Low-dose vaginal estrogen preparations (vaginal creams, pessaries, and rings) designed for local delivery of CEE, estradiol, and estriol (approved outside the United States) for the treatment of VVA, became widely available in the 1970s. These are safe (endometrial data for up to 1-2 years) and effective when low doses are used several times weekly[69] (creams and pessaries) or over several months (rings), and usually result in minimal systemic absorption, particularly once the vaginal epithelium thickens in response.[13,23,70,71]

Systemic options for management of menopausal symptoms including GSM that combine both androgenic and estrogenic actions include esterified estrogens with methyltestosterone, and tibolone, that exerts estrogenic, progestogenic, and androgenic effects.[72,73] No testosterone preparation is currently approved for use in women, and tibolone is not universally available.

Local DHEA therapy

Intravaginal DHEA (prasterone) has been approved by the US Food and Drug Administration for the management of moderate to severe dyspareunia due to menopause (see Supplemental patient cases 2, 3, 5, http://links.lww.com/MENO/A320). It is yet to be approved in other countries. It is hypothesized that intravaginal DHEA is a substrate converted by enzymes within the vagina (intracrine metabolism)[50] into estrogens and androgens such as androstenediol, androstenedione, testosterone, and DHT (Fig. 3). In placebo-controlled clinical trials, daily insertion of DHEA vaginal ovules decreased vaginal pH, improved the vaginal epithelial maturation index and vaginal epithelial thickness and integrity, and increased vaginal secretions resulting in improvement in

dyspareunia and all domains of sexual function as assessed by the Female Sexual Function Index.[74] These trials reported an increase in serum estradiol from 3.33 to 5.04 pg/mL and testosterone from 12 to 15 ng/dL, remaining within the normal postmenopausal range. Endometrial effects after 1 year of therapy were not clinically significant.[75-78] Intravaginal DHEA has not been studied in women with a history of breast cancer.

Systemic testosterone therapy

Data for the direct effects of systemic testosterone therapy on urogenital health in women are scant. The first report of the administration of subcutaneous testosterone propionate pellets (22-400 mg; average dose 100 mg) in naturally and surgically menopausal women was that this treatment neither suppressed nor enhanced the maturation of the vaginal epithelium.[79] Salinger subsequently reported the vaginal effects of systemic testosterone in 12 surgically menopausal women, aged 54 to 85 years.[80] Treatment was daily, or alternate day, intramuscular testosterone propionate, to a total dose of 125 mg, followed by vaginal biopsy 1 week later.[80] Increased vaginal epithelial intermediate and superficial cells, and increased glycogen deposition were reported.[80] A single dose of 5 mg of oral methyltestosterone was associated with a slightly greater increase in vaginal pulse amplitude (indicating augmented vaginal blood flow) compared with placebo, after exposure to an erotic video, in 10 healthy sexually active menopausal women.[81] More recent studies of systemic transdermal testosterone therapy, either alone or combined with estrogen therapy, have not provided data for the effects on vaginal health.[82-85]

Local testosterone therapy

The few studies that have investigated intravaginal testosterone for VVA have ranged in size from 10 to 80 participants, and have involved either a single dose, or durations of 4 to 12 weeks.[50,86-90] The systemic absorption of a single intravaginal dose of 2 mg testosterone, in a double-blind, placebo-controlled crossover study of premenopausal women, resulted in supra-physiologic testosterone levels with no change in serum estradiol (measured by radioimmunoassay).[89] An open-label study of menopausal women indicated intravaginal testosterone may lower vaginal pH and increase the proportion of vaginal lactobacilli, compared with a lubricant gel.[86] In another study, intravaginal testosterone (5 mg/dose) was combined with vaginal CEE and compared with CEE-alone or a lubricant gel.[90] As both active treatment arms included CEE, the independent effects of testosterone are uncertain. Serum free testosterone increased, but the levels reported were not as high as those reported by Apperloo et al.[89] The three studies of intravaginal testosterone in women with breast cancer taking an aromatase inhibitor (AI) provide inconclusive data potentially due to concerns about AI efficacy or compliance with the study protocol. Improvements in vaginal maturation index,[50] lessened dyspareunia,[50] and sexual function[87] were observed in the studies that employed a 0.3 mg intravaginal dose of testosterone.

Melisko et al[88] reported on the effects of intravaginal testosterone (5 mg) versus an estradiol-releasing vaginal ring (7.5 mcg estradiol/24 h), over 12 weeks, in women with early-stage breast cancer taking aromatase inhibitors. Improvements in vaginal rugae, pallor, petechiae, elasticity, and dryness were seen in both treatment arms.[88] Effects on sexual function were reported as greater for the estradiol ring without adjustment for baseline values.[88] In the intravaginal testosterone arm, 24% of the participants had elevated serum estradiol levels (baseline range <2-31 pg/mL; treatment range 14-113 pg/mL), measured by liquid chromatography-tandem mass spectrometry, raising concerns about AI efficacy or compliance under study circumstances. Total testosterone levels were elevated in women treated with testosterone (mean 171 ng/dL and median 67 ng/dL at week 12).[88] Although these data are provocative, adequately powered placebo-controlled clinical trials are needed to provide efficacy and safety before intravaginal testosterone can be considered for clinical use, particularly in breast cancer survivors.

Compounded topical estradiol 0.01% and testosterone 0.1% applied twice daily to the vestibule (average duration 20 weeks) resulted in decreased pain, and structural and functional improvements to the vestibule of premenopausal women with provoked vestibulodynia who had used combined hormonal contraceptives (average duration 7 years) (see Supplemental patient cases 1, 2, 4, 6, http://links.lww.com/MENO/A320).[91] Similar studies are yet to be completed in a postmenopausal population.

CONCLUSIONS

Genitourinary physiology in women likely involves both androgen and estrogen action. The diagnosis of GSM is based on symptoms, history, and physical examination. Early documented treatments of symptomatic postmenopausal women involved administration of ovarian extracts that may have included both androgens and estrogens. The use of estrogenic preparations effectively treats GSM. Recently, there has been increased interest in rigorous clinical investigation of appropriate dose, delivery, and risk/benefit profile of androgen therapy in women. Contemporary vaginal hormone treatments include vaginal estrogen and vaginal DHEA. Although the available data are insufficient to support the use of testosterone for the treatment of GSM, the data justify further studies to evaluate the use of vaginal testosterone for symptomatic women.

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