Postmenopausal Vulva and Vagina

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Miranda A. Farage, Kenneth W. Miller,
and Howard I. Maibach

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M.A. Farage, MSc, PhD (✉)
Clinical Innovative Sciences, The Procter and Gamble Company, 6110 Center Hill Avenue, Cincinnati, OH 45224, USA
e-mail: Farage.m@pg.com

K.W. Miller, PhD
Global Product Stewardship, The Procter and Gamble Company, Cincinnati, OH USA
e-mail: Miller.kw.1@pg.com

H.I. Maibach, MD
Department of Dermatology, University of California, School of Medicine, San Francisco, CA, USA
e-mail: MaibachH@derm.ucsf.edu

27.1 Introduction

Menopause occurs when ovarian function ceases and estradiol production decreases to miniscule levels. Although peripheral androgen conversion by the adrenals continues to produce a low level of estrogen after menopause, overall circulating levels decline dramatically from greater than 120 pg/mL to about 18 pg/mL [1]. The perimenopausal transition begins sometime after the age of 45 and lasts about 4 years. A constellation of symptoms emerges as follicular function declines. The most notable is menstrual cycle irregularity, reflecting an increase in the number anovulatory cycles and cycles with a prolonged follicular phase. Other symptoms can include cramps, bloating or breast tenderness, vasomotor symptoms ("hot flashes"), migraine headaches, and vaginal dryness. Menopause has transpired when a woman has not menstruated for a year [2]. Median age of menopause in a multiethnic sample of American women was 51.4 years [3].

Vulvovaginal and urethral epithelia have high levels of estrogen receptors that mediate hormonal action on the tissue. Consequently, the dramatic drop in circulating estrogen that accompanies menopause profoundly affects urogenital tissue structure and function. This chapter discusses postmenopausal vulvovaginal changes, with an emphasis on alterations in vulvar skin physiology, tissue atrophy, urinary changes, and susceptibility to infection. Vulvar dermatoses that are more common in older women are also discussed.

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27.2 Vulvar Skin Physiology

Skin hydration, coefficient of friction, and permeability of vulvar skin differ from that of exposed skin (reviewed in [4, 5]). Although menopause affects these parameters on exposed skin, age-related effects on vulvar skin appear negligible (Table 27.1). In brief, keratinized skin of the labia majora is more hydrated than forearm skin as measured by trans-epidermal water loss [6], and its coefficient of friction is higher [7]. Following menopause, small differences in these parameters have been measured on exposed skin, but changes in the water barrier function and friction coefficient of vulvar skin are insignificant [7].

Skin penetration of hydrocortisone and testosterone also has been compared on the forearm and on the vulva. (For perspective, penetration of testosterone but not hydrocortisone is mediated by androgen receptors.) In young women, vulvar skin is more permeable to hydrocortisone than forearm skin; however, following menopause, skin penetration of this steroid drops on the forearm but not on the vulva. By contrast, comparable testosterone penetration rates were measured at both sites in younger women, and menopause had no impact on testosterone penetration at either site [8].

Studies with the model irritant, sodium lauryl sulfate, revealed differences in susceptibility to skin irritation between exposed skin and vulvar

Table 27.1 Comparative skin physiology and menopausal status

	Site	Menopausal status[a]	Observation	Significance[b]	Reference
Water barrier function (TEWL, g/m^2·h)					
	Forearm	Premenopausal	3.7 ± 0.4	$p < 0.05$	Elsner and Maibach [6]
		Postmenopausal	2.6 ± 0.3		
	Vulva	Premenopausal	14.8 ± 1.5	n.s.	
		Postmenopausal	13.5 ± 1.8		
Friction coefficient, μ					
	Forearm	Premenopausal	0.49 ± 0.02	$p < 0.05$	Elsner et al. [7]
		Postmenopausal	0.45 ± 0.01		
	Vulva	Premenopausal	0.60 ± 0.04	n.s.	
		Postmenopausal	0.60 ± 0.06		
Hydrocortisone penetration (% dose absorbed)					
	Forearm	Premenopausal	2.8 ± 2.4	n.s.	Oriba et al. [8]
		Postmenopausal	1.5 ± 1.1		
	Vulva	Premenopausal	8.1 ± 4.1	$p < 0.01$	Schagen van Leeuwen et al. [9]
		Postmenopausal	4.4 ± 2.8		
Testosterone penetration (% dose absorbed)					
	Forearm	Premenopausal	20.2 ± 8.1	n.s.	Oriba et al. [8]
		Postmenopausal	14.7 ± 4.2		
	Vulva	Premenopausal	26.7 ± 8.0	n.s.	
		Postmenopausal	24.6 ± 5.5		
Visual erythema scores (scored on day 2 after 24-h postexposure to 1 % sodium lauryl sulfate)					
	Forearm	Premenopausal	9	$p = 0.03$	Elsner et al. [10]
		Postmenopausal	5		
	Vulva	Premenopausal	0	n.s.	
		Postmenopausal	0		

Adapted with kind permission from Miranda Farage and Howard Maibach [11]

[a]Group sizes (water barrier function and friction parameters): premenopausal, 34 subjects, postmenopausal, 10 subjects. Group sizes (hydrocortisone and testosterone penetration): 9 subjects in each age group visual erythema score to sodium lauryl sulfate. Sodium lauryl sulfate application: 10 subjects per age group

[b]*n.s.* not significant

skin. Forearm skin was far more susceptible to the model irritant, aqueous sodium lauryl sulfate (1 % w/v): this agent caused intense erythema on the forearms of premenopausal women but no visually discernible response on the vulva in either pre- or postmenopausal women [10].

27.3 Vulvovaginal Atrophy

Vulvovaginal atrophy often develops as hormonal stimulation declines through the menopausal transition (reviewed in [11, 12]). Reportedly, 10–50 % of postmenopausal women exhibit clinical signs and symptoms (Table 27.2) [14–16].

Table 27.2 Signs and symptoms of urogenital atrophy

	Signs	Symptoms
Vulvar changes	Sparse pubic hair	Itching, burning, soreness
	Shrunken labia	
	Inelastic labial skin	
	Introital narrowing or stenosis	
	Peri-introital lacerations	
	Phimotic clitoral hood	
	Fibrosed glans clitoris	
	Irritation of the posterior fourchette	
Vaginal changes	Smooth, pale, friable vaginal mucosa	Vaginal dryness
	Limited vaginal secretions	Coital discomfort or dyspareunia
	Vaginal pH >4.5	Malodorous discharge (in cases of infection)
	Higher proportion of immature basal cells on Pap smear	Burning leukorrhea (desquamative inflammatory vaginitis)
Urinary changes	Eversion of urethral mucosa	Urinary frequency
	Ecchymoses	Dysuria
		Nocturia
		Urinary tract infection

Adapted with permission from Farage et al. [13]

Pubic hair becomes sparse, the labia majora lose subcutaneous fat, and the labia minora and vestibule atrophy [17, 18]. In addition, the introitus narrows, the clitoral hood may become phimotic, and the exposed glans clitoris may fibrose. At the cytological level, estrogen-induced parakeratosis of vulvar stratum corneum, which is highest in the third decade of life, is rarely observed by the eighth decade [19].

Vaginal changes also ensue. The vaginal vault becomes shorter and narrower, losing its typical folds (rugae). Blood flow decreases and vaginal lubrication declines. As the epithelium thins, it becomes susceptible to friction-induced bleeding. Moreover, the loss of a glycogen-rich environment both disfavors colonization by lactic acid-producing microbes [20] and reduces hydrogen ion production by vaginal epithelial cells [21, 22]. Consequently, vaginal pH rises above 4.5, which heightens susceptibility to vaginal infection. A Papanicolaou smear of the upper third of the vagina reveals a higher proportion of parabasal cells and lower levels of superficial squamous cells [23–25].

Genital symptoms include decreased vaginal secretions, vaginal irritation, vulvar pruritus, dyspareunia, and postcoital bleeding [12]. Urinary symptoms include urethral discomfort, increased frequency, and dysuria [12]. If the vulvovaginal microbiota becomes disturbed, malodorous vaginal discharge, vulvovaginal inflammation, or recurrent urinary tract infection may accompany atrophic changes. In the patient free of infection, a vaginal pH of greater than 5 is a sign of hypoestrogenism [20, 23].

Only about 25 % of women who experience symptoms mention them to their health-care provider, as many consider their discomfort to be an inevitable consequence of aging. However, urinary pain, vulvovaginal irritation, or dyspareunia secondary to vaginal atrophy may prompt a woman to seek treatment. Low-dose, intravaginal estrogen therapy ameliorates vulvovaginal atrophy without significant systemic side effects and is the conservative and recommended choice when hormone supplementation is considered solely for the relief of this condition [26, 27]. Randomized trials of an ultralow-dose, 10-μg

estradiol tablet demonstrated efficacy in normalizing vaginal pH and vaginal cytology and in reducing the most bothersome symptoms of atrophy [28, 29]. This dose exhibited low overall systemic absorption and was associated with no significant evidence of endometrial hyperplasia [28]. The North American Menopause Society concludes that opposing progestogen is generally not indicated at the low estrogen doses administered locally for vaginal atrophy [26, 27].

Intravaginal administration of dehydroepiandrosterone (DHEA), an androgenic sex steroid precursor, has been proposed as an alternative approach to treating postmenopausal vaginal atrophy and associated sexual dysfunction [30, 31]. Locally applied DHEA is converted by vaginal cells to estrogens and androgens without affecting serum concentrations of estradiol or testosterone, thereby avoiding effects on other organs [32]. In randomized trials, treatment improved clinical signs of atrophy (pH, cytology, vaginal secretions, and epithelial thickness) and measures of sexual health [30, 31]. However, in contrast to intravaginal estradiol therapy, which requires application of a tablet two to three times a week, DHEA requires daily dosing of a cream preparation, a regimen that women may find more onerous [33]. The North American Menopause Society (NAMS) Web site (menopause.org) is a good source of information on treatment options for health conditions associated with menopause.

27.4 Urogenital Infections

27.4.1 Urinary Tract Infections

Escherichia coli is the primary organism involved in urinary tract infections (UTIs), and the vagina is a reservoir for urethral colonization [34–36]. As circulating estrogen declines, cell densities of lactic acid-producing microbes fall, and the incidence of vaginal colonization with *E. coli* rises [37]. This elevates the risk of UTIs. Insulin-dependent diabetes and a prior history of recurrent UTIs are associated with higher risk of UTIs after menopause [38]. Although the number of studies is limited [39, 40], a meta-analysis found evidence that intravaginal estradiol therapy may reduce the risk of urinary tract infection [41]. However, the therapy does not have regulatory approval in the USA for this indication.

27.4.2 Sexually Transmitted Infections

Many people remain sexually active in old age and can be at risk of acquiring sexually transmitted infection. Transmission of genital herpes simplex remains pertinent, and both women with an intact cervix and women who have undergone a hysterectomy can acquire trichomonadal, gonorrheal, or chlamydial infection. With advent of modern treatment, HIV/AIDS is now a chronic illness in the developed world; infected people can now live into their 70s or longer and may transmit the disease. The use of condoms should be encouraged. Sexually transmitted infection among older adults is a sensitive subject that may be facilitated in the clinical setting with a nonthreatening conversation and by using patient education pamphlets.

27.4.3 Desquamative Inflammatory Vaginitis (DIV)

Women over age 40 can suffer from desquamative inflammatory vaginitis, a rare inflammatory vaginal infection that occurs primarily in white women [42, 43]. It produces a copious, purulent discharge, and the vulva and vaginal vault appear glazed due to epithelial sloughing. Vaginal pH is greater than 4.5, but the "whiff test" is negative (no fishy odor when a drop of vaginal secretion is added to 10 % aqueous potassium hydroxide). Microscopy reveals an outpouring of inflammatory white cells (a hallmark sign), a paucity of lactobacilli, large numbers of other bacteria, and a preponderance of immature, squamous vaginal epithelial cells. Typical treatment is a 2-week course of clindamycin. Prognosis is good if there is a favorable initial response, but in some cases, long-term maintenance therapy is required.

27.5 Urinary Incontinence

Urinary incontinence is underreported condition. It may emerge prior to menopause, but incidence increases with age. Reported prevalence rates vary depending on the condition (stress, urge, or mixed incontinence) and demographic variables (age, race, parity, body mass index, etc.) [44]. Reported rates range from 10 to 40 % among subgroups of community-dwelling individuals [45, 46] and from 43 to 77 % among nursing home residents [47].

Stress and urge incontinence have different symptoms and underlying pathology (Table 27.3). Stress incontinence involves the uncontrolled loss of urine induced by sudden pressure on the abdominal organs (such as a cough, a sneeze, heavy lifting, exercise, or coital penetration). It stems from a weakened sphincter at the junction of the bladder and urethra. Stress incontinence may be first experienced by younger women aged 30–50 when the bladder sphincter is weakened by childbirth. However, its incidence peaks during the perimenopausal period (between the ages 45 and 49) [46], possibly because aging manifests the underlying weakness. Another important factor is obesity, which places additional stress on the bladder. Obese women (BMI ≥30) have twice the risk of developing stress incontinence independent of age and parity. Epidemiological data indicate that each 5-unit increase in BMI is associated with 20–70 % increase in urinary incontinence risk [48].

Urogenital prolapse, the downward descent of the internal urogenital organs toward the vagina due to weakened support, can coexist with stress incontinence. Relaxation of the musculature of the vaginal vault and weakening of the pelvic muscles due to childbirth contributes to urogenital prolapse.

Mild stress incontinence is manageable with pelvic muscle training (Kegel exercises), by limiting fluid intake, by more frequent voiding, and with the use of feminine pads. Pelvic floor muscle exercises are more effective in younger than older women [49]. Devices for stress incontinence include pessaries and urethral orifice plugs, but most women are disinclined to use them.

Table 27.3 Types of urinary incontinence in adult women[a]

	Stress	Urge
Patient population	Women aged 30–50, especially those who have given birth. Incidence rises with age	Older, usually postmenopausal women (>age 50)
Symptoms	Uncontrolled urine loss when sudden pressure is applied to the bladder (e.g., sneezing, coughing, lifting heavy objects, intercourse)	Increased frequency and urgency Inability to suppress urine loss
Causes	Weakness of the sphincter muscle at the junction of the bladder neck and the urethra	Overactive bladder muscle (i.e., stronger, more frequent bladder contractions at lower urine volumes); weakened outlet
Risk factors	Childbirth; obesity; genital prolapse; Caucasian race	Childbirth may contribute to the problem in younger women by weakening the outlet; the risk after age 50 is independent of childbearing history and may reflect age-related changes
Mechanism	Nerve or sphincter muscle damage or damage to the connective tissue supporting the bladder neck	Impaired nerve-brain reflexes regulating bladder wall contractions; shortening and thinning of the urethra after menopause; slower and less efficient voiding (retention). Childbirth may weaken the outlet, making the impact of bladder contractions more apparent
Treatment	Pelvic floor muscle training (Kegel exercises)	Behavioral modifications
	Surgery (least conservative)	Antimuscarinic drugs

Adapted from Farage et al. [13]
[a]Mixed stress-urge occurs in 30 % of cases

Duloxetine, a serotonin and noradrenaline reuptake inhibitor used to treat mood disorder, reduces the frequency of stress incontinence in randomized controlled trials in younger and postmenopausal women [9, 50, 51]. It is approved for this indication in Europe but not in the USA. In overweight or obese women, weight loss is a first-line intervention for stress urinary incontinence. For severe cases of stress incontinence, surgery is the least conservative remaining option for therapy; however, a paucity of data exists on the effectiveness of surgery in the older postmenopausal patient.

Urge incontinence involves the strong urge to urinate and inability to voluntarily control urine loss. Urge incontinence is unpredictable and more distressing when involving large urine losses. An abnormality in the sensory reflex mechanism causes heightened contractions (spasms) in the bladder wall, exerting pressure on the bladder neck and creating a feeling of urgency at lower urine volumes than is typical. Childbirth may contribute to sphincter weakness, so that the impact of bladder contractions is more apparent.

Several therapeutic approaches exist for this condition. Efficacious antimuscarinic drugs (e.g., oxybutynin, Tolterodine) block cholinergic muscarinic receptors associated with uncontrolled bladder contractions [52]. Common side effects are dry mouth and constipation. Anticholinergic drugs are contraindicated in patients with documented untreated narrow-angle glaucoma. Behavioral interventions include moderating fluid intake (although low intakes may increase contractions at lower urine volumes); bladder retraining through scheduled voids and conscious urge suppression; limiting caffeine, alcohol, and diuretics; and adding dietary fiber or probiotics to avoid constipation. Kegel exercises may alleviate the contribution of a weakened sphincter but will not affect bladder contractions.

Interstitial cystitis is a poorly understood condition with symptoms that may contribute to urinary frequency and urge incontinence (reviewed in [53, 54]). One prevailing theory is that compromise of the protective mucus layer of bladder mucosa (possibly from prior injury, subclinical infection, or autoimmune destruction) is a precipitating event. Potassium ions, present at high concentration in urine, cross this "leaky" epithelium, triggering chronic inflammation, injury, and neuronal damage to the bladder interstitium. Interstitial cystitis manifests as symptoms of urgency, frequency, burning pain associated with bladder filling, and dysuria. Patients with interstitial cystitis but not those with healthy bladders are sensitive to instilled potassium (potassium sensitivity test), which elicits reduced bladder capacity and pain. In the early stages of the condition, the patient may not recognize the increased voiding as dysfunctional; however, pain and greater frequency develop as the disease progresses. Most patients with this condition also experience dyspareunia. Interstitial cystitis often coexists with vulvodynia [55–57] and that both conditions may have a neurogenic component [58]. Because interstitial cystitis is associated with bladder pain, dysuria, high voiding frequency, low void volumes, and nocturia, it shares the symptomatic characteristics of overactive bladder syndrome or urge incontinence.

For the active, community-dwelling older woman with urinary incontinence [59], feminine protection is the self-treatment option of choice. She will search for other options only when symptoms become too difficult to manage or when she fears her symptoms signal pathology. Consequently, it is up to the clinician to broach the subject sensitively as part of the medical history: simple algorithms (such as the Three Incontinence Questions [3IQ] questionnaire [60]) can be offered to assist the patient in defining the nature and cause of her symptoms (stress, urge, or mixed incontinence).

For the older woman unable to maintain adequate perineal hygiene independently, incontinence dermatitis can become a significant problem. Several factors contribute to its development [59] (see Chap. 17 in this book) (Fig. 27.1). First, chronic exposure to urinary moisture makes the skin more susceptible to friction damage; in the older adult, excess skin hydration is dissipated more slowly than in younger people [61]. Bacterial action on the urine generates urinary ammonia, which elevates the local pH; this alters skin barrier function and

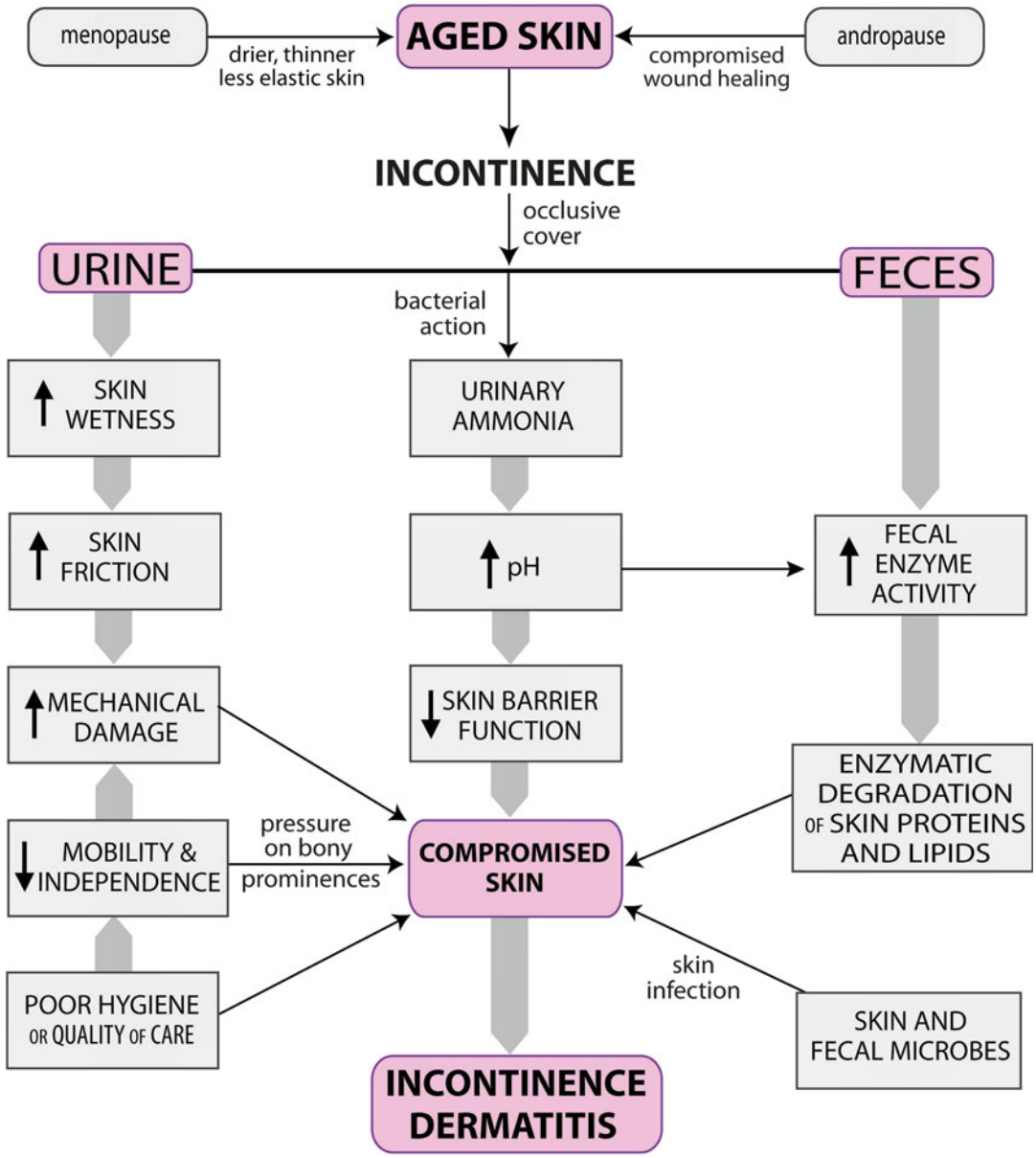

Fig. 27.1 Risk factors for incontinence dermatitis in the older person

activates fecal enzymes, which further compromise skin integrity and increase skin susceptibility to microbial infection [62–65]. Atrophied genital tissue is especially susceptible to pH changes and to enzymatic action. Moreover, in the incapacitated patient, reduced mobility creates higher shear forces on the tissue, a trigger for the development of decubitus ulcers (pressure sores). Lastly, those with impaired cognition may be unable to alert caregivers to incontinent episodes. These factors underscore the need for vigilant hygiene and physical assistance for the older adult with incontinence.

In community-dwelling individuals receiving home care, helpful interventions include prompted or timed toileting, use of incontinence garments, use of antimuscarinic drugs where appropriate [66, 67], and assistance with

perineal care. In nursing homes, urine containment with incontinence products is a first-line intervention. Catheterization is sometimes used but carries the risk of infection. Behavioral interventions such as prompted voiding and timed voiding are used to a limited degree, and antimuscarinics are only an adjunct treatment [68]. Prompted voiding involves caregivers checking and querying patients, giving toileting prompts, and reinforcing initiative on the part of the patient. In randomized trials, prompted voiding over the course of 3 months was associated with small improvements in daytime incontinence in nursing homes where the population had substantial cognitive and mobility limitations [69]. Timed voiding is bringing the patient to the toilet at fixed intervals regardless of whether she requests it or has voided during the previous interval.

In the USA, an estimated 16 billion dollars annually is spent on urinary incontinence management [70]; in nursing homes, an hour per day is spent on dealing with incontinence at a total cost per incontinent patient of approximately $10,000 per year [37]. By 2030, it is estimated that one in eight people worldwide will be over the age of 65, and the economic impact of incontinence management will become even more significant [71].

27.6 Vulvar Dermatoses

Lichen sclerosus affects the skin and the vulvovaginal mucosa (reviewed in [72]). Incidence peaks bimodally, rising in adolescents and in peri- or postmenopausal women. Symptoms are intense vulvar itch, soreness, pain, and dyspareunia, but there is no abnormal vaginal discharge. White polygonal plaques with a wrinkled appearance appear bilaterally on the vulva; the labia, vestibule, and introitus as well as the perineum can be affected. Advanced disease is typified by a "keyhole" or "figure-eight" configuration of sclerotic tissue surrounding the introitus and anus. Potent topical corticosteroids or macrolides are used to manage symptoms and retard disease progression.

Erosive lichen planus is a rare, chronic disorder that affects only the mucosa of the vagina and vulvar vestibule; vulvar skin is unaffected [72]. Peak incidence is between the ages of 30 and 70. Signs and symptoms include intense vulvar itch and pain, dyspareunia, excessive discharge, and postcoital bleeding. Discharge is due to erosive shedding, and the vaginal epithelium may bleed upon speculum insertion. These signs and symptoms mimic those of desquamative inflammatory vaginitis, but the distinguishing features of erosive lichen planus are the absence of infection and the presence of white, lacy plaques on the vulvar vestibule and inner aspects of the labia minora. White plaques on the oral mucosa (buccal mucosa, gingiva, palate, or tongue) are a common extragenital manifestation. Erosive lichen planus requires the use of potent topical steroids (e.g., clobetasol propionate) or topical macrolides (tacrolimus). Oral corticosteroids (e.g., prednisone) are a second-line treatment for more recalcitrant cases.

27.7 Summary

Vulvovaginal atrophy secondary to hypoestrogenism affects 10–50 % of postmenopausal women. Genital symptoms include vulvar irritation and pruritus, decreased vaginal secretions, vaginal burning, dyspareunia, and postcoital bleeding; urinary symptoms include urethral discomfort, frequency, and dysuria. Low-dose, intravaginal estrogen therapy is an option to relieve symptoms of vulvovaginal atrophy and improve quality of life. Although the risk factors and precipitating events vary, postmenopausal women are also more likely to experience stress or urge incontinence. Stress incontinence, linked to childbirth or obesity, is uncontrolled urine loss provoked by abdominal pressure on a weakened bladder sphincter. Urge incontinence is the inability to suppress voiding and is likely due to age-related changes in the nervous system that cause abnormal bladder spasms; however, interstitial cystitis, thought to result from a disrupted bladder mucosal barrier, mimics some of the symptoms of urge incontinence. Women are

unlikely to seek treatment until their symptoms become highly disruptive: health-care providers can assist by sensitively broaching the subject and by providing literature that describes these conditions and available treatment options. Vigilant perineal hygiene in the older person who is unable to care for herself is critical to avoiding incontinence dermatitis. Lastly, certain rare infections and vulvar dermatoses are more prevalent in postmenopausal women. Desquamative inflammatory vaginitis is a persistent inflammatory vaginal infection that erodes the vaginal mucosa and requires aggressive antibiotic treatment. Lichen sclerosus is a vulvar dermatosis of the skin as well as the mucosa. White, wrinkled polygonal plaques manifest bilaterally and may become sclerotic. Erosive lichen planus affects only the mucosa and causes discharge with shedding of the vaginal epithelium. Although its signs and symptoms mimic those of desquamative inflammatory vaginitis, its distinguishing features are the absence of infection and the presence of white, lacy plaques on the vulvar vestibule and inner aspects of the labia minora. Potent topical corticosteroids are used in treatment of both these dermatoses.

References

1. Pandit L, Ouslander JG. Postmenopausal vaginal atrophy and atrophic vaginitis. Am J Med Sci. 1997; 314(4):228–31.
2. Burger HG. The menopausal transition. Baillieres Clin Obstet Gynaecol. 1996;10(3):347–59.
3. Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, Skurnick J. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol. 2001; 153(9):865–74.
4. Oriba HA, Elsner P, Maibach HI. Vulvar physiology. Semin Dermatol. 1989;8(1):2–6.
5. Farage MA, Maibach HI. Morphology and physiological changes of genital skin and mucosa. Curr Probl Dermatol. 2011;40:9–19. doi:10.1159/000321042.
6. Elsner P, Maibach HI. The effect of prolonged drying on transepidermal water loss, capacitance and pH of human vulvar and forearm skin. Acta Derm Venereol. 1990;70(2):105–9.
7. Elsner P, Wilhelm D, Maibach HI. Frictional properties of human forearm and vulvar skin: influence of age and correlation with transepidermal water loss and capacitance. Dermatologica. 1990;181(2): 88–91.
8. Oriba HA, Bucks DA, Maibach HI. Percutaneous absorption of hydrocortisone and testosterone on the vulva and forearm: effect of the menopause and site. Br J Dermatol. 1996;134(2):229–33.
9. Schagen van Leeuwen JH, Lange RR, Jonasson AF, Chen WJ, Viktrup L. Efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence. Maturitas. 2008;60(2):138–47. doi:10.1016/j.maturitas.2008.04.012.
10. Elsner P, Wilhelm D, Maibach HI. Effect of low-concentration sodium lauryl sulfate on human vulvar and forearm skin. Age-related differences. J Reprod Med. 1991;36(1):77–81.
11. Farage MA, Maibach H. Lifetime changes in the vulva and vagina. Arch Gynecol Obstet. 2006;273(4):195–202. doi:10.1007/s00404-005-0079-x.
12. Bachmann GA, Nevadunsky NS. Diagnosis and treatment of atrophic vaginitis. Am Fam Physician. 2000;61(10):3090–6.
13. Farage MA, Miller KW, Ledger WL. Confronting the challenges of postmenopausal urogenital health. Aging Health. 2010;6(5):611–26.
14. Greendale GA, Judd HL. The menopause: health implications and clinical management. J Am Geriatr Soc. 1993;41(4):426–36.
15. Stenberg A, Heimer G, Ulmsten U, Cnattingius S. Prevalence of genitourinary and other climacteric symptoms in 61-year-old women. Maturitas. 1996; 24(1–2):31–6.
16. van Geelen JM, van de Weijer PH, Arnolds HT. Urogenital symptoms and resulting discomfort in non-institutionalized Dutch women aged 50–75 years. Int Urogynecol J Pelvic Floor Dysfunct. 2000;11(1): 9–14.
17. Erickson KL, Montagna W. New observations on the anatomical features of the female genitalia. J Am Med Womens Assoc. 1972;27(11):573–81.
18. Jones IS. A histological assessment of normal vulval skin. Clin Exp Dermatol. 1983;8(5):513–21.
19. Nauth HF, Boger A. New aspects of vulvar cytology. Acta Cytol. 1982;26(1):1–6.
20. Caillouette JC, Sharp Jr CF, Zimmerman GJ, Roy S. Vaginal pH as a marker for bacterial pathogens and menopausal status. Am J Obstet Gynecol. 1997; 176(6):1270–5; discussion 1275–7.
21. Gorodeski GI. Effects of estrogen on proton secretion via the apical membrane in vaginal-ectocervical epithelial cells of postmenopausal women. Menopause. 2005;12(6):679–84.
22. Gorodeski GI, Hopfer U, Liu CC, Margles E. Estrogen acidifies vaginal pH by up-regulation of proton secretion via the apical membrane of vaginal-ectocervical epithelial cells. Endocrinology. 2005;146(2): 816–24.
23. Brizzolara S, Killeen J, Severino R. Vaginal pH and parabasal cells in postmenopausal women. Obstet Gynecol. 1999;94(5 Pt 1):700–3.

24. Hess R, Austin RM, Dillon S, Chang CC, Ness RB. Vaginal maturation index self-sample collection in mid-life women: acceptability and correlation with physician-collected samples. Menopause. 2010;15 (4 Pt 1):726–9.
25. McEndree B. Clinical application of the vaginal maturation index. Nurse Pract. 1999;24(9):48, 51–2, 55–6.
26. North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause. 2010;17(2):242–55.
27. Sturdee DW, Panay N. Recommendations for the management of postmenopausal vaginal atrophy. Climacteric J Int Menopause Soc. 2010;13(6):509–22. doi:10.3109/13697137.2010.522875.
28. Panay N, Maamari R. Treatment of postmenopausal vaginal atrophy with 10-mug estradiol vaginal tablets. Menopause Int. 2012;18(1):15–9. doi:10.1258/mi.2012.011120.
29. Simon J, Nachtigall L, Gut R, Lang E, Archer DF, Utian W. Effective treatment of vaginal atrophy with an ultra-low-dose estradiol vaginal tablet. Obstet Gynecol. 2008;112(5):1053–60.
30. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez JL, Girard G, Baron M, Ayotte N, Moreau M, Dube R, Cote I, Labrie C, Lavoie L, Berger L, Gilbert L, Martel C, Balser J. Intravaginal dehydroepiandrosterone (prasterone), a physiological and highly efficient treatment of vaginal atrophy. Menopause. 2009;16(5):907–22.
31. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez JL, Girard G, Baron M, Ayotte N, Moreau M, Dube R, Cote I, Labrie C, Lavoie L, Berger L, Gilbert L, Martel C, Balser J. Effect of intravaginal dehydroepiandrosterone (prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause. 2009;16(5):923–31.
32. Labrie F, Cusan L, Gomez JL, Cote I, Berube R, Belanger P, Martel C, Labrie C. Effect of intravaginal DHEA on serum DHEA and eleven of its metabolites in postmenopausal women. J Steroid Biochem Mol Biol. 2008;111(3–5):178–94.
33. Panjari M, Davis SR. Vaginal DHEA to treat menopause related atrophy: a review of the evidence. Maturitas. 2011;70(1):22–5. doi:10.1016/j.maturitas.2011.06.005.
34. Navas-Nacher EL, Dardick F, Venegas MF, Anderson BE, Schaeffer AJ, Duncan JL. Relatedness of Escherichia coli colonizing women longitudinally. Mol Urol. 2001;5(1):31–6. doi:10.1089/109153601750124285.
35. Norinder BS, Luthje P, Yadav M, Kadas L, Fang H, Nord CE, Brauner A. Cellulose and PapG are important for Escherichia coli causing recurrent urinary tract infection in women. Infection. 2011;39(6):571–4. doi:10.1007/s15010-011-0199-0.
36. Farage MA, Miller KW, Sobel JD. The vaginal microbiota in menopause. In: Farage MA, Miller KW, Maibach H, editors. Textbook of aging skin. Berlin: Springer; 2010. p. 883–93.
37. Borrie MJ, Davidson HA. Incontinence in institutions: costs and contributing factors. CMAJ. 1992; 147(3):322–8.
38. Jackson SL, Boyko EJ, Scholes D, Abraham L, Gupta K, Fihn SD. Predictors of urinary tract infection after menopause: a prospective study. Am J Med. 2004;117(12):903–11.
39. Eriksen B. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. Am J Obstet Gynecol. 1999;180(5):1072–9.
40. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med. 1993;329(11): 753–6.
41. Cardozo L, Lose G, McClish D, Versi E, de Koning Gans H. A systematic review of estrogens for recurrent urinary tract infections: third report of the hormones and urogenital therapy (HUT) committee. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12(1): 15–20.
42. Sobel JD, Reichman O, Misra D, Yoo W. Prognosis and treatment of desquamative inflammatory vaginitis. Obstet Gynecol. 2011;117(4):850–5. doi:10.1097/AOG.0b013e3182117c9e.
43. Sobel JD. Desquamative inflammatory vaginitis: a new subgroup of purulent vaginitis responsive to topical 2% clindamycin therapy. Am J Obstet Gynecol. 1994;171(5):1215–20.
44. Mallett VT. Female urinary incontinence: what the epidemiologic data tell us. Int J Fertil Womens Med. 2005;50(1):12–7.
45. Anger JT, Saigal CS, Litwin MS. The prevalence of urinary incontinence among community dwelling adult women: results from the National Health and Nutrition Examination Survey. J Urol. 2006;175(2): 601–4.
46. Hannestad YS, Rortveit G, Sandvik H, Hunskaar S. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trondelag. J Clin Epidemiol. 2000;53(11): 1150–7.
47. Offermans MP, Du Moulin MF, Hamers JP, Dassen T, Halfens RJ. Prevalence of urinary incontinence and associated risk factors in nursing home residents: a systematic review. Neurourol Urodyn. 2009;28(4):288–94.
48. Subak LL, Richter HE, Hunskaar S. Obesity and urinary incontinence: epidemiology and clinical research update. J Urol. 2009;182(6 Suppl):S2–7.
49. Choi H, Palmer MH, Park J. Meta-analysis of pelvic floor muscle training: randomized controlled trials in incontinent women. Nurs Res. 2007;56(4):226–34. doi:10.1097/01.NNR.0000280610.93373.e1.
50. Cardozo L, Lange R, Voss S, Beardsworth A, Manning M, Viktrup L, Zhao YD. Short- and long-term efficacy and safety of duloxetine in women with predominant stress urinary incontinence. Curr Med Res Opin. 2010;26(2):253–61. doi:10.1185/03007990903438295.

51. Li J, Yang L, Pu C, Tang Y, Yun H, Han P. The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. Int Urol Nephrol. 2013;45(3):679–86. doi:10.1007/s11255-013-0410-6.
52. Malone-Lee JG, Walsh JB, Maugourd MF. Tolterodine: a safe and effective treatment for older patients with overactive bladder. J Am Geriatr Soc. 2001;49(6):700–5.
53. Dasgupta J, Tincello DG. Interstitial cystitis/bladder pain syndrome: an update. Maturitas. 2009;64(4):212–7. doi:10.1016/j.maturitas.2009.09.016.
54. Butrick CW, Howard FM, Sand PK. Diagnosis and treatment of interstitial cystitis/painful bladder syndrome: a review. J Womens Health (Larchmt). 2010;19(6):1185–93. doi:10.1089/jwh.2009.1702.
55. Kahn BS, Tatro C, Parsons CL, Willems JJ. Prevalence of interstitial cystitis in vulvodynia patients detected by bladder potassium sensitivity. J Sex Med. 2010;7(2 Pt 2):996–1002. doi:10.1111/j.1743-6109.2009.01550.x.
56. Parsons CL, Bullen M, Kahn BS, Stanford EJ, Willems JJ. Gynecologic presentation of interstitial cystitis as detected by intravesical potassium sensitivity. Obstet Gynecol. 2001;98(1):127–32.
57. Peters K, Girdler B, Carrico D, Ibrahim I, Diokno A. Painful bladder syndrome/interstitial cystitis and vulvodynia: a clinical correlation. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(5):665–9. doi:10.1007/s00192-007-0501-y.
58. Bullones Rodriguez MA, Afari N, Buchwald DS. Evidence for overlap between urological and nonurological unexplained clinical conditions. J Urol. 2013;189(1 Suppl):S66–74. doi:10.1016/j.juro.2012.11.019.
59. Farage MA, Miller KW, Berardesca E, Maibach HI. Incontinence in the aged: contact dermatitis and other cutaneous consequences. Contact Dermatitis. 2007;57(4):211–7. doi:10.1111/j.1600-0536.2007.01199.x.
60. Brown JS, Bradley CS, Subak LL, Richter HE, Kraus SR, Brubaker L, Lin F, Vittinghoff E, Grady D. The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. Ann Intern Med. 2006;144(10):715–23.
61. Roskos KV, Guy RH. Assessment of skin barrier function using transepidermal water loss: effect of age. Pharm Res. 1989;6(11):949–53.
62. Berg RW. Etiology and pathophysiology of diaper dermatitis. Adv Dermatol. 1988;3:75–98.
63. Berg RW, Buckingham KW, Stewart RL. Etiologic factors in diaper dermatitis: the role of urine. Pediatr Dermatol. 1986;3(2):102–6.
64. Buckingham KW, Berg RW. Etiologic factors in diaper dermatitis: the role of feces. Pediatr Dermatol. 1986;3(2):107–12.
65. Andersen PH, Bucher AP, Saeed I, Lee PC, Davis JA, Maibach HI. Faecal enzymes: in vivo human skin irritation. Contact Dermatitis. 1994;30(3):152–8.
66. Burgio KL, Goode PS, Richter HE, Markland AD, Johnson 2nd TM, Redden DT. Combined behavioral and individualized drug therapy versus individualized drug therapy alone for urge urinary incontinence in women. J Urol. 2010;184(2):598–603. doi:10.1016/j.juro.2010.03.141.
67. Burgio KL, Locher JL, Goode PS, Hardin JM, McDowell BJ, Dombrowski M, Candib D. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. JAMA. 1998;280(23):1995–2000.
68. Fink HA, Taylor BC, Tacklind JW, Rutks IR, Wilt TJ. Treatment interventions in nursing home residents with urinary incontinence: a systematic review of randomized trials. Mayo Clin Proc. 2008;83(12):1332–43.
69. Hu TW, Igou JF, Kaltreider DL, Yu LC, Rohner TJ, Dennis PJ, Craighead WE, Hadley EC, Ory MG. A clinical trial of a behavioral therapy to reduce urinary incontinence in nursing homes. Outcome and implications. JAMA. 1989;261(18):2656–62.
70. Wilson L, Brown JS, Shin GP, Luc KO, Subak LL. Annual direct cost of urinary incontinence. Obstet Gynecol. 2001;98(3):398–406.
71. Farage MA, Miller KW, Berardesca E, Maibach HI. Psychosocial and societal burden of incontinence in the aged population: a review. Arch Gynecol Obstet. 2008;277(4):285–90. doi:10.1007/s00404-007-0505-3.
72. Farage MA, Miller KW, Ledger WJ. Determining the cause of vulvovaginal symptoms. Obstet Gynecol Surv. 2008;63(7):445–64.