Vulvar Diseases

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Abbreviations

ACT	Adoptive cell transfer
AJCC	American Joint Committee on Cancer (2009 Melanoma Staging and Classification)
CAH	Congenital adrenal hyperplasia
CMV	Cytomegalovirus
EBV	Epstein-Barr virus
ELPV	Erosive lichen planus of the vulva
FDA	The U.S. Federal Drug Agency
FGM	Female genital mutilation
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
GUD	Genital ulcer disease
HDI	High dose interferon
HPV	Human papillomavirus High dose interferon
HVLNE	Hemivulvectomy with superficial inguinal lymphadenectomy
ISSVD	International Society for the Study of Vulvovaginal Disease
LGV	Lymphogranuloma venereum
LS	Lichen sclerosus
LSC	Lichen simplex chronicus
PCR	Polymerase chain reaction
PM	Peripheral (free) margin
PSA	Prostate-specific antigen
RVLNE	Radical vulvectomy with inguino-femoral lymphadenectomy
SCC	Squamous cell carcinoma
SJS	Stevens-Johnson's syndrome
SLN	Sentinel lymph nodes
STI	Sexually transmitted infection
TIL	Tumor-infiltrating lymphocytes
VIN	Vulvar intraepithelial neoplasia
VLP	Vulvar lichen planus
VVS	Vulvo-vestibulitis syndrome
WLE	Wide local excision

Key Points

- The vulva is a gynecologic organ with dermatologic anatomy. The spectrum of potential vulvar diseases is large, although only a few of them are uniquely vulvar.
- Vulvar infections are the most common, while vulvar cancer is very rare.
- There is no uniform classification of vulvar disease. Vulvar dermatoses are grouped according to the principles of willanism. The vulva is also an important signaling organ of endocrine and genetic pathology, as well as sexual abuse and human rights violation.
- Diagnostic and therapeutic arsenal is large. Nevertheless, only a few drugs are marketed as vulvar or for vulvar conditions.

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- New achievements in dermatology, gynecology, microbiology, pharmacology, molecular biology, and oncology can improve the prognosis and quality of life in many vulvar diseases substantially.
- The vulva is a mirror of female health and well-being.

Definition

The vulva is the female external genitalia and includes the mons pubis, labia majora, labia minora, clitoris, vestibulum, and vestibular glands. The length and width of labia majora et minora vary in a large scale, depending on physiological age, genetic, and cultural factors. Arterial blood to the vulva is provided by the internal pudendal artery (from the iliac artery) and external pudendal artery (from the femoral artery) and venous return by pudendal veins into internal iliac veins. Vulvar lymphatics drain to inguinal and femoral nodes. Lymph from the midline vulva drains bilaterally. Innervation of vulva is performed by several nerves and their branches: pudendal, ilioinguinal, posterior femoral cutaneous, and genitofemoral. The vulva lies in close proximity to the lower abdomen, inguinal and perianal regions, vagina, urethra, and anus. The microbial diversity and load of the vulvar area are much higher than in other parts of the skin. The predominant bacterial genera sequenced in the vulvar area are Corynebacterium, Staphylococcus, Lactobacillus, Actinobacteria, Prevotella, Clostridia, and Propionibacterium and the predominant fungi are Malassezia, Cryptococcus, Rhodoturula, Cladosporium, Saccharomyces, and Penicillium.

Clinical Presentation

Vulvar Ulcers

Genital ulcer disease (GUD) is a general term used to describe genital ulcers in both sexes. Vulvar ulcers may have multiple causes (Table 104.1). Syphilis ulcer is typically a single, not painful, infiltrated lesion accompanied by unilateral inguinal lymphadenopathy. Herpetic ulcers are numerous, painful erosions or ulcers covered with whitish film accompanied with inguinal lymphadenopathy. Vulvar involvement can also occur in herpes zoster and varicella. Ulcus molle has a painful, purulent ulcer and purulent inguinal lymphadenopathy. In donovanosis or granuloma inguinale, multiple granulomatous ulcers and inguinal mass or pseudobubo are observed. Lymphogranuloma venereum (LGV) develops in three phases: from papule to ulcer, then to red and swollen inguinal lymph nodes, and finally to genital elephantiasis. Tuberculosis can also present itself with vulvar ulcers and mimic sexually transmitted infection (STI). In vulvar diphtheria, ulcers are covered with a pseudomembrane, and there are additional nasopharyngeal and systemic signs. Primary cytomegalovirus (CMV) infection can cause acute, painful vulvar ulcers.

In Behçet's disease, painful genital ulcers can be one of the diagnostic symptoms in addition to other extragenital signs, e.g., oral ulcers, uveitis, positive pathergy test, and skin lesions. Ulcus vulvae acutum or Lipschütz ulcer is a rare, purulent, necrotic vulvar ulcer which most often develops together with flu-like illness in prepubertal girls. The etiology of Lipschütz ulcer is not known but possibly involves Epstein-Barr virus (EBV), CMV, mumps virus, and influenza A infection. *Mycoplasma pneumonia* can be associated with acute, extensive, painful, destructive vulvar ulcers in adult women. Ulcerative vulvitis in Reiter's syndrome is another rare form of vulvar ulcers with additional signs of conjunctivitis, arthritis, and psoriasiform skin lesions. Crohn's disease can involve the vulva and cause deep ulcers and formation of fistulas. Pyoderma gangrenosum very rarely involves the vulva and typically has painful, necrotic ulcers. Invasive vulvar cancer and other vulvar neoplasias can cause ulcers. Idiopathic vulvar ulcers can be HIV/AIDS associated. Other miscellaneous causes of vulvar ulcers include opportunistic infections, radiation, drugs, postsurgical wounds, chemicals, biologic substances, and mixed infections.

Table 104.1 Diagnosis and management of infectious vulvar ulcers and vulvitides

Pathology	Etiology	Diagnostic tests	Treatment
Syphilis ulcer	*Treponema pallidum pallidum*	Dark-field microscopy	Benzathine penicillin G 2.4 MU IM single injection (for primary syphilis)
		PCR	Alternatives: Tetracycline, doxycycline, erythromycin (all PO)
Herpes ulcer	*Herpes simplex virus 1, 2*	Serology—HSV 1 and HSV 2 IgM	Famciclovir—125–1000 mg PO 2–3× daily, 1–7 days
		Immunofluorescence	Valaciclovir—500–1000 mg PO 2–3× daily, 3–7 days
		PCR	
Candida vulvitis	*Candida albicans ~ 90%*	KOH microscopy, culture, PCR	Systemic treatment for acute infection:
	Candida glabrata—2– 10%		Fluconazole 150 mg PO single dose
	Candida krusei—1–3%		Itraconazole 200 mg PO 2× daily, 3 days
			Ketoconazole 400 mg PO 2× daily, 3 days
			(For local treatment, please see Table 104.6)
Streptococcal ulcer/ vulvitis	Group A beta-hemolytic streptococcus	Microscopy, culture	Penicillin V 500 mg PO 3× daily, 14 days
	Group B streptococcus		Erythromycin 500 mg PO 3× daily, 14 days
			(For local treatment, please see Table 104.6)
Donovanosis	*Klebsiella granulomatis*	Microscopy, Giemsa stain, Donovan bodies	Azithromycin 1 g PO 1× weekly, 3–4 weeks
		Culture	Erythromycin 500 mg PO 4× daily, 21 days
		PCR	Ofloxacin 200 mg 2× a day PO for 21 days
			Ciprofloxacin 500 mg PO 2× daily, 21 days
Lymphogranuloma venereum	*Chlamydia trachomatis*, serovars L1, L2, L2a, L3	PCR, culture	Doxycycline 100 mg 2× day PO for 21 days
			Erythromycin 500 mg 4× a day PO for 21 days
			Azithromycin 1 g 1× a week PO for 3 weeks
Ulcus molle	*Haemophilus ducreyi*	Gram-stain microscopy, culture, PCR	First choice:
			Azithromycin 1 g PO single dose
			Ceftriaxone 250 mg i.m. single injection
			Alternative:
			Ciprofloxacin 500 mg 2× day PO for 3 days
			Erythromycin 2 g per day PO for 7 days

Diagnosis of vulvar ulcers is based on clinical appearance, symptoms, and laboratory methods such as microscopy, culture, polymerase chain reaction (PCR), and biopsy. Treatment follows established guidelines in known cases. Ulcers of unknown etiology are managed by local corticosteroids, oral antibiotics, and immunosuppressive drugs.

Vulvitis and Vestibulitis

Vulvitis, vestibulitis, or vulvo-vestibulitis is an inflammation of the outer female genitals, presenting as redness, itching, burning, pain, and dyspareunia. Vulvitis is rarely isolated but usually develops secondary to a vaginal process (vulvovaginitis) inguinal or perianal pathology. Candida vulvitis or vulvovaginitis is the most common type of infectious vulvitis. Predisposing factors are numerous: asymptomatic carriage, peroral antibiotic use, contraceptives, diabetes, and HIV/AIDS. Treatment is with either local or systemic antifungals; both of them are equally effective. Streptococcal vulvitis or vulvovaginitis due to group A β-hemolytic streptococcus is more often seen in prepubertal girls than adult women, often recurrent, and usually associated with nasopharyngeal or gastrointestinal carriage of bacteria. The treatment is antibacterial. Vulvitis circumscripta plasmacellularis or Zoon's vulvitis is a disease of unknown etiology characterized by shiny, red-brown macules on the labia. Treatment options include high-potency topical corticosteroids, topical calcineurin inhibitors, 5% imiquimod cream, cryotherapy, intralesional injections of triamcinolone, or interferon alpha. Postcoital or seminal vulvitis occurs after unprotected intercourse as either localized vulvar urticaria, vulvar angioedema or generalized urticaria, or facial angioedema. A pathogenic mechanism is type I hypersensitivity reaction possibly caused by prostate-specific antigen (PSA). Acute and subacute vulvar eczema (allergic or irritant) manifests itself clinically as vulvitis. Inguinal erythrasma, intertrigo, and tinea inguinalis can spread from the inguinal region to the labia majora to cause vulvitis. Vulvar psoriasis can have a chronic, symmetrical vulvitis without vaginitis. Diagnosis and treatment of the primary cause improves or cures vulvitis. For idiopathic cases, topical corticosteroids or calcineurin inhibitors are commonly used.

Vulvar Dermatoses

According to the ISSVD (International Society for the Study of Vulvovaginal Disease) 2011 classification, all vulvar dermatoses are divided into eight main groups (with further subdivision) (Table 104.2): (1) skin-colored lesions; (2) red lesions, patches, and plaques; (3) red lesions, papules and nodules; (4) white lesions; (5) dark-colored lesions; (6) blisters; (7) erosions and ulcers; and (8) edema. Histologically the ISSVD recognizes eight patterns of pathological reactions in the vulva: spongiotic, acanthotic, lichenoid, sclerotic, vesiculobullous, acantholytic, granulomatous, and vasculopathic.

Dermatoses which can be seen in the vulva (besides the already mentioned ulcers and vulvites) are numerous: different erythemas, intertrigo, erysipelas, vitiligo, pityriasis versicolor, lichen planus, lichen simplex chronicus, vulvar lentigo, melanoma, psoriasis inversa, condylomata acuminata, Bowenoid papulosis, squamous cell carcinoma, basal cell carcinoma, condylomata lata, molluscum contagiosum, Fox-Fordyce diseases, seborrheic dermatitis, scabies, pubic lice, seborrheic keratosis, furuncle, acne inversa, epidermoid cyst, vulvar polyp, herpes simplex, herpes zoster, varicella, lupus erythematosus, pemphigus vulgaris, bullous pemphigoid, Hailey-Hailey disease, Darier's disease, and Stevens-Johnson's syndrome (SJS). Vulvar involvement can occur in pathologies of other organs and systems, e.g., diabetes (candida vulvitis), Crohn's diseases (ulcers, vulvitis, edema), and HIV/AIDS (secondary ulcers, vulvitis, tumors). Drug eruptions in the vulva most commonly present as fixed drug eruption (erythema fixatum), erythema multiforme, and SJS. Bullous and acantholytic diseases such as pemphigus vulgaris vegetans, Hailey-Hailey disease, and Darier's disease can also involve vulva. Diagnostic principles and treatments used in vulvar dermatoses are similar to other parts of the body.

Table 104.2 ISSVD 2011 classification of vulvar dermatological disorders

1. Skin-colored lesions	(a) *Skin-colored papules and nodules*—Papillomatosis of the vestibule and medial labia minora (a normal finding; not a disease), molluscum contagiosum, warts (HPV infection), scar, vulvar intraepithelial neoplasia (VIN), skin tag (acrochordon, fibroepithelial polyp), nevus (intradermal type), mucinous cysts of the vestibule and medial labia minora, epidermal cysts, mammary-like gland tumor (hidradenoma papilliferum), Bartholin's gland cyst and tumor, syringoma, basal cell carcinoma
	(b) *Skin-colored plaques*—Lichen simplex chronicus and other lichenified diseases, vulvar intraepithelial neoplasia
2. Red lesions: Patches and plaques	(a) *Eczematous and lichenified diseases*—Allergic contact dermatitis, irritant contact dermatitis, atopic dermatitis (Fig. 104.3b), eczematous changes superimposed on other vulvar disorders, diseases clinically mimicking eczematous disease, lichen simplex chronicus, lichenification superimposed on an underlying preceding pruritic disease
	(b) *Red patches and plaques* (no epithelial disruption)—Candidiasis, psoriasis, vulvar intraepithelial neoplasia, lichen planus, plasma cell (Zoon's) vulvitis, bacterial soft tissue infection (cellulitis and early necrotizing fasciitis), extramammary Paget's disease
3. Red lesions: Papules and nodules	(a) *Red papules*—Folliculitis, wart (HPV infection), angiokeratoma, molluscum contagiosum (inflamed), hidradenitis suppurativa (early lesions), Hailey-Hailey disease
	(b) *Red nodules*—Furuncles, wart (HPV infection), prurigo nodularis, vulvar intraepithelial neoplasia, molluscum contagiosa (inflamed), urethral carbuncle and prolapse, hidradenitis suppurativa, mammary-like gland adenoma (hidradenoma papilliferum), inflamed epidermal cyst, Bartholin's duct abscess, squamous cell carcinoma, melanoma (amelanotic type)
4. White lesions	(a) *White papules and nodules*—Fordyce spots, molluscum contagiosum, wart, scar, vulvar intraepithelial neoplasia (VIN), squamous cell carcinoma, milium, epidermal cyst, Hailey-Hailey disease
	(b) *White patches and plaques*—Vitiligo, lichen sclerosus, postinflammatory hypopigmentation, lichenified disease, lichen planus, vulvar intraepithelial neoplasia (VIN), squamous cell carcinoma (SCC)
5. Dark-colored lesions	(a) *Dark- colored patches*—Melanocytic nevus, vulvar melanosis, postinflammatory hyperpigmentation, lichen planus, acanthosis nigricans, melanoma in situ
	(b) *Dark- colored papules and nodules*—Melanocytic nevus, warts (HPV infection), vulvar intraepithelial neoplasia (VIN), angiokeratoma, hidradenoma papilliferum, melanoma
6. Blisters	(a) *Vesicles and bullae*—Herpesvirus infections (herpes simplex, herpes zoster), acute eczema, bullous lichen sclerosus, lymphangioma circumscriptum, immune blistering disorders
	(b) *Pustules*—Candidiasis, folliculitis
7. Erosions and ulcers	(a) *Erosions*—Excoriations, erosive lichen planus, fissures arising on normal tissue (idiopathic, intercourse related), fissures arising on abnormal tissue (candidiasis, lichen simplex chronicus, psoriasis, Crohn's disease, etc.), vulvar intraepithelial neoplasia (eroded variant), ruptured vesicles, bullae and pustules, extramammary Paget's disease
	(b) *Ulcers*—Excoriations (related to eczema, lichen simplex chronicus), aphthous ulcers (Lipschütz ulcer, secondary to other diseases—Crohn's, Behçet's), Crohn's disease, herpesvirus infection, ulcerated squamous cell carcinoma, primary syphilis (chancre)
8. Edema	(a) *Skin- colored edema*—Crohn's disease, idiopathic lymphatic abnormality (congenital Milroy's disease), postradiation and postsurgical lymphatic obstruction, postinfectious edema (esp. staphylococcal and streptococcal cellulitis), postinflammatory edema (esp. hidradenitis suppurativa)
	(b) *Pink or red edema*—Venous obstruction (e.g., pregnancy, parturition), cellulitis (primary or superimposed on already existing edema), inflamed Bartholin's duct cyst/abscess, Crohn's disease, mild vulvar edema (may occur with any inflammatory vulvar disease)

Pathologies of Vulvar Glands

Bartholin's gland is located in the lower third of the vulva. Its main purpose is to lubricate the labial opening of the vagina. Bartholin's gland pathologies are obstruction of the duct, inflammation, cyst, abscess, benign tumors (nodular

hyperplasia, adenoma, adenomyoma), and adenocarcinoma.

Bartholin's gland cyst and abscess is an interlabial mass or two bilateral lesions. Bartholin's gland abscess is typically caused by *E. coli*, *Bacteroides*, and *Prevotella* species, as well as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Pseudomonas aeruginosa*. Treatment modalities for Bartholin's duct cyst and abscess include gland incision and drainage, catheterization (fistulization), marsupialization, and excision. Catheterization and marsupialization are the most effective methods, while aspiration alone is the least effective with the highest recurrence rate. CO_2 laser vaporization can achieve a cure rate of above 95% in a single session. Rectovaginal fistula can occur after surgical removal of Bartholin's gland.

Skene's gland and duct are periurethral structures histologically and functionally resembling the male prostate and are called female prostate. Skene's gland is also the principal source of prostate-specific antigen (PSA) in female. Main pathologies are Skene's cyst, pseudocyst, abscess, calculi, and carcinoma. Skene's duct cyst can have symptoms of superficial, external dyspareunia and voiding difficulties. Skene's abscess presents as vulvar pain, enlarged labium majus, and erythema around the urethra. Diagnosis is clinical and done with ultrasound and MRI. Treatment is incision and drainage or excision. Paraurethral cyst arising from Skene's glands can also be seen in female newborns. Clinically it usually looks as a round, yellowish interlabial nodule. Diagnosis can be made in prenatal ultrasound. Invasive treatment is similar to adults, although a nonsurgical approach is more relevant, because paraurethral cysts often disappear spontaneously in the first year of life.

Fox-Fordyce is a disease of apocrine glands with folliculocentric papules and pruritus. Physical trauma can contribute to its development including laser hair removal. Treatment is with different topical agents (retinoids, clindamycin, corticosteroids) and oral retinoids or contraceptives. In resistant cases, mechanical destruction or surgical removal of apocrine glands can be done.

Acne inversa or hidradenitis suppurativa can affect the vulva in females and is characterized by recurrent, painful, deep-seated nodules and abscesses of apocrine gland-bearing skin. Diagnosis and staging is aided by ultrasound. Treatment includes systemic antibiotics, retinoids, and biologics. In advanced cases only radical surgery and grafting are curative.

Vulvar Edema and Vascular Pathology

Vulvar edema can be caused by infections, neoplasia, pregnancy, systemic diseases, drugs, allergies, medical and surgical procedures, and many other acquired or congenital factors. It can be mild, massive, unilateral, or bilateral with or without vulvar redness, ulcers, erosions, lymphadenopathy, and systemic signs. Common causes of vulvar edema are genital herpes, syphilis (*edema indurativum*), donovanosis, and postsurgical or postradiation lymphedema; less often causes are tuberculosis, Crohn's disease, acquired lymphangioma circumscriptum, and congenital vulvar lymphedema. Massive vulvar edema with ascites can precede preeclampsia and eclampsia in pregnancy. Vulvar elephantiasis can be seen in filariasis, LGV, tuberculosis, donovanosis (pseudo-elephatiasis), localized lympedema, malignancy, obesity, and trauma. Diagnosis of vulvar edema is usually clinical and anamnestical. Treatment can range from ice packs, wet dressings, and hydrotherapy to systemic drugs, hospitalization, intensive care, and surgery.

Arteriovenous malformation of the vulva is a pedunculated soft tissue mass most commonly located on the labia majus. Treatment is by simple excision. Vulvar varicosities can be one-sided or bilateral. Pregnancy is the most common cause. Rare causes include pelvic congestion syndrome and Klippel-Trenaunay-Weber syndrome. Treatment is surgical removal and sclerotherapy.

The Clitoris, Mons Pubis, and Hair

The normal size of the clitoris is about 16 mm in adult females and 6 mm in full-term newborns.

Acquired clitoral hypertrophy is most often caused by virilism and hyperandrogenemia; other causes include neurofibromatosis, pseudohypertrophy, hemangioma, angiokeratoma, and amebiasis. Congenital clitoromegaly can be due to congenital adrenal hyperplasia (CAH), true hermaphroditism, female pseudohermaphroditism, 46,XY gonadal dysgenesis, and androgen exposure in utero.

The mons pubis is a place typical of some vulvar diseases. Pediculosis pubis is rather rarely seen in the industrialized world. Vulvar folliculitis—just the opposite—is very common. Vulvar furuncle and even carbuncle can also develop in the vulvar area. Other diseases typical in the mons pubis are molluscum contagiosum, scabies, melanocytic nevi, seborrheic keratoses, Bowenoid papulosis, seborrheic dermatitis, and trichomycosis. Hirsutism or male pattern pubic hair growth toward the umbilicus occurs in females in hyperandrogenic states of different causes.

Melano-Pigmentary Disturbances

It is estimated that one in every ten women has a pigmented vulvar lesion. Common benign pigmented vulvar lesions include vulvar melanosis, vulvar lentigo, postinflammatory pigmentation, nevi, pigmented seborrheic keratosis, pigmented follicular cysts, and vulvar tattoo. Dysplastic nevi or atypical melanocytic nevi of the genital type and cellular blue nevus can also be observed in the vulva. Pigmented vulvar intraepithelial neoplasia, malignant melanoma, and pigmented basal cell carcinoma are examples of malignant tumors. Dermoscopy is useful as a noninvasive tool to diagnose vulvar pigmentations. Histopathology offers additional diagnostic accuracy, especially for lesions that look suspicious in dermoscopy. Atypical, suspicious pigment lesions are usually excised.

Vitiligo in the vulvar area is rather common. Differential diagnosis is usually with vulvar pityriasis versicolor, lichen sclerosus, lichen simplex chronicus, amelanotic melanoma, and vitiligo-like depigmentations. Treatment of vulvar vitiligo includes calcineurin inhibitors and corticosteroids. Changes in genital pigmentation can also be observed in CAH, Addison's disease, neurofibromatosis, Dowling-Degos disease, and laser-assisted hair removal. Racial differences in vulvar pigmentation are also important.

Vulvar Lichens

The three most common forms are lichen simplex chronicus, lichen planus, and lichen sclerosus (Table 104.3).

Lichen simplex chronicus (LSC) clinically appears as lichenification of labial surfaces with fissures and slight scaling. Intense, sometimes unbearable itch is a chief complaint. The itch-scratch cycle maintains the pathological process. Etiologic factors can be numerous including atopic eczema, contact dermatitis (Fig. 104.3b), and other pruritic anogenital diseases. Many cases are idiopathic. Diagnosis is based on the clinical picture and skin biopsy. Established treatment is with ultrapotent corticosteroid ointments for 4–12 weeks. Second-line treatment is with topical calcineurin inhibitors. Other alternatives are peroral prednisolone and intramuscular triamcinolone.

Vulvar lichen planus (VLP) has three clinical forms in the vulva: classic or papulosquamous, erosive, and hypertrophic. Erosive lichen planus of the vulva (ELPV) is the most common type. Typical symptoms include burning, itch, and dyspareunia. Vaginal scarring and stenosis may occur in long-standing disease. Vulvovaginal-gingival syndrome is a subtype of ELPV, where erosive, desquamative lesions are seen on the vagina or gingiva, usually not simultaneously. First-line treatment for VLP is very potent topical corticosteroids, while alternative treatments are topical calcineurin inhibitors (pimecrolimus 1% and tacrolimus 0.1%). Very potent corticosteroids can achieve symptomatic relief in more than 70%, but complete resolution in not more than 30%. From all ELPV patients, about 5% progress to VIN and 5% to squamous cell carcinoma.

Lichen sclerosus (LS) (Fig. 104.3a) is a chronic disease of the anogenital region. Autoimmune factors

Fig. 104.1 (**a**) Condylomata lata on labia majora and perineum; secondary syphilis. (**b**) Vulval angioedema in a pregnant female (From Dr. J.K.Maniar, MD, FRCP (Edin), Consultant in HIV Medicine; Jaslok Hospital, Saifee Hospital, and Wockhardt Hospital, Mumbai, India). (**c**) Vulvo-perianal vitiligo (From Dr. U. Mchepange, Mbeya Zonal Referral Hospital, Mbeya, Tanzania). (**d**) Hidradenitis suppurativa Hurley grade III (From Dr. K. Berzina private clinic, Riga, Latvia)

such as autoantibodies to extracellular matrix or basement membrane zone, *Borrelia burgdorferi* infection, and hormonal and genetic factors can have a role in pathogenesis. Clinically LS often starts as sharp-demarcated erythema on the clitoris and upper part of the labia minora, then gradually involves all of the labia minora, and spreads to the labia majora and perineum, developing the classic LS picture, single or multiple porcelain-white plaques. Vaginal scarring and narrowing are typical complications of LS. First- and second-line treatment options are similar to other vulvar lichens—potent and very potent corticosteroids and topical calcineurin inhibitors, local or systemic retinoids, PDT, phototherapy, and surgery.

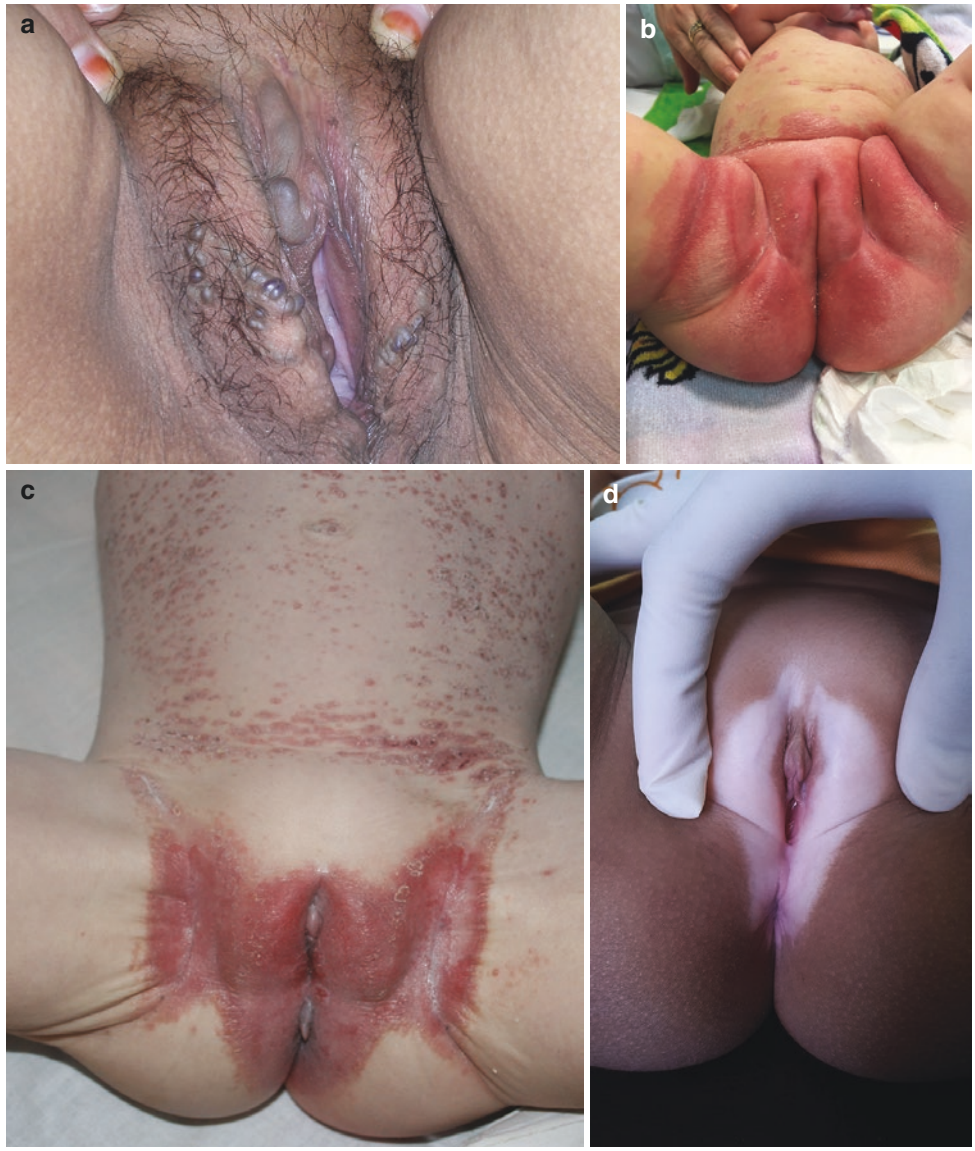

Fig. 104.2 (**a**) Vulval varicosities in pregnancy (Dr. J.K.Maniar,MD, FRCP (Edin), Consultant in HIV Medicine; Jaslok Hospital, Saifee Hospital, and Wockhardt Hospital, Mumbai, India). (**b**) Diaper Candidiasis (From Prof. Dr. Denis Zaslavsky, St. Petersburg State Pediatric Medical University, St. Petersburg, Russia (**c**) Vulval histiocytosis (From Prof. Dr. Denis Zaslavsky, St. Petersburg State Pediatric Medical University, St. Petersburg, Russia). (**d**) Vulval vitiligo (From Dr. J.K.Maniar, MD, FRCP (Edin), Consultant in HIV Medicine; Jaslok Hospital, Saifee Hospital, and Wockhardt Hospital, Mumbai, India)

Benign Tumors of the Vulva

Due to different histological structures, the number of benign vulvar tumors is large. Some examples of benign vulvar tumors include epidermal cysts, hidradenoma papilliferum, syringoma, hemangioma, angiokeratoma, nevi, lipoma, vulvar polyp, angiomyofibroblastoma, vulvar endometriosis, primary Langerhans cell histiocytosis of the vulva, and many others. Their diagnosis and management is similar to other parts of the body.

Syringoma is a benign tumor from the intraepidermal portion of eccrine sweat ducts. A vulvar location is rare. Clinically, it appears as tiny, skin-

Table 104.3 Management of vulvar lichens

Pathology	First-line treatment	Second-line treatment	Third-line treatment/other recommendations
Lichen simplex chronicus	Clobetasol propionate 0.05% ointment 1–2× daily to 2× weekly for 4–12 weeks	Tacrolimus 0.1% ointment/cream 1–2× day; up to 2 years	Prednisolone 20–40 mg PO 1× daily AM for 7–14 days
	Or		Triamcinolone acetonide 40–80 mg IM 1× daily to 1× monthly
	Clobetasol butyrate 0.05% ointment 1× daily to 2× weekly for 4–12 weeks	Pimecrolimus 1% cream 2× daily; up to 2 years	Avoidance of irritants and contact allergens
	or		Breakup of itch-scratch cycle: Sedating antihistamines, sedating tricyclics, selective serotonin reuptake inhibitors
	Betamethasone valerate 0.1% ointment 1× daily to 2× weekly for 4–12 weeks		Repair of epidermal barrier
Lichen planus	Clobetasol propionate 0.05% ointment 1–2× daily to 2× weekly for 4–12 weeks	Tacrolimus 0.1% ointment/cream 1–2× day; up to 2 years	Triamcinolone acetonide 10 mg/ml—0.5–1 ml intralesionally
	or		Triamcinolone acetonide—40–80 mg IM 1× daily to 1× monthly
	Clobetasol butyrate 0.05% ointment 1× daily to 2× weekly for 4–12 weeks	Pimecrolimus 1% cream 2× daily; up to 2 years	Prednisolone 20–40 mg PO 1× daily AM for 7–14 days
	Or		Vaseline—To protect erosive surfaces against urine
	Betamethasone valerate 0.1% ointment 1× daily to 2× weekly for 4–12 weeks		
Lichen sclerosus	Clobetasol propionate 0.05% ointment 1–2× daily to 2× weekly for 4–12 weeks	Tacrolimus 0.1% ointment/cream 1–2× day for up to 2 years	Topical estrogens
	or		Topical testosterone (rarely used due to virilization)
	Clobetasol butyrate 0.05% ointment 1× daily to 2× weekly for 4–12 weeks	Pimecrolimus 1% cream 2× daily; up to 2 years	Retinoids—Local or systemic
	or		Phototherapy—UVA1, UVB, PDT
	Betamethasone valerate 0.1% ointment 1× daily to 2× weekly for 4–12 weeks		Surgery for scarring and stenosis

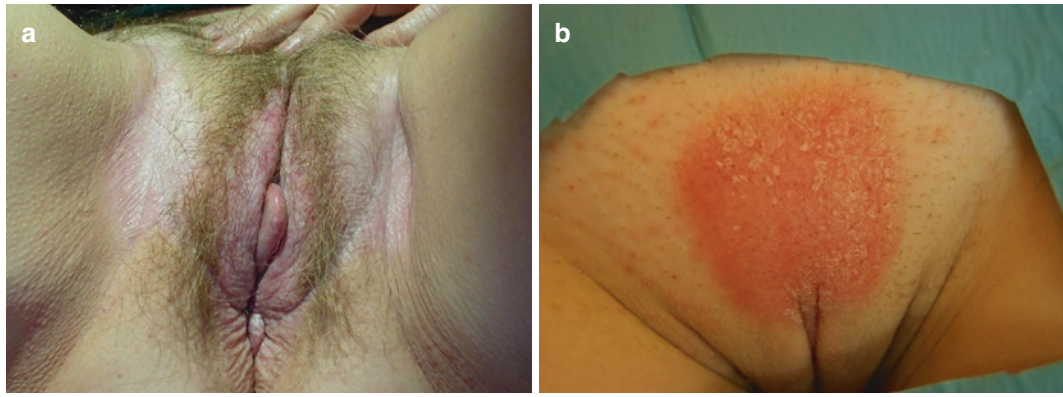

Fig. 104.3 (**a**) Lichen sclerosus. (**b**) Contact dermatitis

colored papules, mainly on the labia majora. Diagnosis is verified histologically. Treatment includes CO_2 laser and radiofrequency. Angiomyofibroblastoma is another rare, benign, well-circumscribed mesenchymal tumor presenting as a nodule or mass on the labia majora. Differential diagnosis is with Bartholin's cyst, lipoma, and aggressive angiomyxoma. Diagnosis is by histology. Treatment is simple excision.

Squamous Intraepithelial Lesions and Vulvar Intraepithelial Neoplasia

According to the 2004 ISSVD classification, vulvar intraepithelial neoplasia (VIN) was divided into three types: usual, differentiated, and unclassified. Usual-type VIN was further subdivided into warty, basaloid, and mixed (warty/basaloid) types. All VINs which neither belong to usual nor differentiated type were unclassified. Now the latest ISSVD classification of 2015 has introduced a new term: "squamous intraepithelial lesions" (SIL) amd is subdividing all premalignat vulvar lesions into 3 groups: L-SIL (Low-SIL), H-SIL (High-SIL; former usual-type VIN) and dVIN (differentiated VIN). Nevertheless, the pathogenesis remains the same as previous for usual-type VIN or differentiated VIN, e.g., L-SIL and H-SIL are HPV-associated, but dVIN develops from lichen sclerosus.

The clinical picture of SIL and VIN is variable and unspecific—elevated, flat, or warty, white, red, or brown lesions. The diagnosis is by direct visual examination, colposcopy, biopsy, and histology. Cytology is not reliable. HPV-DNA testing and the presence of phosphorylated ribosomal S6 in biopsy can be of additional value to sepa-

Table 104.4 Treatment of vulvar premalignancies and cancer

SIL/VIN	L-SIL/H-SIL	*First choice*
		Imiquimod 5% cream 3× a week, 12–20 weeks Resiquimod 0.01–0.03% gel 3× a week, 8–16 weeks
		Second choice
		CO_2 laser excision or vaporization
		Simple vulvectomy
		Skinning vulvectomy
		Others
		Cidofovir 1% gel PDT with topical ALA WLE with 0.5 cm PM
	dVIN (differentiated VIN)	*First choice*
		WLE with 0.5 cm PM
		Second choice
		CO_2 laser excision or vaporization
		Simple vulvectomy
		Skinning vulvectomy
VSCC	FIGO IA	WLE with 1.0 cm PM
	FIGO IB	WLE with 1–2 cm PM
		SLN biopsy (if invasion depth >1 mm)
	FIGO II	HVLNE or RVLNE with 5 cm PM
		Radiotherapy
	FIGO IIIA, IIIB, IIIC	RVLNE with 5 cm PM
		Radiotherapy
		Chemotherapy
	FIGO IVA, IVB	RVLNE with 5 cm PM + pelvic exenteration
		Radiotherapy
		Chemotherapy
		Erlotinib—150 mg/day PO
		Gefitinib—250 mg/day PO
		Afatinib—50 mg/day PO Cetuximab—400 mg/m^2 IV initially, then 250 mg mg/m^2 IV weekly Pembrolizumab—2 mg/kg IV every 3 weeks

(continued)

Table 104.4 (continued)

Vulvar melanoma	AJCC O (in situ melanoma)	WLE with 0, 5–1 cm PM
	AJCC IA, IB	WLE with 1–2 cm PM
		SLN biopsy (if Breslow depth > 1 mm and/or high mitotic rate)
	AJCC IIA—IIC	WLE with 2–4 cm + SLN biopsy or HVLNE or RVLNE with 3–4 cm PM
		Chemotherapy—dacarbazine (DTIC)
		Immunotherapy—nivolumab (anti-PD-1), Ipilumab (anti-CTLA-4) Immuno-chemotherpay: Nivolumab/Ipilumab + dacarbazine (DTIC)
	AJCC IIIA—IIIC	WLE with 2–4 cm PM + LNE or RVLNE with 5 cm PM
		Combined immunotherapy—Nivolumab (or pembrolizumab) + Ipilumab: *Induction phase:* Nivolumab—1 mg/kg IV every 3 weeks + Ipilumab—3 mg/kg IV every 3 weeks *Maintainace phase:* Nivolumab—1 mg/kg IV every 2 weeks
		Chemotherapy—DTIC Immunotherapy: IL-2, IFN-alfa2, HDI Immuno-chemotherapy—DTIC + IFN-alpha or IL-2 Oncolytic virotherapy—T-VEC—Intratumoral injections
	AJCC IV	*Treatment with the highest success rate*
	Metastatic	*Surgical therapy* WLE + LN (if operable/resectable) or RVLNE with 5 cm PM + pelvic exenteration + *Combined immunotherapy* (Nivolumab or Pembrolizumab + Ipilumab) + *Targeted therapy with or two inhibitors* – c-KIT inbibitor (nilotinib or imatinib) – or other (NRAS, BRAF inhibitors)
		Other treatment options RVLNE with 5 cm PM + pelvic exenteration Radiotherapy Chemotherapy—DTIC Polychemotherapy (DVP, BHD, BOLD)
		Immunotherapy: IL-2—600,000–720,000 IU/kg IV every 8 h, 14 doses Radio-immunotherapy
		Checkpoint inhibitors: (a) anti-PD-1: Nivolumab—1–3 mg/kg IV every 3 weeks; total 4 doses Pembrolizumab—2 mg/kg IV every 3 weeks; total 4 doses Lambrolizumab—2–10 mg/kg IV every 2–3 weeks; total 4 doses (b) Anti-CTLA-4: Ipilimumab—3 mg/kg IV every 3 weeks; total 4 doses
		Targeted therapies (c-KIT inhibitors)
		Imatinib—400–800 mg PO daily Nilotinib—400–800 mg PO daily
		Combined therapy: Two immunotherapies, two targeted therapies; two targeted therapies with one immunotherapy etc.
		Oncolytic virotherapy
		Adoptive cell therapy (ACT) TCR-directed therapy Anti-melanoma vaccines

AJCC American Joint Committee on Cancer (2017 Melanoma Staging and Classification), *FIGO* Fédération Internationale de Gynécologie et d'Obstétrique, *HVLNE* hemivulvectomy with superficial inguinal lymphadenectomy, *PM* peripheral margin, *PO* peroral, *RVLNE* radical vulvectomy with inguinofemoral lymphadenectomy, *SCC* squamous cell carcinoma, *VIN* vulvar intraepithelial neoplasia, *WLE* wide local excision

rate SIL and dVIN. Treatment depends on clinical form and anatomical location (Table 104.4). Topical imiquimod and laser ablation is preferred in SIL, surgery is reserved mostly for dVIN.

Cancers of the Vulva

Primary cancers of the vulva are rare and account for approximately 5% of all gynecological malignancies and less than 1% of all malignancies in women. Squamous cell carcinoma is the most common type of vulvar cancer at 90–95%, followed by melanoma at 5%, and adenocarcinomas and other cancers at 5%.

Vulvar Squamous Cell Carcinoma

Two different pathways are proposed for vulvar SCC (VSCC) development—HPV dependent and lichen sclerosus. In the first, high-risk types of HPV, e.g., HPV16, trigger H-SIL development and later non-keratinising VSCC. In the second, keratinizing VSCC develops from differentiated VIN within a background of lichen sclerosus. Diagnosis and treatment of vulvar SCC is according to FIGO staging and treatment recommendation: early-stage vulvar cancer (FIGO I–II), intermediate-stage vulvar cancer (FIGO III), and locally advanced or metastatic (FIGO IV). A microinvasive carcinoma with less than 1 mm stromal invasion and less than 2 cm in size (FIGO stage IA) is surgically excised with a 1 cm resection margin without lymphadenectomy. For SCC invasion deeper than 1 mm, lymph node staging is done, and if sentinel lymph node is positive for metastasis, either unilateral or bilateral lymphadenectomy is performed. In intermediate or locally advanced tumor, treatment depends on tumor location, size, and invasion and lymph node status; main types of operations are wide excision and ipsilateral superficial lymphadenectomy, wide excision and bilateral inguinofemoral lymphadenectomy, and radical vulvectomy with bilateral inguinofemoral lymphadenectomy. Metastatic vulvar SCC is treated with radiotherapy, chemoradiotherapy, and polychemotherapy. New treatment options include drugs targeting EGFR, which is expressed in almost 100% of metastatic SSC. This can be achieved via specific antibodies (cetuximab, panitumab) or inhibiting tyrosine kinase (erlotinib, gefitinib, afatinib), or by boosting anti-cancer immunity (pembrolizumab, ipilumab). Recurrence rate in SCC is high, especially with a tumor size of more than 35 mm, tumor-free surgical margin of less than 8 mm, and depth of stromal invasion of more than 4 mm. Chronic lymphedema and vulvar and groin wounds are typical posttreatment side effects. Vulvar SCC caused by long-standing HPV infection can be prevented by HPV vaccination. Dermatologists can play an important role in early recognition of lichen sclerosus and potentially avoiding lichen sclerosus associated VSCC.

Vulvar Adenocarcinomas

Primary vulvar adenocarcinomas are rare tumors classified into vulvar Paget's disease, sweat gland carcinomas, "breast-like"carcinomas, and vulvar apocrine adenocarcinoma. Vulvar Paget's disease or extramammary Paget's disease is the most common type of primary vulvar adenocarcinomas. Females 65–75 years of age are typically affected. Itching, eczema-like lesions on the labia, and enlarged inguinal lymph nodes are typical clinical presentations. Pruritus can be long-standing, with several years before diagnosis. Treatment is surgical excision, CO_2 laser, imiquimod and PDT, cryosurgery and PDT.

Skene's gland adenocarcinoma is a rare neoplasm of the female periurethral glands histologically resembling prostate adenocarcinoma. Diagnosis is made histologically. Immunohistochemical staining with PSA and preoperative and postoperative measurements of PSA are of diagnostic value. Treatment is by excision.

Bartholin's gland carcinoma is another rare neoplasm of the vulva. Histologically squamous, adenoid cystic, transitional, and combined types are recognized. Treatment is by hemivulvectomy with or without lymph node dissection, total vulvectomy and bilateral inguinofemoral lymph node dissection with or without radiotherapy and chemotherapy. Local

recurrence and distant metastases are seen in one-third of patients.

Vulvar Melanoma

The vulva is the most common site of mucosal melanomas. Vulvar melanoma is the second most common vulvar malignancy after SCC. Postmenopausal women are typically affected, the median age is 68 years. Prognosis in metastatic vulvar melanoma is generally worse than in cutaneous. Recurrence rate is 30–50%. The average 5-year survival rate is 36%. Vulvar melanomas differ from cutaneous and vaginal melanomas having a high percentage of c-KIT mutations. Pigmented lesion or vulvar mass, pain, itching, and bleeding are characteristic symptoms of vulvar melanoma. Anatomical distribution favors the clitoris and labia minora in 60–70%. The most common types in vulva are: superficial spreading (48%), nodular (35%), mucosal lentiginous (7%), spindle cell (5%) and amelanotic (2%) melanoma. Amelanotic melanomas can simulate lichen sclerosus or be associated with it. Differential diagnosis for amelanotic melanoma includes also dVIN and SCC. Diagnosis of vulvar melanoma is established histologically with the help of immunohistochemistry melan-A, MART-1 antibodies, S100, HMB-45. Most commonly Breslow, but also Clark or Chung system is used for microstaging. AJCC staging system is used for vulvar melanoma similar to cutaneous. Correct and precise mapping of sentinel lymph nodes (SLN) in the inguinal and femoral area can be substantially improved with 3D fusion images of SPECT and CT scans. Positive SLN are found in 20–30% of cases of vulvar melanoma. Molecular screening for activated c-KIT mutations shall be done. Treatment depends on anatomical location, size of tumor, depth of invasion, and stage of disease (Table 104.4).

Wide local excision (WLE) is preferred over more radical operations such as hemivulvectomy or radical vulvectomy with bilateral inguinofemoral lymphadenectomy (RVLNE). The same principles for peripheral (free) margin (PM) apply as in cutaneous melanoma, e.g., for Breslow's thickness <1 mm PM is 1 cm. Local imiquimod therapy has been tried with partial success in vulvar melanoma.

For metastatic melanomas, dacarbazine monochemotherapy or polychemotherapy have been used traditionally. Unfortunately, vulvar as well as mucosal melanomas have a low response rate to chemotherapy. Dacarbazine (DTIC) monotherapy has achieved up to 23% response rate in clinical trials, although only 5% of patients are responding. However, it could be possible to achieve much higher rates of DTIC treatment success, when using lipid nanoformulations in combination with all-trans retinoic acid, creating a kind of "micellar DTIC" with much better physiochemical properties. Radiotherapy may reduce the local recurrence but not the overall survival and often causes intolerable side effects in vulvar area. The effectiveness of radiotherapy can be improved by combining it with check-point inhibitors, e.g., anti-PD1 (radio-immunotherapy), and especially varying the radiotherapy dose from a high to low. This activates immune cells and weakens tumor storma, facilitating the penetration of the anti-PD1 drugs.

In recent years several new therapeutic agents, classes of drugs, and treatments have been registered or are in clinical trials for metastatic melanoma, among them check-point inhibitors and target-therapies such as CTLA-4 antibodies (ipilimumab, tremelimumab), interleukin-2, BRAF inhibitors (vemurafenib, dabrafenib), anti-PD-1 (nivolumab, pembrolizumab), MEK inhibitors (trametinib), c-KIT inhibitors (imatinib, sorafenib), adoptive cell transfer, and combined therapies.

Ipilimumab at 3 mg/kg alone or in combination with interleukin-2 or gp-100 has shown complete response in 6–17% of patients, 2-year survival rate in 24%, and 5-year survival rate from 13 to 23%. Pembrolizumab or nivolumab alone can stop metastatic vulvar melanoma progression in around 50% of cases. Nivolumab plus ipilumab can prevent intracranial progression of melanoma brain metastasis for more than 6 months in 64% of patients.

From the targeted therapies vemurafenib and other BRAF inhibitors are not really useful in vulvar melanomas, because of low prevalence (<4%) of BRAF V600E mutations. For patients with

metastatic vulvar melanoma, the highest hopes and expectations can be attributed to c-KIT inhibitors most probably in combination with checkpoint inhibitors. In clinical trials imatinib 400–800 mg/day has shown complete response in 6%, partial response in 23%, and total disease control in 53%; 1-year survival rate was achieved in 40–51% and 2-year survival rate in 16–20%. Similar results have been obtained with nilotinib.

Adoptive cell transfer or therapy (ACT) is a relatively new individualized method with high and durable response. In ACT, tumor-infiltrating lymphocytes (TIL) are taken from the melanoma of the patient, cultured, and reinfused back. The three main methods of ACT are transfer of autologous TILs or T-cells expressing chimeric antigen receptors (CAR-T), or TCR-directed therapy. Melanoma germline antigens and cell membrane proteins are the potential targets of TCR-directed therapy. The response rate of ACT ranges from 20 to 70% depending on the method.

Oncolytic virotherapy is another emerging tool in treatment of human cancers. Currently there are two drugs available for metastatic melanoma: Rigvir (ECHO-7 picornavirus; registered in Latvia, Armenia, Georgia) and Imlygic™ (talimogene laherparepvec (T-VEC), recombinant HSV-1; approved by FDA in 2015). T-VEC has shown good results alone or in combination with anti-PD1 and anti-CTLA-4. Last, but not least, a substantial progress is seen in the anti-melanoma vaccine development. The first trial of an RNA anti-melanoma vaccine (FixVac) has been conducted recently. FixVac is a nanoparticulate liposomal RNA, which can induce effector T-cell response against tumor-associated antigens (TAA) by activating immature dendritic cells to drive TAA presentation on both MHC class I and II molecules. Good results were obtained in the combined use of FixVac and anti-PD1. Another interesting development is the anti-melanoma vaccine AGI-101H, which can upregulate Bcl6 stimulating T-cell activity against melanoma.

With the new treatment developments, there is a place for optimism that metastatic melanoma will become a chronic-manageable disease sooner than expected, if not completely curable.

Vulvar Itch and Vulvodynia

Vulvar itch or pruritus vulvae is a very common and important symptom. Besides anamnesis and clinical aspects, the age of the patient is important. In young women, vulvar pruritus is most often caused by infections and allergies—vulvovaginal candidiasis, enterobiasis, diabetes, scabies, pediculosis pubis, and vulvar eczema; in postmenopausal women, it is more often caused by lichen sclerosus, VIN, and other benign and malignant tumors. Treatment is with local or systemic anti-infectives, corticosteroids, calcineurin inhibitors, surgery, and oncologic drugs.

Vulvodynia presents with vulvar pain, burning sensation, and dyspareunia without obvious physical cause for at least 3 months. Formerly it was known as “burning vulva syndrome” and more correctly can be called “aidoiodynia.” Some 10–20% of females are estimated to be affected worldwide. Vulvodynia can be generalized involving all vulvar structures or localized to some parts, e.g., clitorodynia and hemivulvodynia. Vulvo-vestibulitis syndrome (VVS) is a type of focal vulvodynia. Disturbed pain perception, vulvar hypersensitivity, psychosexual problems, and vaginal infections are proposed pathogenic factors of vulvodynia. Diagnosis is based on anamnesis, clinical examination, pain assessment via Q-tip test, and tampon test. Treatment is done with amitriptyline cream, vaginal cream with conjugated estrogens, pelvic floor physiotherapy, biofeedback, cognitive-behavioral therapy, systemic amitriptyline, gabapentin, botulinum toxin A, posterior vestibulectomy, and simple vulvectomy.

Vulvar Injury, Mutilation, and Structural Pathologies

The vulva can be traumatized or deformed by sharp or blunt trauma, rape, sexual abuse, mutilation, diseases, chemicals, and other agents.

Female circumcision or female genital mutilation (FGM) is a ritual religious practice of some communities mainly in Africa and the Middle East. The top three countries practicing

FGM are Egypt, Sudan, and Mali. The average age when girls are circumcised is 10 years. Depending on the extent, FGM is graded into four types. The most common is FGM type II, when the clitoris and labia minora are removed. FGM is bound with many complications: psychosocial trauma, acute and chronic pain, bleeding, infections, cysts, narrowing of the vaginal opening, and partum and postpartum risks. Treatment is mostly symptomatic using analgesics, anti-infectives, neuroleptics, and lubricants. Surgical correction or reconstruction can be tried in some cases.

Structural pathologies of the vulva can include acquired defects (synechia, fusion of labia, stenosis) or congenital anomalies such as agenesis of labia, imperforate hymen, malformations of clitoris, hypospadia of female urethra, hermaphroditism, and female pseudohermaphroditism. Treatment is mostly surgical.

Diagnosis

Correct diagnosis of vulvar diseases involves experience both in gynecology and dermatology (Table 104.5). Anamnesis of the disease, age, social and ethnic background, sexual habits, and medication use is important as well as history of gynecologic and dermatologic pathologies. Vulvovaginal inspection shall be followed by full-body examination, paying special attention to the perineum, lower abdomen, axilla, oral mucosae, scalp, and lymph nodes. Sexual partners or legal representatives of children or teenagers must be consulted or examined. All pruritic lesions of the vulva deserve a very careful examination, because they can be an early sign of malignancy. Different methods of microscopy, culture, PCR, serology, and blood analysis can diagnose most of the causes of vulvar ulcers, erosions, and vulvites. Biopsy and histopathology remain a golden standard in most dermatological diagnosis. Vulvar pigment lesions can be examined with dermatoscopy and laser confocal microscopy. Hormonal and genetic investigations are necessary for endocrine and structural pathologies. Women with hirsutism shall be tested for polycystic ovary syndrome, androgen-secreting tumors, adrenal hyperplasia, Cushing syndrome, and thyroid function. Ultrasonography, CT, PET-CT, MRI, 3D fusion images of SPECT have become popular, noninvasive methods to diagnose cysts, urethral and periurethral pathologies in females, sentinel lymph nodes and distant metastases. Newer methods for detecting SLN include contrast-enhanced ultrasound (CEUS).

Table 104.5 Diagnostic methods in vulvar diseases

Method	Indication
Microscopy	Herpes, syphilis, donovanosis, ulcus molle
Culture	Bacterial, fungal, viral infections
Patch test, prick	Allergic vulvitis, vulvar edema
Dermatoscopy	Pigmented and vascular vulvar lesions, different other dermatoses, scabies, pediculosis
Colposcopy	VIN, squamous cell carcinoma
Confocal microscopy	Similar to dermoscopy
Histology and immunohistochemistry	Vulvar melanoma, VIN, SCC, any other unknown clinical condition
Pain assessment tests	Vulvodynia
Blood and hormonal analysis	Autoimmunity, infections, hirsutism
Ultrasound, MRI, CT scan, PET-CT, CEUS	Cysts, abscesses, SCC, melanoma, distant metastases
PCR	Bacterial, fungal, viral infections
Acetic acid	VIN, SCC

General Principles of Treatment

Local treatment options include antibacterial solutions, creams and ointments, hydrotherapy, corticosteroids, estrogens, and testosterone-containing creams (Table 104.6). Antimicrobial treatment for infectious vulvar ulcers or vulvovaginitis is well established internationally in many guidelines. Noninfectious and nononcologic ulcers or vulvar inflammations are

Table 104.6 Local treatments in vulvar diseases

Drug/formulation/dosage	Indication
1. *Antifungals*	
1.1. Nystatin, 100,000 U vaginal tablet, 2–6× a day or in severe cases every 1–2 h till complete healing and then additional 8–10 days	Candida vulvitis, intertrigo
1.2. Ketoconazole, 2% cream, 2× daily for 2–4 weeks	Candida, dermatophytes, seborrheic dermatitis
1.3. Econazole nitrate, 1% cream, 1–2× a day for 2–4 weeks	
1.4. Miconazole nitrate, 2% cream, 7 days; vaginal applicator, 1× daily at night: 100 mg for 7 days, 200 mg for 3 days, 1200 mg single dose	
1.5. Butoconazole, 2% cream, 7 days; 2% sustained release cream 5 g, 1 day	
1.6. Terconazole, 0.4% cream, intravaginally 1× daily for 7 days; 0.8% cream or 80 mg vaginal suppositories, intravaginally 1× daily for 3 days	
1.7. Tioconazole, 6.5% ointment, intravaginally at night, single dose	
1.8. Ciclopirox olamine, 0.77% cream, 2× daily for 4 weeks	
2. *Antibacterials*	
2.1. Tetracycline, 3% ointment, 1–3 daily, 5–10 days	Bacterial vulvar infections, ulcers
2.2. Meclocycline, 1% cream, 1–2× daily, 5–10 days	
2.3. Fusidic acid, 2% cream/ointment, 1–3× daily, 5–10 days	
2.4. Metronidazole, 5% vaginal cream, 1× daily intravaginally for 6 days	
2.5. Clindamycin, 2% vaginal cream, 1× daily intravaginally for 3 days	
2.6. Mupirocin, 2% ointment, 1–3× daily, 5–10 days	
2.7. Silver sulfadiazine, 1% cream, 1–2× daily till healing	Wounds, burns
3. *Hormones*	
3.1. Estriol, 0.05% vaginal cream, intravaginally 1× daily 1 week, then 2× weekly	Atrophy, dry vagina, pruritus vulvae, dyspareunia, vaginal stenosis, lichen sclerosus
3.2. Estradiol, 0.01% vaginal cream, 2–3× daily on vulvae	
3.3. Conjugated estrogens, vaginal cream, intravaginally continuously (21 days on, then 7 days off) or cyclically (2× weekly)	
3.4. Testosterone propionate, 2% cream/ointment/gel, 2× daily for 3–4 months; not more than 50 g in the first 2 months and not more than 10–25 g in the next 2 months	
4. *Antiseptics/astringents*	
4.1. Aluminum acetate, 5% solution	Microbial vulvitis
4.2. Burow's solution, 5% aluminum acetate diluted in water (1:20–1:40)	
4.3. Tannic acid, 2% solution	
4.4. Boric acid, 1% solution	
4.5. Ichthammol, 2% solution	
4.6. Potassium permanganate, 1: 10,000 solution	
4.7. Hydrogen peroxide, 1–3% solution	
4.8. Povidone-iodine, 4%, 5%, 10% solutions;10% ointment; 2.5% dry powder spray	
4.9. Silver nitrate, 0.5%, 1%, 10% solutions	
5. *Anti-parasite*	
5.1. Permethrin, 5% cream, over whole body (except head) for 12 h	Scabies
5.2. Benzyl benzoate, 10%/25% emulsion, 1–3 applications over whole body for 72 h	
5.3. Lindane, 1% lotion, whole body application (except head); wash off after 8–12 h	
5.4. Permethrin, 1% cream rinse, apply for 10 min to dry hair, then wash off	Pubic lice
5.5. Lindane, 1% shampoo, apply for 4 min to dry hair, then wash off	
5.6. Ivermectin, 0.5% lotion, apply for 10 min to dry hair, then wash off	
6. *Antiviral*	
6.1. Aciclovir, 5% cream, 5× daily for 5–10 days	Genital herpes
6.2. Penciclovir, cream, every 2 h, 4–5 days	
6.3. Podophyllotoxin, 5 mg/1 ml solution, 2× a day for 3 consecutive days; maximum—4 weeks	Genital HPV infection
6.4. Imiquimod, 5% cream, 3× a week; maximum—16 weeks	
7. *Antineoplastic*	
7.1. Imiquimod, 5% cream, 3× a week; maximum—16 weeks	Basal cell carcinoma, L-SIL, H-SIL
7.2. Fluorouracil, 5% cream, 1–2× daily; maximum—12 weeks	

(continued)

Table 104.6 (continued)

Drug/formulation/dosage	Indication
8. *Esthetic*	
8.1. Botulinum toxin type A, solution of 50/100/200/500 U in vials, 25–200 U per treatment or individually matched doses	Vulvodynia
8.2. Fillers—Hyaluronic acid, solution 20 mg/ml in vials, 0.5–6 ml per treatment	
9. *Anesthetic*	
9.1. Lidocaine, 2% gel, 1 fingertip unit (0.5 g) 1× daily	Pruritus vulvae, vulvodynia
9.2. Lidocaine (25 mg)/prilocaine (25 mg), 5% cream, 1 fingertip unit (0.5 g) 1× daily	

treated with corticosteroids and other immunosuppressives. Although ultrapotent and potent topical corticosteroids remain standard treatment options for vulvar lichens, calcineurin inhibitors are as effective but with better safety profile. Topical calcineurin inhibitors can also be used for psoriasis inversa, contact dermatitis, seborrheic dermatitis, and vitiligo. Amitriptyline vaginal cream is another advancement in vulvodynia treatment to decrease systemic drug use (Table 104.6 and 104.7).

Vulvar surgery helps to solve not just purely surgical or oncological problems but is used in

Table 104.7 Systemic and surgical treatments in vulvar diseases

Medication/device	Specification	Indication
Antibiotics	Azithromycin	Bacterial ulcers and vulvitides, vulvar furuncle, abscess, secondary infected wounds
	Erythromycin	
	Clindamycin	
	Penicillins	
	Cephalosporins	
Antifungals	Fluconazole, itraconazole, ketoconazole	Vulvovaginal candidiasis
Antivirals	Acyclovir, famciclovir, valacyclovir	Genital herpes, vulvar herpes zoster
Retinoids		
Immunosuppresives	Corticosteroids, azathioprine, methotrexate, thalidomide	Autoimmune bullous diseases, atopic dermatitis, psoriasis, vulvar lichens
Biologics	1. Anti-TNF, anti-IL-12/anti-IL-23p40	1. Psoriasis, autoimmune bullous diseases
	2. c-KIT inhibitors	2. Metastatic vulvar melanoma
	3. EGFR tyrosine kinase inhibitors	3. Metastatic squamous cell carcinoma
Cryotherapy	Cryogun, cryoprobe, cryo-application	HPV infection, seborrheic keratosis
PDT	With topical ALA	L-SIL, H-SIL
Phototherapy	UVB, UVA, PUVA, re-PUVA	Psoriasis, lichen sclerosus
Ablative laser surgery	CO_2, erbium:YAG	SIL, VIN, Bartholin's/Skene's abscess
Vascular lasers	Nd-YAG, KTP, PDL	Hemangioma, venous lake
Pigment lasers	Q-switched Nd-YAG, alexandrite	Bening pigmented lesions
Radiofrequency	Surgical	Similar to ablative lasers
Surgery	1. Incisional/excisional surgery	1. Bartholin's/Skene's abscess
	2. Skinning vulvectomy	2. a. Squamous intraepithelial lesions (SIL) b. Vulvar intraepithelial neoplasia (VIN)
	3. Wide local excision	3. Vulvar intraepithelial neoplasia
	4. Hemivulvectomy	4. Vulvar cancer
	5. Radical "en bloc" vulvectomy	5. Advanced vulvar cancer
	6. Lymphadenectomy—Superficial inguinal or inguinofemoral	6. Vulvar cancer
	7. Plastic/esthetic vulvar surgery	7. Vulvar mutilations, scarring, stenosis

chronic inflammatory diseases, vulvar lichens, and vulvodynia as well. Benign lesions are usually treated with simple incision, drainage, marsupialization, ablative and vascular laser, radiofrequency, cryosurgery, esthetic labial surgery and reconstructive vulvar surgery, PDT, and phototherapy. In neoplasia, either wide local excision, hemivulvectomy, or radical vulvectomy with bilateral lymphadenectomy is used. New drugs and treatment against metastatic melanoma and squamous cell carcinoma give hope to the patients and physicians that a 5- to 10-year survival can be achieved in the nearest future. Besides drugs and surgical treatments, psychological support and rehabilitation is important, especially in vulvar cancer, after vulvar injury, mutilation, or radical surgery.

Finally, prevention shall not be forgotten in vulvar diseases. This applies to STI and safe sex behavior, hypoallergenic intimate hygiene and clothing, vaccination against HPV infections, and early recognition of cellular atypia, premalignancy and malignancy.

Further Reading

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