

Vulvar Disease

A Clinicopathological
Approach

Edited by
Debra S. Heller
Robert C. Wallach

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*In loving memory of M. Renate Dische, MD, PhD—mentor, friend,
inspiration, and supporter of women—and in recognition of the
pioneering study and teaching of Henry C. Falk, MD.*

Preface

Vulvar disease is a source of patient distress, provokes multiple consultations with physicians, and is a challenging diagnostic area for gynecologists, dermatologists, and pathologists. Some gynecologists may be insecure or unfamiliar with the various vulvar problems, and their training and experience may not encompass the spectrum of disease found on the vulva, especially the dermatologic entities. Dermatologists who see vulvar disease may not be as familiar with the gynecologic vulvar disease entities. Pathologists, except for the rare subspecialists with high-volume practices, can often be challenged in this area.

This book is a collaboration between a gynecologic pathologist with training and experience in obstetrics and gynecology (Debra S. Heller) and a gynecologic oncologist who has a special interest in vulvar disease (Robert C. Wallach), with input from gynecologists, dermatologists, and pathologists with interest and expertise in the field. In addition, a CD-ROM containing all the images in the book is meant to provide additional teaching and reference material.

This monograph is primarily intended to be a coalescence of views from the several disciplines represented, covering clinical as well as pathologic appearances, with treatment guidelines. It is hoped that this focus of attention on vulvar disease will provide a multidisciplinary reference resource to help us all better serve women with vulvar disease.

Debra S. Heller
Robert C. Wallach

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An Approach to the Evaluation of Vulvar Lesions and Complaints

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ANATOMY

Many women are uncertain about their genital anatomy and may present complaining of vaginal itching or simply itching “down there.” The vulva comprises the entire external genitalia from the mons pubis anteriorly to the anus posteriorly and laterally to the genito-crural folds. Included in this area are the labia majora, labia minora, clitoris, urethral meatus, vestibule, posterior fourchette, hymen, and the Bartholin's, Skene's, and minor vestibular glands and the vestibular bulbs.

The labia majora and mons contain adipose and fibrous tissue, covered by skin with numerous sebaceous and hair follicles. The labia minora do not contain adipose tissue, and their skin has sebaceous glands but not hair follicles. On the inner aspect of the labia minora is Hart's line, which delineates the junction between skin and the mucous membrane. The boundaries of the vulvar vestibule are Hart's line laterally and the hymenal ring medially, and this area contains numerous glands that secrete mucus. The vestibular bulbs are located within the bulbocavernosus muscles on either side of the vestibule and contain erectile tissue. The clitoris contains both erectile tissue and a very high density of nerve fibers.

The blood supply of the vulva is from branches of the internal and external pudendal arteries, and lymphatic drainage is primarily to the external and internal iliac nodes via the groins. Branches of the pudendal nerve provide most of the motor and sensory innervation to the vulva.

ETIOLOGY

The evaluation of vulvar lesions can be challenging because there are a variety of potential causes including infectious diseases, nonneoplastic epithelial disorders, and benign and malignant neoplasms. In addition, these conditions will frequently coexist;

for example, the patient with recurrent vulvovaginal candidiasis may develop contact dermatitis from frequent application of irritating topical products to the affected skin. In addition, some women present with chronic vulvar itching and burning due to dysesthetic vulvodynia and will have no obvious physical findings on examination.

Nonneoplastic Epithelial Disorders of the Vulva

This group of disorders includes the conditions that are sometimes referred to as the vulvar dystrophies or dermatoses. The current recommended classification system developed by the International Society for the Study of Vulvar Disease for these disorders is (1):

1. lichen sclerosus,
2. squamous cell hyperplasia,
3. other dermatoses.

An updated classification based on pathological criteria is nearing completion.

While some of these conditions are discussed in more detail in other sections, they are briefly reviewed here.

Lichen Sclerosus

Formerly known as lichen sclerosus et atrophicus, lichen sclerosus is a chronic dermatologic condition that is more common in women and may involve both vulvar and extragenital lesions. Patients typically present with severe itching and may also report burning and dyspareunia. The entire vulvar area may be involved, including the clitoris and perianal regions. The skin often has the typical “parchment appearance” with white papules and plaques that may appear crinkled. Fissures, telangiectasias, and stenosis of the introitus may occur. With long-standing disease, there is often alteration of the normal vulvar architecture resulting in absence of the labia minora, adhesions of the labia majora, and phimosis of the clitoris in extreme cases. While it can affect women of any age, it is more commonly seen in the postmenopausal years and approximately 10% to 15% of cases occur in pediatric patients (2).

Squamous Cell Hyperplasia

This category includes lichen simplex chronicus and epithelial hyperplasia, and in the past was often called leukoplakia or hyperplastic dystrophy. Clinically, this typically presents with complaints of itching and burning, and often follows contact with a topical irritant, although the patient may not recall such an exposure. Any part of the vulva may be affected, and the skin may appear erythematous with fissuring and excoriation. Lichenification, or the accentuation of normal skin markings, which results in thickening and raised white plaques, is also commonly seen. The process may be localized or diffuse and can be seen in all of the reproductive stages. This condition frequently may be associated with long-term use of topical therapies such as antifungals or steroids for other conditions, and may be causally related. A history of atopy, allergies, or eczema is also a likely risk factor.

Lichen Planus

A challenging disease to both diagnose and manage, lichen planus is a papulosquamous disorder that may involve both cutaneous and mucosal surfaces. On the vulva, lesions are often violaceous papules that cause pruritus. A whitish reticular pattern may appear on the inner labia majora where there is more exposure to moisture, and

on the vestibular and vaginal mucosa the lesions are usually erythematous erosions. Vaginal disease is often associated with a heavy yellow discharge and significant dyspareunia. Long-standing disease is usually associated with adhesions of the vagina that begin distally and can result in shortening and narrowing or even obliteration of the vaginal canal. The most common site for extragenital disease is the oral cavity, and up to three-quarters of all patients with lichen planus will develop gingival or oral lesions at some point (3).

Other Dermatoses

While the vulva is not usually the primary site for other dermatologic diseases, many skin conditions will involve the genital area at some point. The most commonly seen in clinical practice of these is psoriasis. Vulvar psoriasis may have the classic appearance of erythematous plaques with silvery, dry scale, but if the area is subject to chronic moisture, then it may have a macerated appearance with fissuring (4). The plaques generally are located on the mons or labia majora and extend to the genitocrural creases and buttocks.

Infectious Diseases

Infections involving the vulva are commonly seen in clinical practice and should be included in the differential diagnosis of any vulvar complaint.

Candidiasis

Almost every woman experiences at least one episode of vulvovaginal candidiasis during her lifetime. While women typically report vaginal itching with these infections, the site of symptoms is more accurately the vestibule and inner vulva in most cases. Itching, burning, external dysuria, and dyspareunia are all common. While the presence of a curdy white discharge is quite sensitive for candida, the absence of this sign does not rule out the infection. It is important to question the patient about possible attempts at self-treatment, because the recent application of over-the-counter antifungal creams and suppositories may affect the appearance of the vulva and the vagina. Approximately 90% of vulvovaginal candida infections are due to *Candida albicans* but nonalbicans species, particularly *Candida glabrata*, are becoming increasingly common (5).

Bacterial Vaginosis and Trichomoniasis

While these disorders are typically described as vaginal infections, they may be associated with vulvar symptoms such as itching, burning, external dysuria, and dyspareunia. Therefore, thorough evaluation of vaginal pH and wet mount is important in all patients with vulvovaginal complaints.

Genital Herpes Simplex Virus

Recent studies suggest that the prevalence of genital herpes virus infection in the U.S. population is approximately 25%, and many of those who are infected are unaware of their status; thus, it should certainly be included in the differential diagnosis of any vulvar complaint (6). Primary infection usually presents with multiple extensive and painful vesicles that rapidly become shallow ulcers and may be anywhere on the vulva as well as vagina and cervix. Patients may also have systemic symptoms of viral infection such as fever, fatigue, and myalgias. Recurrent infections

are typically less severe with fewer lesions and no systemic complaints. Some patients report prodromal tingling or itching prior to the appearance of lesions, but others may be asymptomatic. While the possibility of herpes infection is usually quite distressing to the patient, testing for herpes simplex virus (HSV) should be considered in the evaluation of any vulvar blister, ulcer, or fissure of uncertain etiology.

Genital Warts

Condylomata acuminata or genital warts are caused by the human papilloma virus (HPV). Patients may complain of vulvar irritation or itching and typically note the appearance of multiple small warty lesions of the vestibule, inner labia minora, and perianal region.

Other Sexually Transmitted Infections

While less common than HSV and condylomata, many other sexually transmitted infections may present with a vulvar lesion. The lesion of primary syphilis is typically a painless erythematous ulcer with a smooth base and well-defined edges. Granuloma inguinale presents with multiple erythematous granulomatous ulcers that are usually quite friable. Chancroid, caused by the bacterium *Hemophilus ducreyi*, usually presents as either a pustule with surrounding erythema or a tender vulvar ulcer with a ragged edge and necrotic base. Lymphogranuloma venereum is seen mainly in tropical climates and presents initially with a small papule or ulcer, and then progresses to involvement of the inguinal lymph nodes.

Folliculitis, Cellulitis, and Abscesses

Because of the nature of the vulvar skin with numerous follicles and glands, these infections are not uncommon on the vulva. Personal hygiene practices such as shaving and application of powders may exacerbate these conditions in susceptible women. Poorly controlled diabetes mellitus and immune suppression from AIDS or other conditions also increase the risk. Small pustules or furuncles are frequently seen and patients should be encouraged to avoid picking at these lesions because it can worsen the infection. Infections and blockage of the ducts of the Bartholin's glands, Skene's glands, or minor vestibular glands will result in abscess formation, which necessitates incision and drainage or marsupialization as well as antibiotic therapy. Cellulitis of the vulva may result from the spread of any of the above conditions as well as following repair of obstetrical lacerations or other surgical procedures of the vulva. While rare, necrotizing fasciitis of the vulva should be suspected in the patient with signs of sepsis in the presence of cellulitis (7). Hidradenitis suppurativa is a chronic inflammatory condition of the apocrine glands, which can involve the groin area in addition to the axillary regions. Draining sinus tracts will be present along with local induration and scarring of the skin of the labia majora, mons, genitocrural folds, and buttocks.

Solid or Cystic Tumors

Cysts, nodules, and tumors of a variety of types may be present on the vulva and patients will typically report the presence of "a lump down there" when presenting for evaluation. Sebaceous and epidermal inclusion cysts are frequently seen on the skin of the labia majora and minora, and in the vestibule. Bartholin's duct and vestibular cysts are also quite common. A urethral diverticulum or Skene's duct cyst may also present as a vulvar mass. Lipomas and fibromas may develop in the labia

majora or mons. Leiomyoma and endometriomas are less commonly seen. Other benign lesions such as acrochordons, seborrheic keratoses, and nevi may also be found on the vulvar skin.

Vulvar Intraepithelial Neoplasia

This term refers to preinvasive lesions that are warty, basaloid, or differentiated in type. The warty and basaloid types that are often multifocal occur in younger women, and are usually HPV related, while the localized, differentiated type occurs in older women and are usually HPV negative. Natural history studies documenting progression from vulvar intraepithelial neoplasia to invasive vulvar cancer are marred by low numbers, previous treatment, short follow-up times, and lack of stratification based on HPV status. Nevertheless, studies have shown that patients who undergo treatment have a low chance of developing invasive disease. Although it has long been felt that the majority of those with untreated vulvar intra-epithelial neoplasia (VIN) III do not progress to invasion, this is somewhat controversial (8). Patients with immunosuppression are particularly vulnerable and are prone to recurrences, which mirror their immune status.

VIN lesions show a variety of clinical presentations—from a red or pigmented macular lesion to a raised, whitish plaque that can occur anywhere on the vulvar structures. Lesions can appear as hypopigmented in darker-skinned women. Histologically, they show increased numbers of undifferentiated cells with nuclear atypia, disorganized epidermal maturation, hyperkeratosis and parakeratosis, and abnormal mitotic figures. Under colposcopic examination, vascular abnormalities can be absent or minimal, especially when hyperkeratosis is present. Therefore, the best diagnostic maneuver is liberal biopsy with either a Keyes punch biopsy or a cervical biopsy instrument under local anesthesia. Often hemostasis can be achieved with silver nitrate sticks or a single absorbable stitch. The application of 5% acetic acid can sometimes help to delineate a lesion for directed biopsy. Treatment is either excision if focal, or laser ablation if widespread or involving the clitoral structures. Since there is a high rate of undetected microinvasive or invasive disease, liberal biopsy at the time of laser ablation is advised.

Vulvar Cancer

Vulvar carcinoma should be suspected in a woman with complaints of long-standing duration or those that do not resolve with standard treatment. Although mostly a disease of postmenopausal women, there has been a trend toward younger age at diagnosis. Many patients will attempt to ignore symptoms or to engage in a variety of self-treatments prior to presentation. Many physicians will treat lesions with topical steroids or estrogens prior to consideration of biopsy. The old adage, “if cancer is the question, tissue is the issue,” holds most true for the vulva and early biopsy of suspicious lesions is advised. Lesions can be ulcerated, nodular, or superficially spreading. A finding of microangiogenesis with mosaicism or any other abnormal vascular pattern is particularly suspicious.

In a review of the clinical events preceding a diagnosis of squamous cell carcinoma of the vulva, Jones and Joura noted that 88% experienced symptoms for more than six months, 31% had three or more medical consultations, and 27% had applied topical estrogens or topical steroids (9). Luckily, these cancers are relatively rare, comprising less than 5% of all gynecologic cancers. As expected, the majority of vulvar cancers are squamous in histology. However, malignant melanoma is the second most common cancer type. Other histologic subtypes are basal cell, adenocarcinomas, and a variety of soft-tissue sarcomas—leiomyosarcomas, angiosarcomas,

rhabdomyosarcomas, epithelioid carcinomas, and Kaposi's sarcomas. A number of pelvic and genital tumors such as cancers of the uterus (urethral metastases), bladder, vagina, cervix and anorectum, and others can metastasize to the vulva. For this reason, women with pelvic and lower genital tract cancers need to be monitored for coexistent lesions in the vulva and vice versa.

Interestingly, HPV is seen in only 10% to 50% of invasive lesions as compared to 90% of invasive cervical cancers. There seem to be two distinct histologic subtypes. One is associated with HPV and has warty or basaloid features, and the other, keratinizing squamous carcinomas, is not HPV related. Both vulvar intraepithelial neoplasia and chronic vulvar inflammatory lesions are associated with higher rates of progression to invasive disease.

Treatment is individualized and can involve a combination of surgery, chemoradiation, and reconstructive techniques. There is a trend to treat early lesions with local deep resection with unilateral inguinal node dissection. Advanced lesions confined locally can be managed by neoadjuvant chemoradiation with surgical excision and reconstructive flap placement. Treatment of advanced metastatic disease is palliative.

Vulvodynia

While not typically associated with any lesions apparent on the vulva, vulvodynia should be considered in the differential for complaints of chronic vulvar itching and/or burning. Generalized vulvodynia generally manifests as chronic, unprovoked vulvar burning in menopausal women but may be provoked. Localized vulvodynia presents with pain restricted to the vestibule, or other focal area, and provoked with pressure or touch to the area but may be unprovoked. While women with vulvodynia localized to the vestibule may have erythema of the vestibular mucosa at times, these disorders are thought to be due to neuropathic pain and therefore are not usually associated with significant physical findings on examination.

Trauma

In the emergency care setting, traumatic injuries to the vulva may be seen. Accidental injuries may occur in the setting of athletic activities such as bicycling or from a fall, and may cause lacerations or hematomas. Sexual assault and accidental injuries associated with sexual activity are the most common cause of vulvar trauma (7).

Obstetrical lacerations and episiotomies may be associated with chronic perineal pain as well as the formation of neuromas or scar tissue. Genital piercing is becoming increasingly common and generally involves the labia minora or clitoris. It may be associated with cellulitis or trauma during sexual activity.

Female genital cutting or circumcision is practiced in many countries in Africa and some in Asia. While this custom exists within the complex, religious, cultural, and familial structure of these societies, it is important for physicians to be familiar with the potential health consequences of this practice. There are three types of female circumcision:

- Type I: Excision of the prepuce with or without part or the entire clitoris
- Type II: Excision of the prepuce and clitoris along with part or all of the labia minora
- Type III: Excision of all or most of the external genitalia with closure of the vaginal opening (infibulation)

Chronic pain, recurrent vaginal infections, sebaceous and inclusion cysts, urinary incontinence, difficulty with sexual activity, and obstetrical complications are all potential sequelae (10).

Others

Other chronic dermatologic diseases may affect the vulva. The autoimmune blistering diseases, pemphigoid and pemphigus vulgaris, are rare but can involve the vulvar skin in affected women. Behcet's disease involves the triad of genital and oral ulcers as well as ophthalmologic inflammation and may produce very painful chronic ulcers of the vulva. Crohn's disease may also cause vulvar ulcers and fissures that may precede the intestinal manifestations and therefore make diagnosis challenging (11).

SPECIAL CONSIDERATIONS

There are several categories of patients who may require special consideration in their evaluation.

Pediatric Patients

Developmental anomalies are more likely to present in young patients. These may include clitoral hypertrophy, congenital labial fusion, hypertrophy of the labia majora or minora, imperforate or microperforate hymen, transverse or longitudinal vaginal septum, or ambiguous genitalia. Pediatric patients may also develop vulvovaginitis. *Candida* and *Escherichia coli* are the most common organisms causing this condition, but sexually transmitted infections may also be seen. Neonatal infections of pathogens such as HSV and HPV may be congenitally acquired, but the presence of these in older children should prompt the suspicion of sexual abuse. Young girls may insert foreign bodies such as small toys or pieces of tissue in the vagina, which may trigger vaginitis symptoms such as itching and discharge (12). In addition, dermatologic conditions such as irritant dermatitis (diaper dermatitis) and lichen sclerosus may be seen in prepubertal girls. In adolescents presenting with viral syndrome symptoms such as fever, fatigue, sore throat, and lymphadenopathy as well as vulvar ulcers, Epstein-Barr virus infection or mononucleosis should be considered (13).

Postmenopausal Women

While atrophy due to the hypoestrogenic state typically affects the vagina initially, the vulva can be involved as well. In particular, the mucosa of the vestibule is quite estrogen sensitive and postmenopausal women who are sexually active are likely to become symptomatic eventually. The mucosa will appear pale and smooth, and the introitus can become quite narrowed if the condition is long standing.

Women with HIV

Immunosuppressed patients typically display multifocal and multicentric disease, and are resistant to standard treatment paradigms. The small vesicles characteristic of herpes simplex can coalesce and form large ulcers, fungal conditions can be persistent despite adequate topical treatment, and vulvar dysplasia can be widespread

and persist or be more prone to recurrence after treatment. Adequate diagnosis in this population depends on one's familiarity with the wide array of vulvar infections, dystrophies, and dysplasias. Again, liberal biopsy as well as culture is the key to confirming a diagnosis. When treating the immunosuppressed for vulvar conditions, a more aggressive approach should be considered, including early intravenous therapy in severe or refractory cases, and antibiotic or viral suppression and/or prophylaxis. In the case of dysplasias, coexisting disease in other sites is the norm rather than the exception. Treatment needs to be tailored and timed with antiretroviral therapy. For example, some dysplasias can show improvement with elevated CD4 counts.

EVALUATION

The evaluation of a patient with a vulvar complaint should include a thorough history and physical examination. Additional diagnostic testing may also be indicated.

History

A complete history of the vulvar problem will include the following:

- Presence, location, and duration of symptoms such as itching, burning, pain, discharge, and visible or palpable lesions
- Aggravating factors such as sexual activity, tight clothing, topical products, and exercise
- Attempts at self-treatment
- All exposure to potential contact irritants including soap, bubble baths, baby wipes, menstrual products, underwear fabrics, and lubricants

It is also important to inquire about potential symptoms of the oral mucosa and other skin sites as well as past medical and gynecologic history.

Physical Examination

Good lighting and a magnifying glass are helpful to achieve a thorough inspection of the vulva. A precise description of lesion type and location should be documented in the medical record. Use of a diagram or photograph can be very helpful. Use of a speculum to examine the vagina and cervix is also important and vaginal pH should be measured. Normal pH range in reproductive age women is 3.8 to 4.2. An elevated pH is suggestive of atrophic change or an infectious process such as trichomoniasis or bacterial vaginosis.

A microscopic evaluation of vaginal discharge with both saline and KOH is essential in every woman with a vulvar or vaginal complaint. Scraping of the vulvar skin and inspection with KOH prep are also useful for possible dermatophyte or tinea infection. Inspection of the nongenital skin and oral cavity is also important.

Other Diagnostics

Fungal cultures are useful when candidiasis is suspected but the office wet mount is nondiagnostic. Routine use of bacterial cultures of the vagina is not indicated due to the wide range of bacteria included in the normal flora. Vulvar lesions suspicious for genital herpes or the other sexually transmitted infections reviewed above should have appropriate cultures or serology testing performed. In the patient with findings

suggestive of allergic dermatitis, referral for patch testing may be warranted. Cutaneous sensory testing is useful in patients with chronic vulvar pain consistent with vulvodynia. The patient should rate her discomfort using a 10-point pain scale when light pressure is applied with a cotton-tipped applicator. In addition, these women often experience tenderness or spasm on palpation of the levator muscles. Diagnostic imaging is rarely useful in evaluating vulvar lesions.

Colposcopy

Colposcopic findings, i.e., a magnified view of vulvar dysplasia can be variable. Compared to cervical dysplasia, which most often has an acetowhite appearance with atypical vascular changes, vulvar dysplasia can occur with minimal colposcopic findings. A mild acetowhite appearance of the vestibule can occur and should not be confused with dysplasia. Examination of the non-hair-bearing areas is most amenable to colposcopy and most often mirrors similar processes on the cervix. Lesions on hair-bearing, keratinized portions can be subtler; these lesions may extend into the pilosebaceous apparatus and may not be entirely visible. An important feature of vulvoscopy is how a lesion looks in comparison to its surroundings.

Lesions that show “leukoplakia” are white and sometimes raised; they can be associated with dysplasia and cancer. “Erythroplakia” refers to a reddened area and is most likely due to an increased density of underlying atypical blood vessels; they can be flat or raised and may show atypical vessels under colposcopic examination. “Melanotic” lesions that are associated 30% of the time with high-grade vulvar dysplasias do not show acetowhitening and rarely show the typical evidence of neoangiogenesis, mosaicism, and punctuations.

A hallmark of cancer is frank demarcation from its surroundings similar to an ulcer. However, not all cancers are ulcerous and they can hide within a premalignant zone. These differences fuel the debate over whether a vulvar cancer arises from a progressive dysplasia or de novo.

Biopsy of the Vulva

The indications for vulvar biopsy include

- lesion with an appearance suggesting malignancy,
- clinical suspicion of chronic dermatologic disease,
- poor response to an initial trial of management, and
- absence of a clear diagnosis.

The indication and an explanation of the procedure should be reviewed with the patient and informed consent obtained. After the site is prepped with an antiseptic solution, local infiltration with lidocaine should be performed. Most practitioners use a Keyes-type punch biopsy instrument to obtain a specimen of at least 3 mm, but a Kevorkian or Kraus biopsy forceps could also be used. In the case of a single lesion to be completely excised, a scalpel should be used. Small biopsy sites (generally less than 5 mm) may usually be made hemostatic with pressure and application of silver nitrate. Larger lesions should be reapproximated with suture. The patient should be counseled on postprocedure care including sitz baths to keep the area clean and use of oral over-the-counter analgesics as needed. A follow-up appointment should be scheduled within two weeks to check biopsy site healing and review pathology and culture results.

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2

Normal Vulva and Developmental Anomalies

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ANATOMY

Vulva

The vulva represents the external female genitalia, whose functions include sexual arousal, entrance for coitus, exit for the newborn, and outlet for the urinary tract. It lies within the anatomical compartment of the perineum, defined superiorly by the pelvic diaphragm, inferiorly by the skin between the buttocks and the thighs, and transversely by a diamond-shaped osteoligamentous frame, whose points are the pubis, ischial tuberosities, and coccyx. The perineum is divided by a transverse line connecting the ischial tuberosities into the anterior (urogenital) and posterior (anal) triangles. The vulva lies within the anterior triangle. It is composed of the mons pubis, labia majora, labia minora, vaginal vestibule, clitoris, urethral meatus, bulbs, greater vestibular (Bartholin's) and paraurethral (Skene's) glands, hymen, and clinical perineum. The clinical perineum is different from the anatomical perineum, and is defined as the skin between the vulva and the anus.

Surface Anatomy

The surface limits of the vulva are anteriorly, the horizontal limit of the pubic hair of the mons pubis, laterally, the genitocrural folds, posteriorly, the anus, and centrally, the hymenal ring of the vaginal introitus (1).

Mons Pubis. The mons pubis is a mound of skin-covered subcutaneous fatty tissue overlying the pubic bone. It is continuous with the subcutis of the anterior abdominal wall superiorly and the labia majora posteriorly. The mons becomes covered with coarse hair and the amount of fat increases at puberty. These gradually decrease after menopause.

Labia Majora. The right and left labia majora are symmetrical, large, lateral folds of subcutaneous fat covered by skin that may be pigmented in light-skinned women. They are continuous with the mons pubis anteriorly and ischiorectal fat posteriorly. They fuse anteriorly at the anterior commissure at the base of the mons pubis and posteriorly at the posterior commissure (fourchette), 3 to 4 cm in front of the anus.

They flatten posteriorly before fusing. The lateral (outer) surfaces are apposed to the medial aspects of the thighs and the medial surfaces are apposed to the lateral surfaces of the labia minora. Like the mons, the lateral surfaces become covered by coarse hair to a varying degree and the amount of fat increases at puberty. The medial (inner) surfaces are covered by hairless, moist skin. The medial surfaces may show small yellow granules, Fordyce spots. Fordyce spots are superficially located sebaceous glands. The uterine round ligaments pass through the inguinal canal to end in the deep fibrofatty tissue of the labia majora. The floors of the labia majora are the right and left superficial perineal (Colles') fasciae.

Labia Minora. The right and left labia minora (nymphae) are quite variable, symmetrical, or occasionally asymmetrical folds of loose fibroelastic tissue without fat. The lateral surfaces are covered by thin, moist, hairless, and pigmented skin. The medial surface may be covered by skin similar to the lateral surfaces or by mucosa. The labia minora are medial to and largely hidden by the labia majora. The medial surfaces appose each other and surround the vestibule of the vagina. The lateral boundaries are the interlabial sulci. The medial boundaries are Hart's lines, which are the visible boundaries between the pigmented skin and the bright pink mucosa. Hart's lines are usually at the bases of the labia minora, but are variable. Anteriorly, each labium minus divides into anterior and posterior parts. The anterior parts unite anteriorly to the glans clitoris to form the prepuce, and the posterior parts unite posteriorly to the clitoris to form the frenulum. The labia minora fuse posteriorly to form the fourchette. Fordyce spots may be seen on the labia minora.

Vestibule of the Vagina. The vestibule is the medial (central), mucosa-covered part of the vulva. On embryologic, anatomic, and architectonic grounds, the correct term is "vestibule of the vagina" not "vulvar vestibule," as sometimes appears in the literature (2). The vestibule is composed of loose fibroelastic and smooth muscular tissue without fat. The boundaries of the vestibule are Hart's lines laterally, the hymenal ring medially, the frenulum of the clitoris anteriorly, the fourchette posteriorly, and Colles' fascia deeply. The vestibule contains the urethral meatus and vaginal opening in the midline. The ostia of the greater vestibular (Bartholin's) ducts may be seen with the naked eye in the five and seven o'clock positions just external to the hymen. Minute, soft, nonbranching, pink polyps, the vestibular papillae, are a normal finding in one-third of women in the reproductive age group, although uncommon after menopause (Fig. 1) (3). They may be acetowhite and must be distinguished from condylomata acuminata. Compared to condylomata acuminata, vestibular papillae are pinker, soft, and nonbranched.

Hymen. The hymen is a diaphragm of loose fibrous tissue covered on both sides by mucous membrane that demarcates the vestibule from the vagina. Before first intercourse, the hymen is of variable shape, but often crescentic and covering only the posterior margin of the vaginal orifice. Less commonly, it may be more complete, but usually still contains one or two openings. At first intercourse, there will often be tearing of the hymen to produce fissures. The appearance of the hymen has been used since time immemorial to determine whether penetration has taken place; however, recent studies of prepubertal non-sexually abused girls indicate a wide range of normal appearance (4,5). Changes that were considered the result of sexual abuse, including a gaping introitus, may be seen in nonabused girls, and may be difficult to distinguish from changes induced by sexual penetration. The tags of mucous membrane following fissuring of the hymen are called the caruncles hymenalis or carunculae myrtiformes.



Figure 1 Vestibular papillomatosis: multiple small nonbranching fronds around the introitus. *Source:* Courtesy of Dr. Ross Pagano, Carlton, Victoria, Australia.

Urethral Meatus. The urethral meatus lies in the midline between the clitoris and the vaginal opening. Its anteroposterior position is quite variable, but it is usually 20 to 30 mm below the glans. The meatus may be everted and may show two or three folds, which become more prominent after menopause. The ostia of the paraurethral glands are not visible to the naked eye.

Clitoris, Superficial Part. The clitoris is composed of the body and crura. The crura are deep impalpable structures. The body can be felt beneath its prepuce, but the only part that is exposed is its terminal portion, the glans. The glans is a smooth-surfaced pink nodule covered by moist, thin hairless skin, which lies in the midline anterior to the urethral meatus. Resting clitoral size varies according to the age of the female, parity, and hormonal status (6). Anatomically, the body of the clitoris is about 40 mm long. Clinically, however, the total length of the glans and body is only 16.3 ± 4.3 mm, the transverse diameter of the glans is 3.4 ± 1 mm, and the length of the glans is 5.1 ± 1.4 mm (7).

Fossa Navicularis. The fossa navicularis is a shallow depression in the vestibule that lies posterior to the vaginal orifice. Its boundaries are anterior, the hymen; posterior, the fourchette, and lateral, the labia minora. It is composed of squamous mucosa overlying a thick lamina propria of loose fibrous and deep fibrous tissue and smooth muscular tissue.

Perineum. The clinical perineum is the skin between the vulva and the anus. It is composed of hair-bearing skin apart from a variably broad hairless strip in the midline and deep fibromuscular tissue. In the midline, the perineal body can be palpated beneath the skin.

Deep Anatomy

Colles' Fascia. The vulva is subdivided into superficial and deep compartments by bilateral transverse fibrous sheets, Colles' (superficial perineal) fasciae, which are the continuation of the deep fascia of the anterior abdominal wall. The superficial compartment contains skin, skin appendages, and fibromuscular tissue

or subcutaneous fat, depending on the site. The deep compartment, the superficial perineal pouch or space, contains the deep part of the body and all of the crura of the clitoris, membranous urethra, vestibular bulbs, greater vestibular (Bartholin's) glands, three pairs of skeletal muscles, and the perineal body. The paired structures and perineal body are contained in fat and/or fibrous tissue.

Inferior Fascia of the Urogenital Diaphragm. The perineum is separated from the pelvis by the urogenital diaphragm. The urogenital diaphragm is composed of the muscles of the levator ani covered superiorly and inferiorly by fasciae. The deep boundary of the vulva is the inferior fascia of urogenital diaphragm or perineal membrane. The crura, bulbs, and bulbospongiosus muscles attach to the inferior fascia of the urogenital diaphragm.

Suspensory Ligament of the Clitoris. The suspensory ligament of the clitoris is a thick, multiplanar, fan-shaped fibrofatty sheet, which extends from the deep fascia of the mons pubis to converge on the body of the clitoris (8). The ligament has superficial and deep components. The superficial component is 70 to 80 mm wide in the mons and 80 to 90 mm long. It attaches to the clitoral body, glans, and medial labia minora. The deep component is up to 10 mm thick and more fibrous. It has a narrow origin from the pubic symphysis and converges on the superolateral clitoral body. After reaching the clitoris, the suspensory ligament divides into right and left arms, which continue posteriorly to reach the labia and bulbs.

Clitoris, Deep Part. Anatomically, the clitoris is much larger than clinically apparent because most of it is deep to the skin. Recent dissections describe it as a triplanar structure projecting 4 to 6 cm anterior to the pubis (6). The body is located in the midline, at the anterior junction of the labia minora, anterior to the vestibule. Only the terminal glans is exposed. The remainder of the body is covered by its prepuce anteriorly and frenulum posteriorly, which are derived from the labia minora. The body is curved with its convexity anterior. It is formed by the fusion of two cylindrical masses of spongy tissue, the corpora cavernosa. A dense fibrous sheath encloses each corpus cavernosum and forms an incomplete septum between the two. The corpora cavernosa separate posteriorly to form the crus of the clitoris. The arms of the crura are up to 90 mm long, lie along, and insert into the inferior borders of the ischiopubic rami of the pubic arch. They also partly insert into the inferior fascia of the urogenital diaphragm. The arms of the right and left crus are covered by the ischiocavernosus muscles. The clitoris is stabilized by the suspensory ligament.

Bulbs of the Vestibule. The vestibular bulbs are paired masses of erectile (spongy) tissue closely related to the anterior and lateral walls of the distal urethra and lateral walls of the distal vagina. When stimulated, the erect bulbs narrow the introitus to aid sexual intercourse. Anteriorly, the bulbs attach to the clitoral body and to each other beneath the clitoris as a narrow bridge anterior to the urethra. They then expand and descend posterolaterally in the superficial perineal pouch to form cylindrical masses in the deep lateral wall of the vagina at the level of the introitus. The degree of posterior extension is variable and may depend upon age (6). The bulbs are usually about 30 mm long and reach at least the three and nine o'clock positions. The bulbs are covered superficially and laterally by the bulbospongiosus muscles and deeply by the perineal membrane (urogenital diaphragm), into which they insert.

Major Vestibular (Bartholin's) Glands. The major vestibular (Bartholin's) glands are mucinous glands that secrete mucus under parasympathetic stimulation during sexual arousal to aid intercourse. The glands are normally impalpable and not identified during surgical procedures. They are paired 5 to 10 mm rounded

bodies that lie in the superficial perineal pouch covered in mixed fibrous and smooth muscle tissue, at the posterior end of the bulbs, and covered by the bulbs and bulbospongiosus muscles. The ducts, which are just visible to the naked eye, open into the vestibule, very close to the hymen at five and seven o'clock of the introitus.

Superficial Perineal Muscles. Three pairs of skeletal muscles, the ischiocavernosus, bulbospongiosus, and superficial transversus perinei muscles, form an incomplete muscular sheet in the superficial perineal pouch (1). These muscles form bilateral triangles with the clitoris, perineal body, and ischial tuberosities as the points. The ischiocavernosus muscles arise from medial surface of the ischial bones, overlie the arms of the crura, and join anteriorly to the body of the clitoris, into which they also insert. The bulbospongiosus muscles arise from the perineal body, overlie the greater vestibular (Bartholin's) glands and bulbs, and fuse just posterior to the clitoris, into which they also insert. The superficial transversus perinei muscles arise from the medial surface of the ischial bones and extend transversely to insert into the perineal body. The ischiocavernosus and bulbospongiosus muscles overlie erectile tissue and their contraction helps with female erection. The bulbospongiosus muscles are also weak vaginal constrictors, the main vaginal constrictor being the levator ani. The transversus perinei muscles help stabilize the perineal body.

Urogenital Diaphragm. The urogenital diaphragm remains a controversial subject. According to Mostwin, it is a continuous fan-shaped mass of skeletal muscles forming part of the levator ani and divided into various parts depending upon its origins and insertions (9). It is orientated transversely and covers the anterior surface of the urethra and distal vagina. The extent to which the fibers encircle the vagina or urethra depends upon the level at which a transverse section is taken through the structures. Beginning anteroinferiorly, the skeletal muscle almost completely surrounds the distal vagina, being deficient only posteriorly. Superoposteriorly, the muscle fibers insert progressively more anteriorly, until, at the level of the proximal one-third of the urethra, the muscle no longer encircles any part of the vagina, but completely encircles the urethra, being thicker anteriorly.

Perineal Body. The perineal body (central tendon of the perineum) is an ill-defined pyramidal-shaped mass of mixed smooth muscle and fibrous tissue between the vagina and the anus. The apex is directed superiorly and base toward the perineal skin. There is only a small amount of subcutaneous fat between the perineal body and the skin. The perineal body serves as a site of attachment for skeletal muscles and fasciae of the perineum. The muscular attachments are the levator ani, urethral sphincters, deep transversus perinei, external anal sphincter, peripheral fibers of the longitudinal smooth muscle of the rectum, bulbospongiosus, and superficial transversus perinei muscles. The fascial attachments are the superior and inferior urogenital diaphragm fasciae and superficial perineal (Colles') fascia.

Arteries. The arterial supply to the vulva comes from branches of the internal iliac and femoral arteries. The internal iliac artery gives rise to the internal pudendal artery, which supplies the medial and deep parts of the vulva, including the erectile tissues, and shares the supply to the labia (1). The internal pudendal artery enters the perineum from the buttock via the lesser sciatic foramen. It passes anteromedially along the ischiopubic ramus within the deep perineal space within a fascial compartment (Alcock's canal) and gives rise to the inferior rectal, perineal, and bulbar arteries before dividing to form the deep and dorsal arteries of the clitoris. These branches pierce the inferior fascia of the urogenital diaphragm to enter the superficial perineal space. The artery of the bulb of the vestibule and the anterior vaginal artery supply the bulb and greater (Bartholin's) gland. The dorsal clitoral artery runs

alongside the dorsal nerves to terminate in the glans. The deep artery of the clitoris supplies the crus. The femoral artery gives off the superficial and deep external pudendal arteries to supply the majority of arterial blood to the skin and superficial fascia of the vulva. The external pudendal artery travels from the groin with the round ligament to enter the labia majora where it anastomoses with the labial branches of the internal pudendal artery.

Veins. Blood is drained from the perineum mainly by the internal pudendal veins, but some is drained by the deep dorsal vein of the clitoris and returned to the vesical plexus or by the external pudendal veins into the great saphenous veins (1). Venous vessels follow the branches of the internal and external pudendal arteries and are named accordingly. Veins from the bulbs of the vestibule, labia majora, and anal canal unite to form two venae comitantes of the internal pudendal artery called the internal pudendal veins. The internal pudendal veins empty into the internal iliac veins. There are no corresponding veins for the deep arteries of the clitoris, and most of the blood from the glans of the clitoris is drained to the deep dorsal vein of the clitoris, an unpaired vessel that runs between the two dorsal arteries. The deep dorsal vein drains into the vesical plexus and communicates with the internal pudendal vein tributaries. The external pudendal veins provide additional drainage from the labia majora and empty into the great saphenous veins.

Lymph. The lymphatic drainage of the anal canal, perineal skin, distal urethra, and vulva follows the branches of the external pudendal blood vessels to the inguinal lymph nodes and then to the external iliac, common iliac, and para-aortic lymph nodes (1). Midline structures, defined as anterior to urethra or posterior to the fourchette, have bilateral lymphatic drainage. The groin lymph nodes consist of superficial and deep groups, depending on whether they are superficial or deep to the femoral fascia (10). The superficial group is further divided into upper and lower groups. The upper superficial nodes are found along the line of the inguinal ligament, and the lower along the terminal part of the great saphenous vein. The deep nodes, one to three in number, lie in the fossa ovalis, medial to the femoral vein. The superficial group most often contains the sentinel node or nodes, but as in other sites, sentinel node studies demonstrate occasional marked variation in lymphatic drainage that cannot be predicted clinically. Lymphatic vessels of the deep perineum, including the deep perineal space, membranous urethra, and upper vagina follow the internal pudendal vessels to the internal iliac nodes.

Nerves. The motor and sensory somatic and autonomic nerve supply to the vulva is derived from L1 to S4 (1). The pudendal nerves supply the somatic motor and sensory nerves to most of the vulva, distal vagina, and anal canal. The right and left pudendal nerves are formed from the S2 to S4 anterior rami of the sacral plexus. Each pudendal nerve travels alongside the internal pudendal artery to give off similarly named branches. The pudendal nerve gives rise to the inferior rectal (hemorrhoidal) nerve, which innervates the external anal sphincter, lower anal canal, and perianal skin. At the posterior margin of the urogenital diaphragm, it divides to form the perineal nerve and the dorsal nerve of the clitoris. The perineal nerve subdivides into many muscular branches and two cutaneous nerves. The two cutaneous branches, the posterior labial branches, pass anteriorly in the superficial perineal space to supply sensory innervation to the posterior labia majora. The mons pubis and anterior labia majora are innervated by the anterior labial nerve (branch of the ilioinguinal nerve), derived from the lumbar plexus. The paired dorsal nerves of the clitoris run alongside the dorsal arteries of the clitoris in the deep perineal space to supply the corpora cavernosa, anterior labia minora, and glans.

Parasympathetic fibers enter the perineum through the urogenital hiatus along with the branches of the vesical plexus and cavernous nerves. Parasympathetic sensory nerves monitor a sense of fullness of the anal canal and vagina. Parasympathetic motor function increases vaginal secretions and causes erection.

Vagina

The vagina is a muscular tube, 70 to 90 mm long, posterior to the urethra and bladder, and anterior to the rectum. It extends from the hymenal ring to the cervix. The upper half is curved anteriorly to lie on the bladder. Proximally, the vagina is covered by peritoneum posteriorly. The upper vagina is attached posteriorly to the uterosacral ligaments, laterally to the cardinal ligaments, and anteriorly to the base of the bladder. The cervix projects downwards and backwards through the upper anterior vaginal wall, and shortens the anterior wall by 20 mm, compared to the posterior wall. The circumferential recess formed by the angle between the projecting cervix and the upper vagina is the fornix, which is divided into anterior (shallow), posterior (deep), and lateral components. At the upper end, the cervix holds the vagina open, but most of the resting vagina is collapsed with its anterior wall in contact with the posterior wall to form a H- or crescent shape on cross section. The urethra is attached to the anterior vaginal wall. The lower one-third of the vagina passes through the urogenital diaphragm. Below the diaphragm, the vagina is supported by the perineal body and perineal muscles.

The vagina is composed of three layers: mucosa, muscularis, and perimuscular layers. The mucosa is rugose, with the degree of rugosity depending on hormonal status. The muscularis is thin. In the lower vagina, the perimuscular layer is directly continuous laterally with the vestibular bulbs.

The lymphatic drainage of the upper two-thirds of the vagina follows that of the cervix to the internal and external iliac nodes. The lower one-third drain follows that of the vulva to the superficial inguinal nodes.

Urethra

The female urethra is a muscular tube 4 cm long and 6 mm in diameter. The urethra begins at the internal urethral orifice on the anterior urinary bladder wall. It is composed of long, upper pelvic and short, lower perineal parts. For the great part of its length, the pelvic urethra travels anteroinferiorly behind the pubic symphysis. It is attached to the vagina at the vaginocervicourethral angle and at the distal two-thirds. The space between these two attachments is the vesicovaginal space, which contains loose connective tissue. The pelvic urethra passes through the urogenital diaphragm to emerge as the perineal urethra, which ends as the external urethral orifice (urinary meatus). The perineal urethra is almost surrounded by the vestibular bulbs, apart from the posterior aspect. The urethra is normally collapsed and has longitudinal grooves allowing its lumen to be distensible. It is composed of a mucosa and a muscle coat, which consists of smooth muscle with an inner layer of longitudinal bundles and a middle layer with circular bundles (internal urethral sphincter) externally intermingled with circularly orientated striated muscle (external urethral sphincter). The internal sphincter is continuous with the vesical sphincter and, at the outside, with longitudinal extensions of the detrusor muscle of the bladder wall. The external urethral sphincter completely surrounds the upper two-thirds of the urethra, although it is thinner between the urethra and the vagina. It can be felt within the vagina as a transverse ridge beneath the mucosa anteriorly.

The blood supply, innervation, and lymphatic drainage of the pelvic urethra are the same as that of the bladder neck. The perineal urethra, like the vulva, is supplied by the pudendal vessels and nerves, and the lymphatic drainage is to the inguinal nodes.

HISTOLOGY

Labium Majus

The skin of the labium majus is keratinized on both the lateral and the medial surfaces. The epidermis shows the usual four layers of stratum corneum with basket-weave orthokeratosis (keratin), granular cell, prickle cell, and basal layers. Any parakeratosis is abnormal (11). The basal layer may show pigmentation. Rete ridges are present. The dermis is divided into the papillary and reticular dermis. The papillary dermis is superficial, thin, and composed of fine collagen. The reticular dermis is deep, thick, and composed of coarse collagen (Fig. 2). The epidermis and dermis are slightly thicker in the reproductive age group. Hair follicles, sebaceous, apocrine, and eccrine glands are present on the lateral surface of the labium majus, (Fig. 3). Sebaceous glands are situated at the mid-dermal level and open into hair follicles. The hair-bearing skin of the labium majus is one of the few sites on the body (perianal skin, axilla, groin, breast, ear, scalp, and eyelid) where apocrine glands occur. Like sebaceous glands, the apocrine glands also open into the infundibula of hair follicles. On the lateral side of the labium majus, there are fascicles of smooth muscle in the dermis, corresponding to the dartos muscle of the scrotum (Fig. 4). On the medial side of the labium majus, the only appendages found are sebaceous glands. These sebaceous glands open directly onto the skin surface, like those of the labia minora, nipples, eyelids, mouth, and anus. The subcutaneous fat is thick and contains thick-walled blood vessels (Fig. 5).

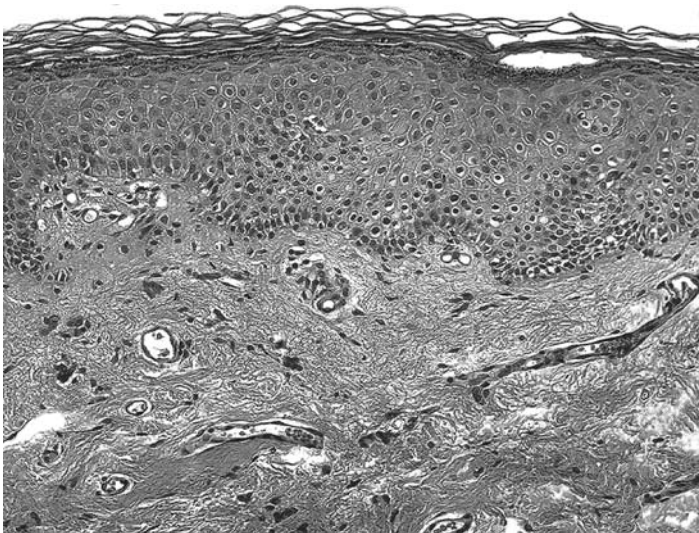


Figure 2 The labium majus shows an epidermis and a dermis. The dermis is composed of the papillary dermis, a superficial thin layer of fine collagen, and the reticular dermis, a deep, thick layer of coarse collagen.

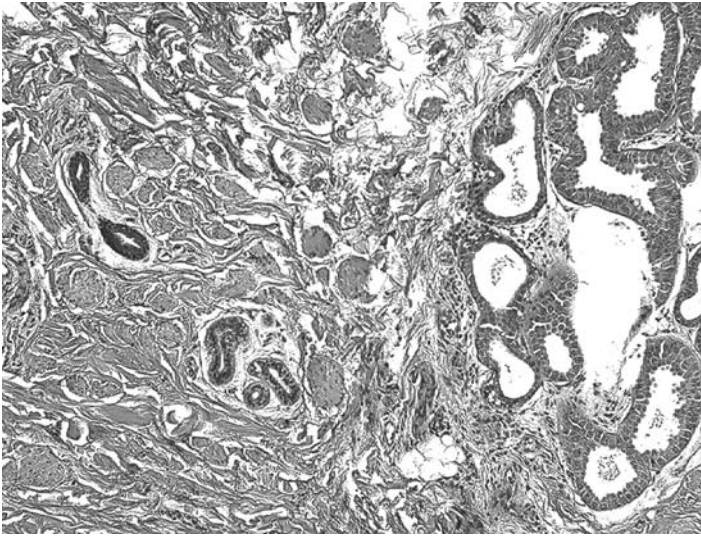


Figure 3 The skin appendages of the labium majus include apocrine glands, which appear large and eosinophilic, and eccrine glands, which appear small and basophilic.

Mons Pubis

The mons pubis resembles the hair-bearing skin of the lateral side of the labium majus including the presence of apocrine glands and smooth muscle bundles in the reticular dermis.

Perineum

The perineum, apart from a variably broad hairless strip in the midline and containing apocrine and mammary like glands, resembles hair-bearing skin elsewhere on the body.

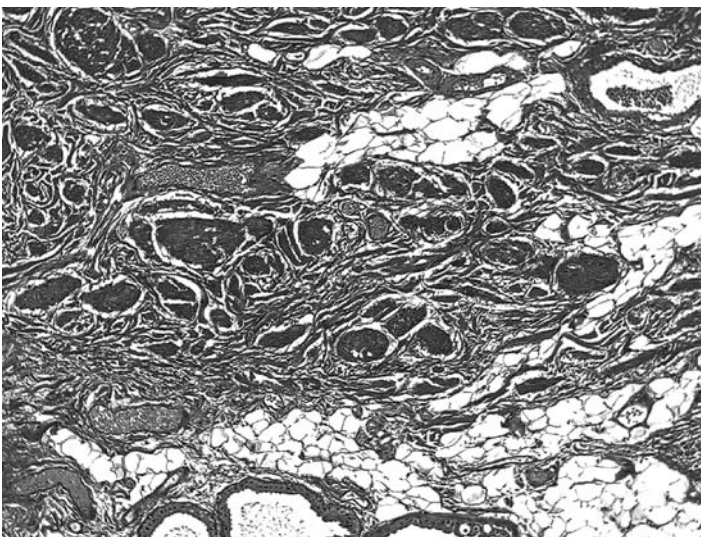


Figure 4 A peculiarity of the labium majus and mons is the presence of numerous bundles of smooth muscle in the reticular dermis, analogous to the dartos muscle in the scrotum.

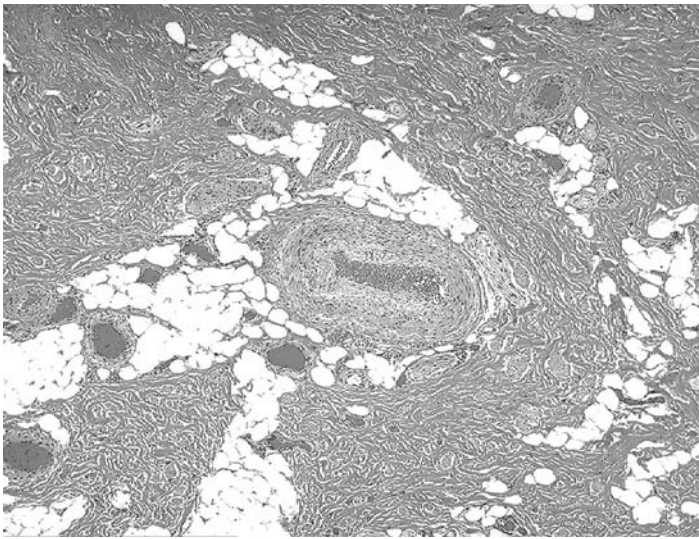


Figure 5 Another peculiarity of the labium majus is the presence of large blood vessels at the junction of the dermis and subcutis.

Interlabial Sulcus

The interlabial sulcus is the main site of mammary-like glands (12). Mammary-like glands are a newly described type of skin appendage confined to the anogenital region. They open by ducts into the interlabial sulcus, and to a lesser extent, perineal and perianal skin. Vulvar mammary-like glands resemble eutopic mammary lactiferous ducts and glands with diverticula, branches, lobules, and the expression of estrogen and progesterone receptors (Figs. 6 and 7). They may also show apocrine metaplasia and some features of eccrine glands. Hidradenoma papilliferum and mammary conditions of the vulva (ectopic breast, ectopic breast tissue, fibroadenoma, phyllodes tumor, and primary breast-like adenocarcinoma) appear to be derived from mammary-like glands (12,13).

Labium Minus

The labium minus is always keratinized, that is, shows a stratum corneum, indicating skin rather than mucosa, on the lateral side (Fig. 8) (11). In our experience, the medial side is also always keratinized, although Jones found that keratinization was absent in 62% (11). Perhaps because the transition to vestibule may be vague, the allegedly mucosal part may be, in fact, vestibule.

Any parakeratosis is abnormal (11). The basal layer of keratinized labium minus may be pigmented and small rete ridges are present. Sebaceous glands are located superficially in the dermis and open directly onto the surface (Fig. 9). Like the labium majus, the epidermis and dermis of the labia minora are thicker in the reproductive age group. The frequency of sebaceous glands on both surfaces of the labium minus varies greatly. The dermis of the labium minus is composed of fine collagen and elastic fibers. Blood vessels and nerves are numerous. There are no hair follicles, eccrine or apocrine glands, or subcutaneous fat on any part of the labium minus.

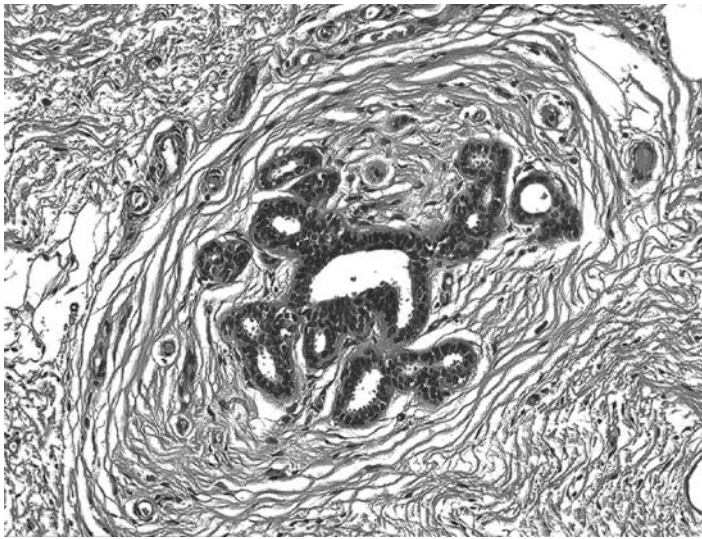


Figure 6 A mammary-like gland from the fourchette. The gland is budding and composed of layers of epithelial cells and myoepithelial cells.

Prepuce and Frenulum of the Clitoris and Fourchette

These resemble the keratinized skin of the labium minus. Hair follicles are absent, but sebaceous glands open directly onto the skin surface.

Vestibule

The vestibule is squamous mucosa composed of nonkeratinized stratified squamous epithelium without rete ridges and a loose lamina propria of fine collagen and elastic

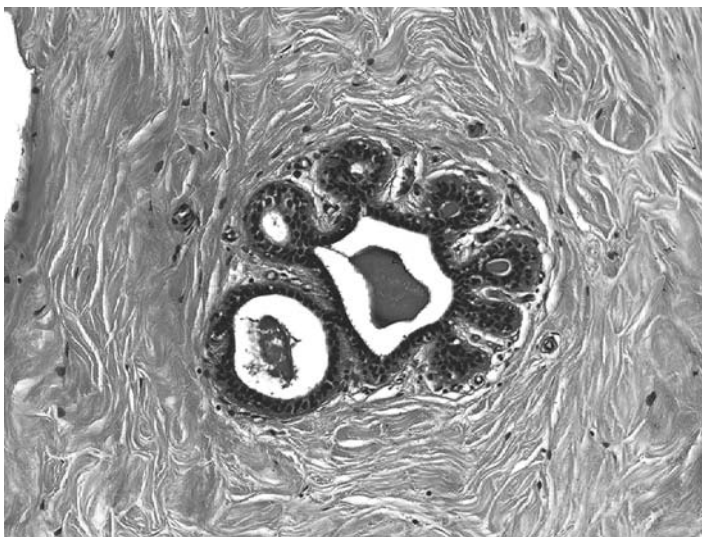


Figure 7 A true mammary duct from the breast appears very similar to the vulvar mammary-like gland in the previous figure.

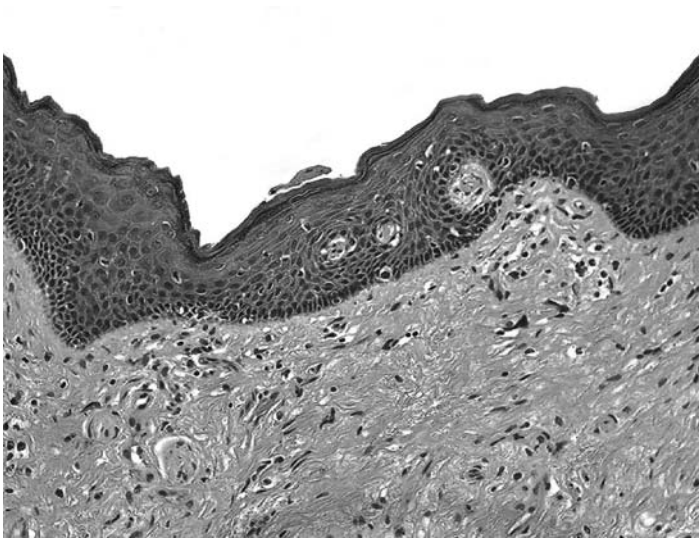


Figure 8 The labium minus is composed of keratinized epidermis and a thick dermis of fine collagen and elastic tissue. There is no fat.

fibers (Fig. 10). Unlike vulvar skin, no basal pigmentation is normally seen. There are spindle and occasionally stellate myofibroblastic cells in the superficial lamina propria. Similar myofibroblastic cells are also seen in the lamina propria of the vagina and lower urinary tract. There is usually a complete absence of skin appendages, although occasionally sebaceous glands are seen. Fibrous, elastic, and smooth muscular tissue forms a thick layer beneath the lamina propria, which gradually passes into the perineal body.

Hymen

The hymen is a thin membrane composed of loose fibroelastic tissue, covered on both surfaces by squamous mucosa.

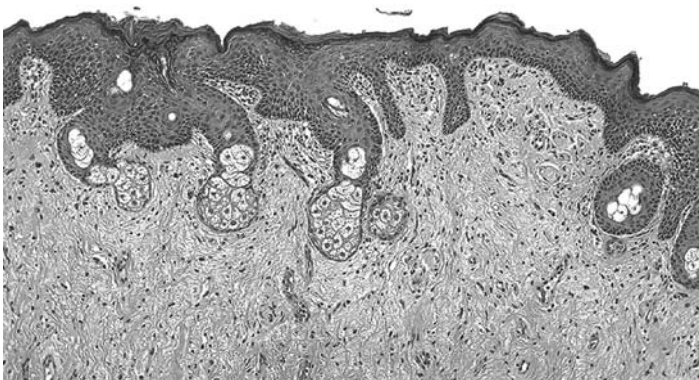


Figure 9 The labium minus contains superficial sebaceous glands that open directly onto the skin surface. The frequency of the sebaceous glands varies greatly. This labium minus has numerous sebaceous glands, whereas the labium minus in the previous figure shows none.

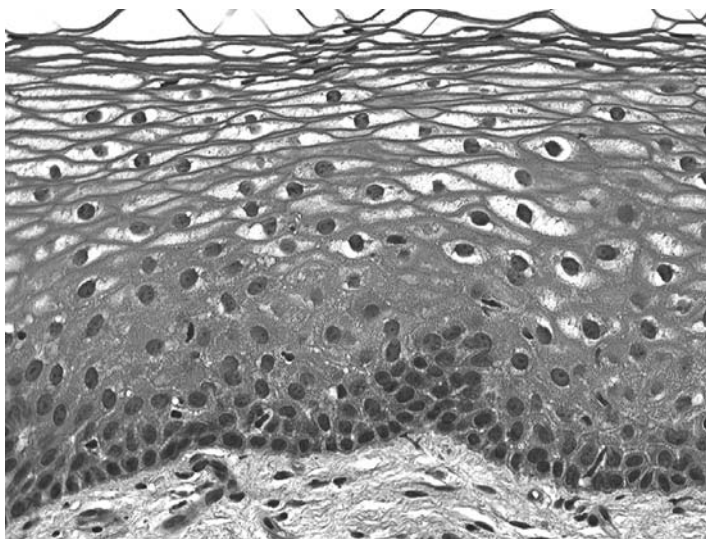


Figure 10 Nonkeratinized squamous epithelium of the vestibule, vagina, and urethra are similar.

Clitoris

Glans

The specific erectile tissue of the glans, which is far better identifiable in neonates, becomes a vague layer of fibroelastic tissue with sinusoidal blood vessels, numerous nerves, and Pacinian corpuscles (Fig. 11). There is a small and solid glandopreputial lamella. Most of the volume of the glans is provided by the tip of the fused corpora cavernosa. The epidermis is keratinized, but unlike the labia majora and minora, it is not hyperpigmented, and does not show skin appendages of any kind.

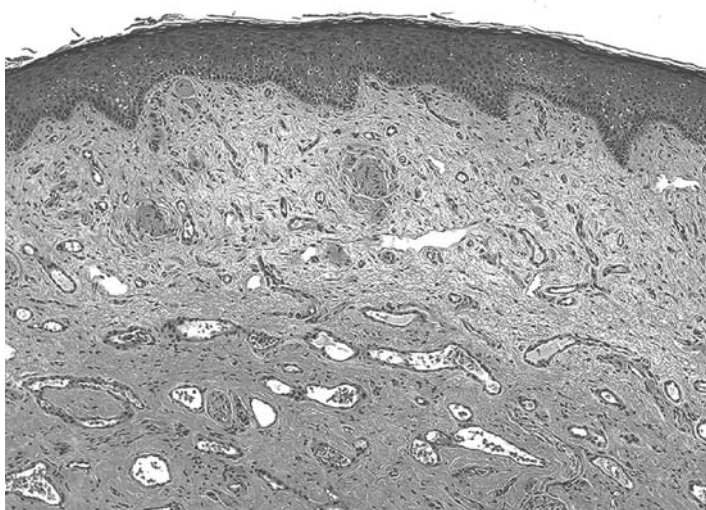


Figure 11 The skin of the glans of the clitoris is composed of keratinized epidermis without appendages and two layers of dermis, with both numerous blood vessels and nerves.

Body

The body is composed of right and left corpora cavernosa surrounded by a sheet of dense collagen (the tunica), which also incompletely divides them (Fig. 12). The corpora cavernosa consist of erectile tissue with numerous, gaping, thin-walled sinusoidal vessels. The sinuses have endothelium but no smooth muscle in their walls. Between the sinusoids, however, there are bundles of smooth muscle, large nerves, and fibrous stroma. Pacinian corpuscles are seen associated with the nerves.

Crura

The crura are composed of corpus cavernous (sinusoidal) tissue, which is surrounded by its tunica. The tunica is absent laterally where the crus attaches to bone. Pacinian corpuscles are seen, but unlike the body, large nerve and vascular trunks are not present.

Bulbs of the Vestibule

The bulbs are composed of cavernous (sinusoidal and erectile) tissue, but the vascular spaces are larger and more gaping, and the trabeculae with conspicuous arteries thicker than in clitoral tissues (Fig. 13). They have only a thin capsule rather than a thick fibrous tunic, and do not become as erect as clitoris. Bulbar tissue merges with the adventitia of the vagina and gradually passes into rich vascular plexuses in the anterior wall of the vestibule. Large neurovascular bundles and pacinian corpuscles are not seen.

Vagina

The vagina shows three layers forming its wall, the mucosa, muscular coat, and adventitia. The mucosa is composed of nonkeratinized squamous epithelium rich in glycogen and lamina propria. The lamina propria is denser toward the surface

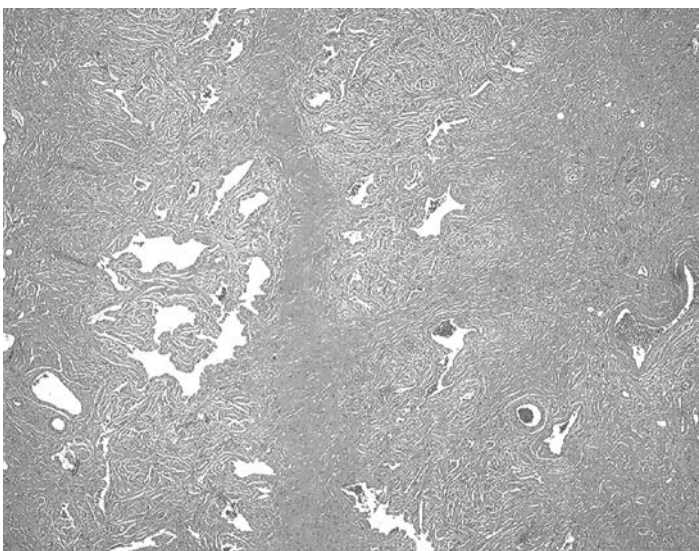


Figure 12 The two corpora cavernosa of the clitoris appear as sinusoidal vascular tissue separated by a septum composed of dense fibrous tissue of the tunica.

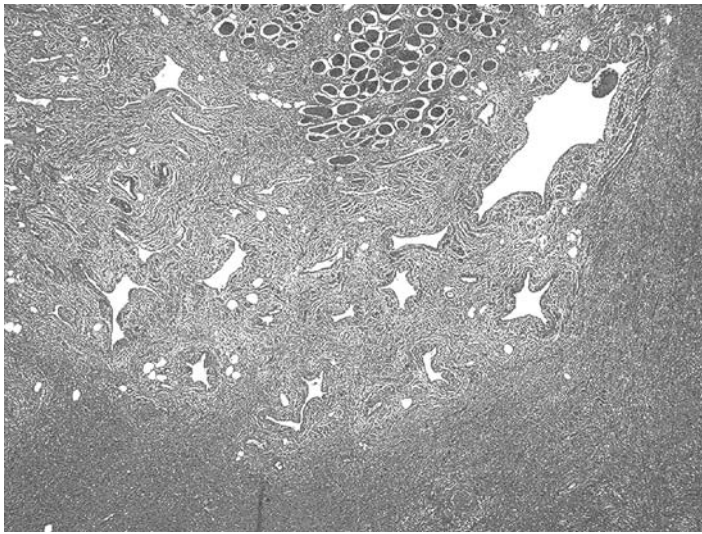


Figure 13 The vestibular bulb is composed of sinusoidal vascular tissue. Compared to the corpora cavernosa (previous figure), the vessels are larger and there is no fibrous tunica. The adjacent skeletal muscle is the bulbospongiosus.

where it characteristically forms delicate and long papillae, and looser toward the muscular layer (Fig. 14). In the anterior vagina, lamina propria papillae are scarce, but in the posterior wall, they are prominent. Numerous elastic fibers are found in the lamina propria. The deeper layers of the lamina propria contain a dense plexus of small veins. The muscularis contains large vessels. There are no glands in the normal adult vagina.

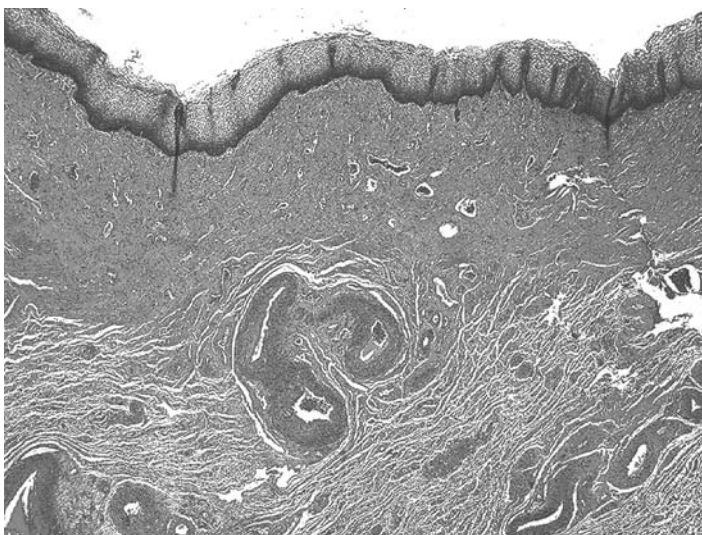


Figure 14 The vagina shows nonkeratinized squamous epithelium and a lamina propria composed of a superficial dense layer and deep loose layer in which there are large blood vessels.

Urethra

The lining of the urethra is variable. Most of the distal two-thirds of the urethra is lined by squamous epithelium, but is regularly interrupted by foci of pseudostratified columnar epithelium. The upper one-third shows transitional epithelium similar to that seen elsewhere in the urinary tract. The epithelium overlies a loose lamina propria, which contains mucinous glands and many thin-walled veins. Beneath this layer, there are inner longitudinal and outer circular layers of smooth muscle. Distally, a sphincter of skeletal muscle surrounds the layers of smooth muscle.

Mucinous Glands

There are vulvar and urethral, but normally no vaginal mucinous glands. The mucinous glands are exocrine and consist of mucinous acini that drain into a duct system lined by pseudostratified columnar epithelium. The largest are the major vestibular (Bartholin's) glands (Fig. 15). These have well-developed lobules and ducts that normally open at the posterolateral five and seven o'clock positions of the introitus, just external to the hymenal ring.

The minor vestibular glands are a variable number of tiny glands found in a ring around the introitus. They are usually seen as incidental histological findings in vestibular biopsies or vestibulectomy specimens. They are located in the lamina propria and are composed of one or a few mucinous acini opening into a duct lined by stratified mucinous epithelium. The ostia open just external to the hymenal ring (Figs. 16 and 17). There is commonly an associated moderate lymphocytic infiltrate, even in asymptomatic women.

Numerous microscopic mucinous glands are observed in the wall of the urethra, but the nature of these glands is still controversial. Wenert et al. found peri-urethral glands formed by prostate-specific antigen (PSA)-staining cells in 66.7% of 33 cases in female urethras removed at autopsy and embedded entirely for histological examination (14). The glands were located at the distal two-thirds of the urethra (95% of females). In 73% of subjects, the glands were exclusively dorsal and lateral,

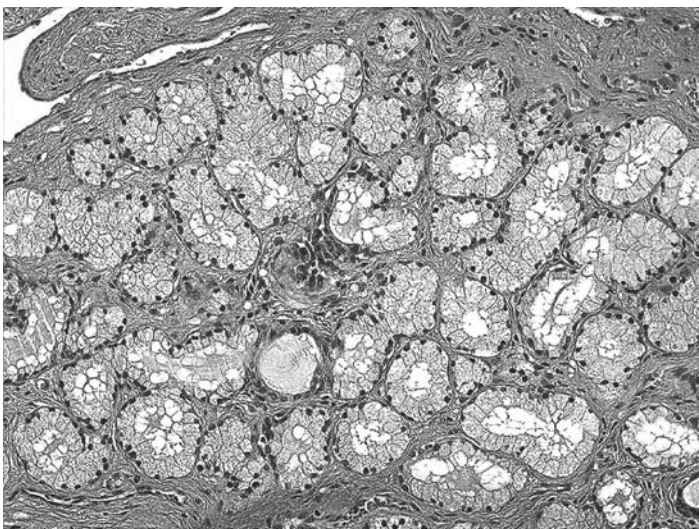


Figure 15 A lobule of mucinous acini of the greater vestibular (Bartholin's) gland.

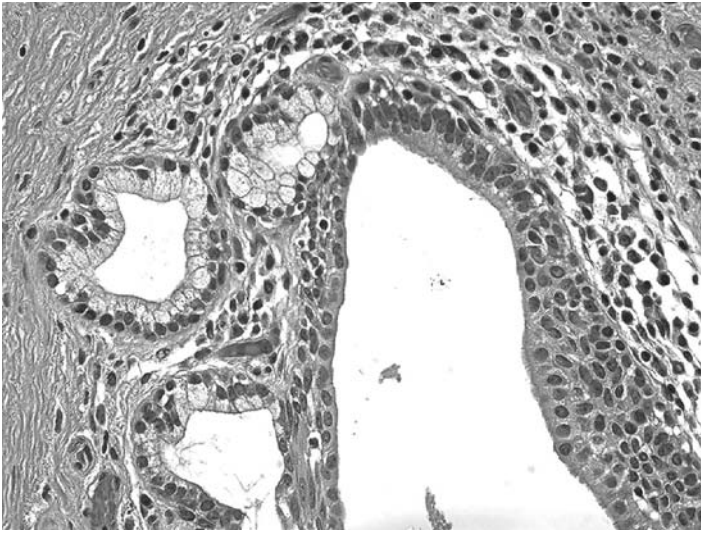


Figure 16 A vestibular gland appears as a few mucinous acini around a duct. The periglandular lymphocytic infiltrate is common in asymptomatic women. Periurethral glands show a similar appearance.

and in 14%, circumferential. The glands were in the lamina propria or deeper tissues, and could be found in the smooth muscle of the septum urethrovaginale. Irrespective of age, they resembled the male prostate before puberty, with immature glands. Wenert et al. do not state whether they also found a population of non-PSA-secreting mucinous glands. Wenert et al.'s (14) findings support homology between male and female embryological development and explain the rare, but well-documented finding of a

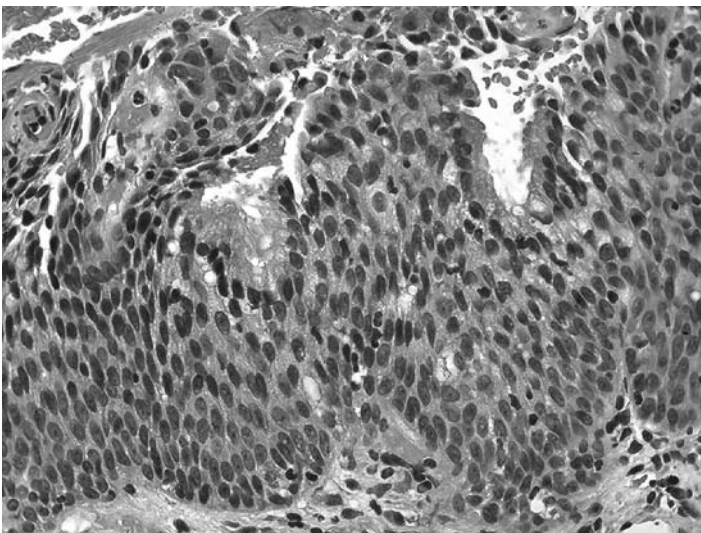


Figure 17 The duct of a minor vestibular gland is lined by pseudostratified columnar epithelium composed of a layer of mucinous cells on the surface overlying several layers of basaloid cells.

small proportion of urethral adenocarcinomas that are PSA-secreting adenocarcinomas. Cohen et al. by contrast, examined two cystourethrectomy specimens in females, and found mucinous glands, but none of these were prostatic acid phosphatase-secreting (15). Further studies into the types, frequency, and location of urethral/paraurethral glands and mucinous glands are needed.

Nonepithelial Cells and Hormone Receptors

Lymphocytes

Mucosa and skin, including that of the vagina, urethra, and vulva have immune surveillance mechanisms termed mucosa-associated lymphoid tissue (MALT) and skin associated lymphoid tissue (SALT) including the vulva. Consequently, occasional single intraepithelial lymphocytes are seen in the epithelium and stroma of all regions of the vulva and urethra. Jones found more in the labium minus than labium majus (11). However, not infrequently, asymptomatic women show a greater number of lamina propria lymphocytes, particularly in the vestibule, where they may be associated with minor vestibular glands and their ducts (Fig. 16). Consequently, the clinical significance of such an infiltrate in symptomatic women is doubtful.

Langerhans' Cells

Langerhans' cells are a specialized type of histiocyte that function as antigen uptake and presenting cells, which are part of the MALT and SALT systems. They migrate from the epithelium to lymph nodes and enter the lymphatic and venous circulations. About 1 intraepithelial Langerhans' cell is found per 10 basal squamous cells. They can be demonstrated immunohistochemically with CD1a (human leukocyte antigen DR receptor) and S100. These markers show the dendritic nature of the cytoplasm.

Melanocytes

The pigment-producing melanocytes reside in the basal layer of skin. While scarcely discernible as small, angulated cells with clear cytoplasm on routine-stained sections, they are much better seen when marked with S100, HMB 45, or MART-1. There is about 1 melanocyte per 10 basal cells. The degree of skin pigmentation relates to melanocyte activity, not number, which is the same in all races. The presence of melanocytes usually ends abruptly at the skin–mucosal junction, and they are only rarely found in the vestibular or vaginal mucosa.

Merkel Cells

Merkel cells are postulated to be keratinocyte-derived specialized neuroendocrine cells functioning in the perception of mechanical stimuli. They appear as single and clustered, subbasal, round, and angular cells with clear cytoplasm in the epidermis, hair follicles, and squamous mucosa. Long cytoplasmic processes keep them in contact with keratinocytes and contiguous nerve fibers in the dermis. Their distribution varies dramatically, but they usually number about 1 per 10 basal cells. They are not usually discerned with routine stains, but mark with CK20, synaptophysin, chromogranin, neuron-specific enolase, neurofilament, CK7, CK8, and CK18, and S100.

Hormone Receptors

The vulva and vagina show estrogen and progesterone receptors in the epithelium, stroma, and fat. Estrogen and progesterone receptors are found in squamous

mucosa, where they are identified in all basal cells with a gradual decrease toward the maturing surface of the epithelium (Fig. 18) (16). They abruptly cease at the skin–mucosal junction and are not found in keratinized skin with the exception of the mammary-like glands. Stromal estrogen and progesterone receptors are confined to superficial fibroblasts, including the stellate or multinucleated myofibroblasts of the lamina propria and dermis. Unlike the mucosa, the stromal receptors extend into skin beyond the skin–mucosal junction. Fat also shows estrogen and progesterone receptors. The lateral, hair-bearing vulva contains androgen receptors (17).

EMBRYOLOGY

For a full account, readers are referred to the recent monograph by van der Putte (18).

Ovaries

Primordial germ cells migrate to the genital ridge to form the gonads. In the fifth-week, the gonads are indifferent and capable of developing into testes or ovaries (19). Gonadal differentiation is achieved through a complex interaction between different expressed genes. The genetic expression of genes on the Y chromosome, particularly SRY, the master regulatory gene, causes the gonad to become a testis. The first sign of testicular development is the presence of Sertoli cells at six to seven weeks. Ovarian development is thought to be related to expression of Dax-1 (20). The first primordial ovarian follicles are seen after 13.5 weeks.

Ureters and Kidneys

Shortly after a pair of mesonephric or wolffian ducts have connected the mesonephroi, primitive kidneys, to the distal hindgut, making this part the cloaca, each duct forms a dorsal diverticulum, the ureteric bud, adjacent to the mesonephric blastema. This bud

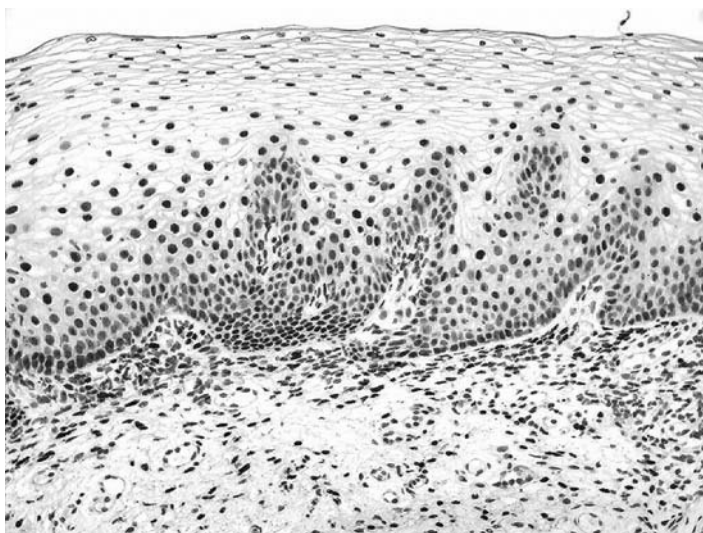


Figure 18 (See color insert) Estrogen receptors are positive (brown-stained nuclei) in the deeper layers of the vestibular epithelium. An identical appearance is seen in the squamous epithelium of the vagina and urethra.

lengthens into the ureter with its pelvis and calyces, and connects the metanephros, definitive kidney to the urogenital derivatives of the cloaca. The original common segment of the duct and ureter is incorporated into the cloaca separating the two systems, which will thereafter part during the formation of the trigone of the bladder.

Tubes, Uterus, and Vagina

At the end of the cloacal period, the wolffian or mesonephric ducts guide Müllerian or paramesonephric ducts, which are newly formed from celomic epithelium at the cranial end of the genital ridges, toward the urogenital sinus derivatives of the cloaca. Approaching the perineum, the two paramesonephric ducts bend inward and fuse into a single tube in the midline. The distal tips, which have remained in direct contact with the lateral mesonephric ducts, then gain access to the sinus by using the orifices of the regressing mesonephric ducts. The original columnar epithelium of the distal part of the fused structure transforms into a broad stratified squamous epithelium that practically fills the developing vaginal lumen. Central degeneration of the epithelium creates the vaginal lumen. Discrepancy between the relatively small vaginal orifice and the greatly expanding vaginal lumen in combination with the movement toward the surface shapes the hymen.

Vulva

The cloaca is a distal expansion of the hindgut covered by the cloacal membrane. Between four and six weeks of embryonic life, marked differences in growth between the anterior and the posterior parts of the cloaca make the cloaca transform into a U-shaped tube, which then splits into the anterior urogenital sinus and the posterior anal canal after the cloacal membrane has disintegrated. The groove-like communication between the two parts is incorporated and will form a hairless median strip on the future clinical perineum. The deeper part of the urogenital sinus differentiates into the urethra and trigone of the bladder. The superficial part becomes the vestibule with its mantle tissue differentiated into erectile and fascial structures. Growth inhibition of most erectile structures and caudalward bending of the original phallic structure flattens the vulva with its small clitoris and prominent labia minora flanking a relatively large persisting urogenital orifice. In the absence of testosterone, the area between this orifice and the anus does not lengthen disproportionately as in the male and forms the clinical perineum. Bilateral concentrations of mesenchyme outside the mantle of the cloaca develop into the perineal muscles and labia majora.

Urethra and Bladder

The urethra is formed from the cranial part of the urogenital sinus. It forms most of the trigone of the bladder and all the urethra in the female and the prostatic urethra in the male. Most of the bladder is derived from the allantois.

DEVELOPMENTAL ANOMALIES

Developmental genital anomalies are divided into those that show ambiguous external genitalia (intersex) and those that are clearly female. The latter group is further divided into those that have only genital abnormalities, those that also have anorectal abnormalities, and those that also have urological abnormalities.

Ambiguous Genitalia (Intersex)

True hermaphrodites are rare individuals who have both testicular and ovarian tissues. The cause appears to be mosaicism, with one cell line containing Y chromosome genes. The gonads may be separate or combined as an ovotestis that may be found above or below the inguinal ring. Pseudohermaphrodites are individuals with a normal genetic sex, but an intersex phenotype for hormonal reasons. The development of the male genitalia is under the influence of testosterone produced by the fetal testis. Androgen from another source such as congenital adrenal hyperplasia will result in masculinization of the genetic female. Androgen that is ineffectual, that is, the androgen insensitivity syndrome will result in feminization of the genetic male fetus. Ambiguous genitalia in true and pseudohermaphrodites may present with an inappropriately large or small phallus, failure or inappropriate fusion or the labioscrotal folds, urethral abnormalities, and inappropriately placed gonads (Fig. 19).

Genital Anomalies Without Intersex

Vaginal Agenesis

Vaginal agenesis is a rare abnormality (1 per 4000–1 per 10,000 females) due to failure of development of the Müllerian duct system (21). This is usually associated with absent corpus and cervix (Mayer–Rokitansky–Kuster–Hauser syndrome), but 7% to 10% will have a normal or rudimentary obstructed uterus. Extragenital, mainly urological, and skeletal abnormalities are seen in 25% to 50%. The ovaries are normal (22).

Transverse Vaginal Septum

Transverse vaginal septa are very rare, with an incidence of 1 in 30,000 to 1 in 80,000 females (23). They may occur anywhere along the length of the vagina, with the



Figure 19 Androgenized female infant, inferior view. *Source:* Courtesy of Dr. John Cassey, Newcastle, New South Wales, Australia.

majority in the upper half. The atretic segment is usually less than 1 cm thick and may have a small perforation. The most likely cause is a defective development of the fusing Müllerian ducts. Presentation may be similar to imperforate hymen. There may be a higher genital tract abnormality.

Longitudinal Vaginal Septum

Longitudinal vaginal septum is caused by defective medial fusion of the Müllerian ducts and is typically associated with uterus didelphys (Fig. 20) (24). Septate vagina is distinguished from the much rarer double vagina, which has two separate muscle coats. There may be an obstructed hemivagina, which may be associated with ipsilateral renal anomalies.

Lower Vaginal Agenesis

Lower vaginal agenesis is due to failure in the development of the distal part of the vagina. The agenesis appears as a fibrous segment replacing the lower vagina. Patients present like those with an imperforate hymen. The upper vagina, cervix, corpus, tubes, and ovaries are normal.

Imperforate Hymen

The hymen is the residuum of the vaginal plate between the Müllerian and the mesonephric ducts, and urogenital sinus contributions to the vagina. Normally, this becomes perforated at 20 weeks of intrauterine life. A partial rim, usually posterior, is often left, which is ruptured at first intercourse to leave tags of mucosa, the carunculae myrtiformes. In one in 2000 female births, the hymen remains imperforate.



Figure 20 (See color insert) Septate vagina, inferior view. *Source:* Courtesy of Dr. John Cassey, Newcastle, New South Wales, Australia.

Imperforate hymen is usually diagnosed on routine examination of the neonate. It may present in the neonate with a lower abdominal swelling due to accumulated secretions or in the teenager with delayed menarche, urinary retention, or pain (Fig. 21). Severe endometriosis due to retrograde menstruation may complicate untreated imperforate hymen. Rarely, there may be associated lower urinary tract or anorectal congenital maldevelopments.

Cysts

Gartner's (mesonephric) duct cysts are formed from remnants of regressed mesonephric ducts, and are the commonest cause of vaginal cyst. They may be unilateral or bilateral and are seen from the fornices to the introitus. Size is up to 10 cm in diameter and presentation is usually in infancy or in the reproductive age group.

Cysts of the canal of Nuck derive from the processus vaginalis, which is a peritoneal extension from the inguinal ring to the labium majus. It usually closes in utero. Its persistence may result in a peritoneal-lined cyst. This is the female equivalent of the indirect inguinal hernia of the male. It may show postural variation or present for the first time as a pneumatocele during laparoscopy.

Müllerian cysts are lined by ciliated or mucinous epithelium. These are usually small and are located in the lower vagina or around the introitus. They may be present at birth or expressed at a later age.

Paraurethral duct cysts may also be congenital or acquired. The congenital form has an incidence between one per 2000 and one per 7000 live births (25).

Vulvovaginal with Urological Abnormalities

Rarely, an ectopic ureter may drain into the vagina. Patients present with urinary incontinence that may be misdiagnosed as vaginal discharge. Urological investigation



Figure 21 (See color insert) Imperforate hymen in a teenager, inferior view. *Source:* Courtesy of Dr. John Cassey, Newcastle, New South Wales, Australia.

is required to determine the urinary tract anatomy. Epispadias is a rare malformation seen in the pediatric age group where there is a deficiency of the urethra anteriorly. Patients are incontinent. The clitoris is bifid and there is anterior separation of the labia. The urethra is short and patulous. Pubic bone separation will be seen on X ray or will be palpable. Hypospadias is abnormal location of the urethral meatus on the anterior vaginal wall. There may be incontinence, meatal stenosis, pooling of urine in the vagina, and occasional vaginal and uterine abnormalities. Rarely, Gartner's duct cysts, especially if in infants and/or of large size, are associated with ureteric abnormalities.

Vulvovaginal with Anorectal Abnormalities

In anorectal malformation, a defect in the dorsal cloaca may lead to an abnormal anterior bending anal canal. This may issue into the posterior wall of the female urogenital tract at the trigone of the bladder or anywhere between the vicinity of the vaginal orifice and the usual site of the anus.

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3

Noninfectious Inflammation and Systemic Diseases of the Vulva

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INFLAMMATORY DERMATOSES

Eczema

Vulvar eczema is characterized by erythema and scaling on the outer labia majora and erythema and fissures and erosions on the inner aspects. Vulvar eczema is pruritic, often out of proportion to the clinical findings. The skin may become edematous, excoriated, and lichenified because of scratching.

Irritant Contact Eczema

This is the commonest form of vulvar eczema in clinical practice. This is usually seen in the elderly and is often because of urinary incontinence. It is also more likely to occur in fair-skinned individuals who have sensitive skin at other sites as well (Fig. 1).

Allergic Contact Eczema

Allergic contact eczema is a Type IV cell-mediated allergic reaction that takes 48 to 72 hours to develop following exposure to the offending allergen. This type of allergy is uncommon on the vulvar skin alone and is likelier to be found if there is perianal eczema as well. The commonest allergens include topical antibiotics and preservatives in the ointments or creams that are being used. The topical steroid itself can on rare occasions be responsible. It is important to patch test the patient if the vulvar rash is worsening with treatment.

Seborrheic Eczema

This is the second most common type of vulvar eczema that tends to affect other flexural sites including the axillae, submammary, and inguinal folds. There may also be scalp involvement. On occasions it may be very difficult to differentiate this form of eczema from flexural psoriasis; however, with the former there should be no nail involvement (Fig. 2).



Figure 1 (See color insert) Irritant eczema. Glazed erythema of the most exposed areas in a patient with urinary incontinence.

Atopic Eczema

This does not tend to occur on the vulvar skin alone and the vulvar eczema that is associated with atopy is usually an irritant eczema, because the skin of atopic individuals has a lower threshold for irritant reactions.

Treatment of all types of eczema includes the avoidance of irritants such as bubble baths and shampoos and the use of a soap substitute. A mild-to-moderately potent topical corticosteroid ointment will help the inflammation and relieve the itch. Barrier ointments are helpful if the patient is incontinent (Table 1).



Figure 2 Seborrheic eczema. Orange red erythema of the labia majora area extending into the genitocrural folds and perianal area.

Table 1 Eczema

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Eczema	Itch, pain if fissured, excoriated, and eroded	Ill-defined erythema mainly on labia majora and minora with edema and lichenification	Psoriasis and Hailey–Hailey	Soap substitute, emollients, and mild to moderate topical steroid

Psoriasis

The anogenital skin can be involved as part of generalized psoriasis but the form more characteristically seen on the vulva is flexural psoriasis. The erythema is well defined and there may be scale on the hair-bearing parts, i.e., the mons pubis and outer labia majora (Fig. 3A and B). The inner aspects of the labia majora tend to be red and fissured and nonscaly because the environment is damp and occluded. The labia minora are red and edematous. It is helpful to look at other sites to confirm the diagnosis of flexural psoriasis, e.g., scalp, axillae, submammary areas, periumbilical, inguinal, genitocrural folds, and natal cleft. In addition, there may be dystrophic nail changes with pitting and subungual hyperkeratosis.

The main complaint is itch and often there is also a burning sensation. On examination there is well-defined erythema, particularly in the interlabial sulci with fissuring and a buildup of keratinous debris. The changes may extend to involve the perianal area and the natal cleft.

Treatment: A soap substitute, i.e., emulsifying ointment or aqueous cream and a moderately potent topical corticosteroid, e.g., betamethasone once a day. A barrier ointment, e.g., zinc ointment may also help (Table 2).

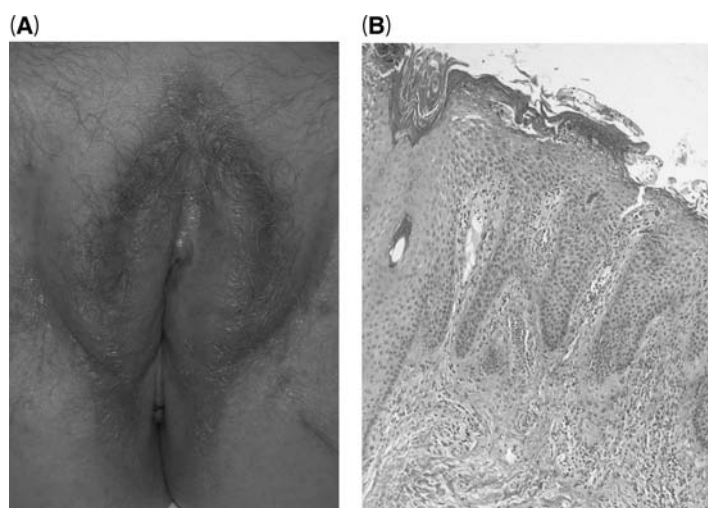


Figure 3 (See color insert) (A) Flexural psoriasis. Well-margined erythema of anogenital skin with some crusting. (B) Psoriasis. Characteristic elongated rete ridges and papillae, dilated vessels within papillae, and intraepithelial (Munro's) microabscess.

Table 2 Psoriasis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Psoriasis	Itch, burning pain if fissured or eroded	Beefy red and well-defined erythema	Eczema. Lichen planus, Reiter's disease, and extramammary Paget's	Soap substitute, emollients, and moderate to potent topical steroid; barrier ointments

Reiter's Disease (Reiter's Syndrome and Circinate Ulcerative Vulvitis)

This condition is characterized by a nonsuppurative polyarthritis frequently accompanied by urethritis, cervicitis, and conjunctivitis. Reiter's disease is commoner in males and it may be triggered by an enteric or a lower genital tract infection. There seems to be a predisposition in those individuals who are positive for the human leukocyte antigen B27. The cutaneous manifestations probably represent a particular form of psoriasis. Circinate balanitis is well recognized. The corresponding vulvitis is much rarer but has been described (1). The lesions that occur can be eroded, ulcerative, or scaly.

Histologically, the changes are of those seen in pustular psoriasis with hyperkeratosis, parakeratosis, psoriasiform hyperplasia, an absent granular layer, and collections of polymorphs in the epidermis (2). Treatment is the same as for psoriasis (see previous section).

Lichen Planus

Lichen planus (LP) can affect the anogenital skin or vagina in isolation or at the same time as a generalized outbreak, when about 20% of patients will have genital lesions (3). The vulvar lesions are similar to those seen on nongenital skin sites and may be violaceous or erythematous papules, white or annular plaques, and erosions with or without a lacy white border. Sometimes, the main findings are erosions and ulcerations. If the LP is confined to the vulva and/or vagina, the lesions are more likely to be erosive (Fig. 4). Examination of the oral mucosa is helpful as LP may be found on the tongue (Fig. 5), palate, gingiva, and lateral buccal mucosa. There is a small risk (> 4%) of squamous cell carcinoma (SCC) arising on a background of LP.

The other clinical forms of vulvar LP include

Pigmented Flexural LP

The lesions are characteristically distributed in the inguinal and genitocrural folds. The individual lesions are brown pigmented patches, some so deeply pigmented that they resemble melanocytic nevi. Early lesions may have a violaceous erythematous appearance. This form of LP will also be found in the other flexural sites particularly the inframammary areas and axillae.

Vulvo-Vaginal-Gingival LP (Syndrome of Hewitt and Pelisse)

This is a distinctive erosive form of LP that is clinically very similar to mucous membrane pemphigoid (4,5). In the past, many cases labeled desquamative vaginitis were



Figure 4 Lichen planus. Eroded areas on a background of pallor. The architecture remains well preserved.

probably this entity. Vulvo-vaginal-gingival LP principally affects the inner aspects of the labia minora, vestibule, and vagina; the lesions are painful and itchy. Patients will complain of dyspareunia, dysuria and, if there is vaginal involvement, an increased vaginal discharge, and postcoital bleeding. Clinically, the vulvar lesions are eroded and have a distinctive fine white lacy border. The anal margin may also



Figure 5 Lichen planus on the dorsal aspect of the tongue.



Figure 6 (See color insert) Vulvovaginal lichen planus. Glazed erythema on the inner aspects of the labia minora bordered on the left-hand side with a white edge.

be involved. The vaginal lesions are velvety red erosions or bright red glazed erythema patches (Fig. 6), which when touched are friable and bleed. Vaginal synechiae and adhesions occasionally develop, leading to vaginal stenosis. The cervix may also be involved. The oral involvement is a glassy red erythema of the gingivae (Fig. 7), but more typical lesions of LP can be found on the tongue or lateral buccal mucosae. Very unusual sites of involvement have been described on the conjunctiva (6), lachrymal gland canal (7), esophagus (8), and the auditory canal (9).

Lichen Planopilaris

This is a very rare variant that affects the hair-bearing skin of the vulva (10).

Hypertrophic LP

This variant is often the most difficult to diagnose and treat. The clinical appearance is of sheets of hyperkeratotic whitened epithelium that encase the vulva and often extend perianally. There is usually a loss of the labia minora with introital narrowing and the clitoris may be buried (Fig. 8A). The disease is often so long standing that the typical histological features of LP are not found. The diagnosis is confirmed by a biopsy and the typical changes are irregular acanthosis with a saw-tooth appearance of the rete pegs, an increased granular layer, and disruption of the basal layer with a



Figure 7 (See color insert) Lichen planus. Glazed erythema of the gingiva with striae in the sulcus.

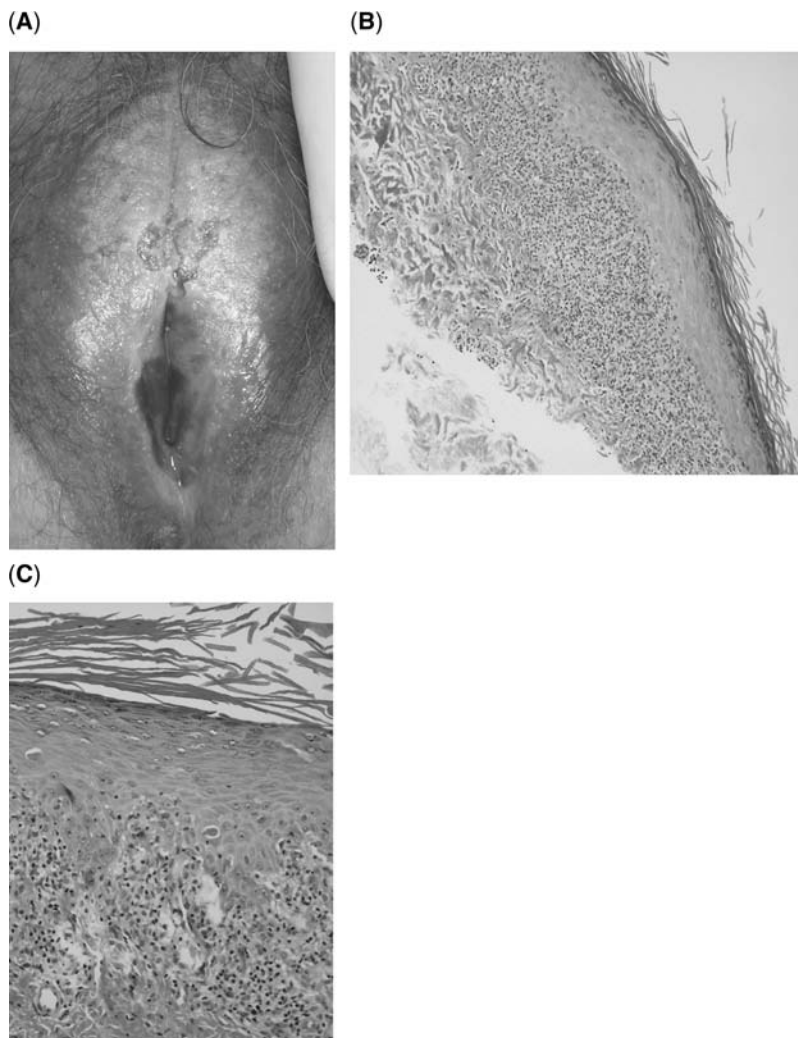


Figure 8 (A) (*See color insert*) Hypertrophic lichen planus (LP). There is loss of the labia minora and the clitoris is buried. The vulval skin is white and hyperkeratotic with erythema in the inner aspect. (B) LP—characteristic band-like infiltrate of chronic inflammatory cells in the dermis, saw-tooth deformity of the rete ridges, and hyperkeratosis. (C) (*See color insert*) LP—saw-toothed deformity of rete ridges, uneven hypergranulosis, and orthokeratotic hyperkeratosis.

closely apposed dermal band-like lymphocytic infiltrate (Fig. 8B and C). The acanthosis and hyperkeratosis are marked in the hypertrophic form and because of the chronicity of this form the characteristic band-like infiltrate is not obvious but will be found focally. Eosinophilic colloid bodies may be seen. Immunofluorescent (IMF) studies will reveal uneven fibrinogen staining of the basement membrane and IgM cytotid bodies. These studies also help to differentiate LP from the other blistering diseases, particularly mucous membrane pemphigoid.

The main differential diagnosis is usually lichen sclerosus (LS) but mucous membrane pemphigoid, pemphigus, lupus erythematosus, and morphea could also be included. In some cases the differentiation between LS and LP can be extremely difficult and a diagnosis depends on a combination of clinical, histological, and IMF

findings and response to treatment. Frequently, there are cases of LP misdiagnosed as Zoon’s vulvitis.

Treatment: First-line treatment is with potent topical steroids. If the vagina is involved, topical steroids can be introduced with a vaginal applicator, or steroid foams or suppositories that are available for inflammatory bowel conditions can be used (11). Topical retinoids are useful for hyperkeratotic and hypertrophic LP and recently topical tacrolimus has been used (12). Other treatments tried with variable success include oral steroids, oral and topical retinoid, methotrexate (13), cyclosporin, and azathioprine (Table 3).

Zoon’s Vulvitis (Plasma Cell Vulvitis)

There is some doubt whether plasma cell vulvitis (PCV) is a distinct clinicopathological entity as many of the reports in females of Zoon’s are probably LP (14). A plasma-cell-rich infiltrate in a vestibular biopsy may be a misleading finding because plasma cells are commonly found in inflammatory conditions of the vestibule because it is a mucosal epithelium, so PCV is probably not a single disease entity but represents a reaction pattern to other inflammatory conditions such as LP (Fig. 9A and B). The criteria needed to make the diagnosis have varied in the literature and the essential histological features include epidermal thinning, absent horny and granular layers, and distinctive lozenge-shaped keratinocytes with widened intercellular

Table 3 Lichen Planus

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Lichen planus	Itch, pain if eroded; dyspareunia if vestibular involvement; vaginal discharge and postcoital bleeding if vaginal involvement	Lesions may be papulosquamous, eroded, ulcerated, pigmented macules; there is often post-inflammatory pigmentation and scarring	Lichen sclerosus, mucous membrane pemphigoid, VIN, extra-mammary Paget’s and Hailey–Hailey disease.	Potent topical steroids as ointments, foams, or suppositories. Oral steroids may be required for severe disease. In steroid-resistant disease topical pimecrolimus or tacrolimus. Second-line treatment includes azathioprine, methotrexate, and retinoids. Blunt dissection to open up stenosed vagina.

Abbreviation: VIN, vulvar intra-epithelial neoplasia.

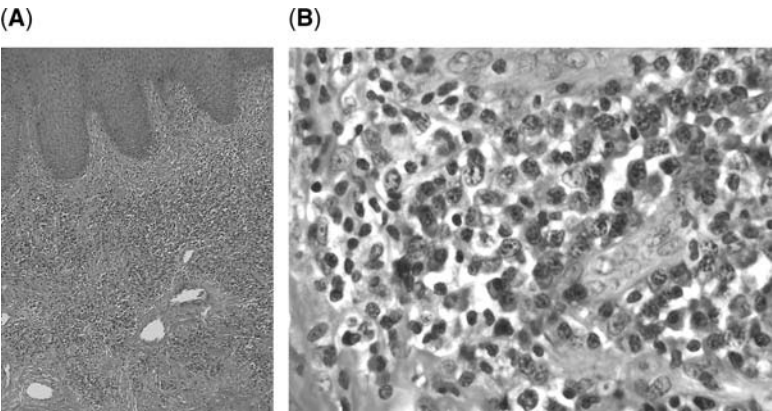


Figure 9 (A) Plasma cell vulvitis of Zoon—a dense inflammatory infiltrate is seen in the dermis, composed predominantly of plasma cells. (B) Plasma cell vulvitis of Zoon—higher power shows the dense plasma cell infiltrate. This condition is often seen in association with other conditions. In this case, there was also an active herpes infection.

spaces; while in the dermis there is a dense inflammatory infiltrate composed largely of plasma cells with dilated blood vessels and abundant hemosiderin. Clinically, the lesions are fixed erythematous patches with a varnished appearance. The majority of the reports of this condition in women describe the lesions in the vestibule and labia minora, whereas the typical site in men is the glans and prepuce. The glans clitoridis seems to be rarely, if ever, affected.

Treatment: Topical steroids help if the changes are because of LP but if the lesions are fixed, the topical steroids have little effect. Patients often complain of pain and topical 5% lidocaine can be used. Irritancy may play a role if the barrier function of the epithelium is impaired and the addition of a barrier ointment may be useful (Table 4).

Chronic Vulvar Purpura

Occasionally, one finds patients with purpuric patches, often at the vestibule, in which hemosiderin and plasma cells are found without any specific epidermal change and the term chronic vulvar purpura may be a more accurate description. It is probably a capillaritis similar to lichen aureus (Fig. 10A and B), because pressure factors are thought to be relevant in the extravasation of blood (Table 5) (15).

Crohn's Disease

Anogenital lesions occur in about 30% of patients with intestinal Crohn's, either as a direct extension of active intestinal disease or as a secondary disease. Vulvar disease

Table 4 Zoon's Vulvitis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Zoon's	Asymptomatic, itch, or burning	Glassy red erythema	VIN, lichen planus	Rx underlying condition; topical lidocaine and barrier ointments

Abbreviation: VIN, vulvar intra-epithelial neoplasia.

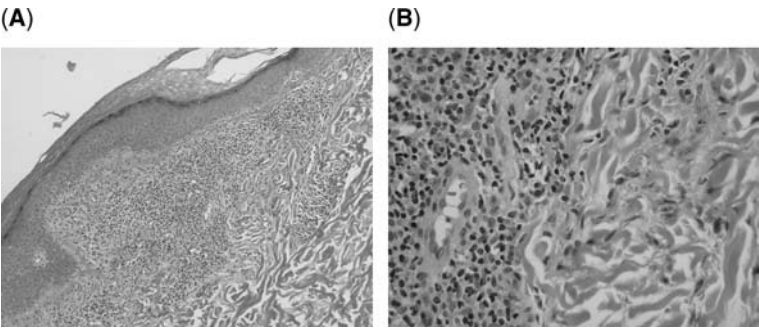


Figure 10 (A) Lichen aureus—lichen aureus is in the differential diagnosis of a band-like dermal infiltrate of chronic inflammatory cells. (B) Lichen aureus—increased numbers of dermal vessels (*left*) and hemosiderin (*right*) are seen.

may present many years before intestinal involvement and in some cases there is vulvar edema and lymphangiectasia only, with no evidence of granulomatous inflammation (Fig. 11C) (16,17). The more usual presentation is ulceration, abscess, sinus, and fistula formation with a granulomatous histology. There may be deep linear fissures (knife cut sign) along the skin creases (Table 6).

Hidradenitis Suppurativa

This is a chronic inflammatory disease occurring on skin containing apocrine glands. It is commoner in women and occurs in the anogenital area as well as the axillae, breasts, thighs, and buttocks. It is a problem of follicular occlusion with the consequent complications of obstruction to the outflow of other apocrine and sometimes sebaceous glands (18). It can be associated with similar conditions such as conglobate acne and pilonidal sinus. Bacteria play a secondary but important role, in the inflammatory process that results leads to scarring and sinus formation. The onset of the disease is after puberty, suggesting that there is a hormonal influence. The skin lesions include comedones often with two pores (bridged comedones), pustules, tender dermal nodules, abscesses, and linear sinus tracks (Fig. 12A and B). Lesions can ulcerate and there is often a persistent purulent discharge. There may also be the complications of episodic cellulitis, fistula formation to the bladder and rectum, and on very long-standing disease, squamous cell carcinoma (SCC). The important differential diagnosis is Crohn’s disease but there have been examples of hidradenitis suppurativa and Crohn’s disease coexisting (19,20).

Treatment: Weight reduction is important, as well as antiseptic washes. Acute episodes are treated with antibiotics depending on the results of cultures of the skin lesions. Long-term antibiotic treatment with tetracyclines or erythromycin may help

Table 5 Chronic Vulvar Purpura

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Chronic vulvar purpura	Itch or burning	Ecchymotic patches in vestibule	Lichen planus	Topical lidocaine if symptomatic, barrier ointments

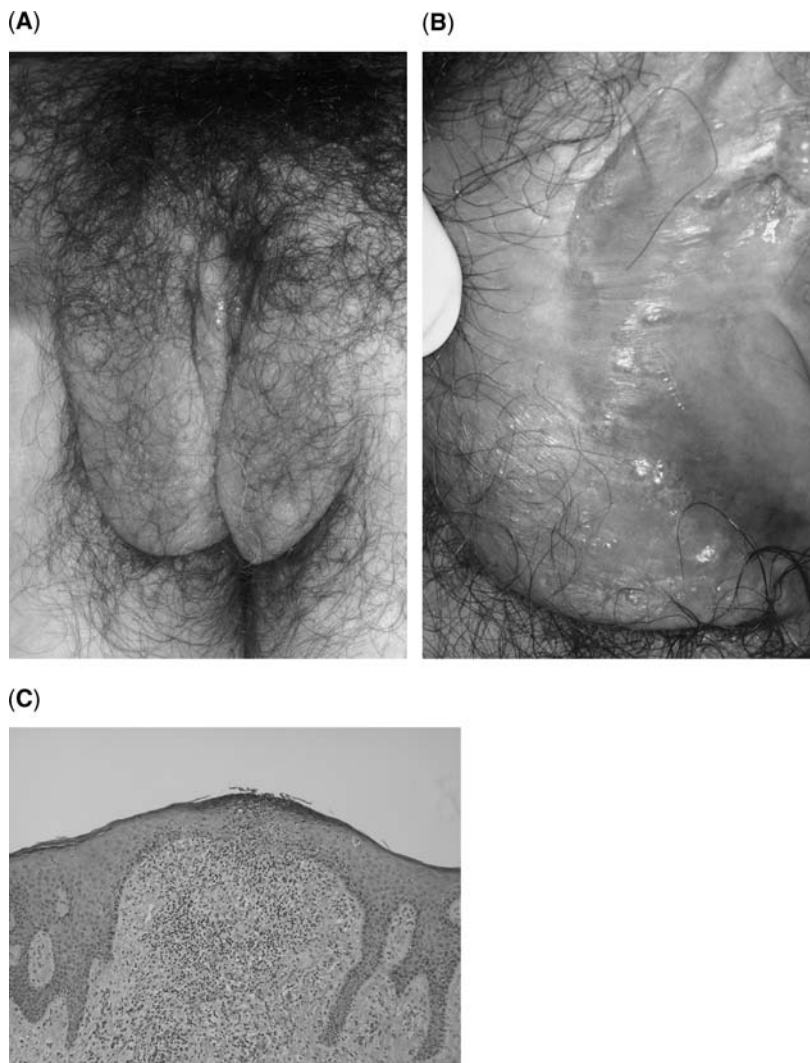


Figure 11 Crohn's disease. (A) Bilateral edema of the labia majora with vesicle-like lymphangiectasia. (B) (*See color insert*) Inner aspect of vulva in Figure 9 showing lymphangiectasia. (C) Granulomatous inflammation with non-necrotizing granulomas is the characteristic finding, although sometimes hard to identify.

in milder forms. Oral retinoids have had some success but they require prolonged courses and because of their teratogenicity they cannot be used in women who are planning to have children. Surgery is the best option in severe cases refractory to all medical treatment (Table 7).

Lichen Sclerosus

LS is a lymphocyte-mediated inflammatory disease characterized by pallor and scarring. It is commoner in females and can affect any age but the majority of patients are either prepubertal or menopausal (21–26). The etiology is unknown, but there is evidence to support that LS is an autoimmune disorder, and in females it may be

Table 6 Crohn’s Disease

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Crohn’s disease	Pain and, less often, itch. Wetness if lymphatics are leaking lymph	Edema,erythema, and ulceration. Deep, wide fissures. Edematous perianal skin tags	Hidradenitis suppurativa and pyoderma gangrenosum	Topical potent steroid ointments. Oral metronidazole. Treatment of GIT involvement Infliximab for fistulas Exploration of sinus tracts to exclude fistula formation

Abbreviation: GIT, gastrointestinal tract.

associated with other autoimmune disorders such as vitiligo in children and thyroid disease in older women.

The classical lesions seen on the extragenital skin are ivory white papules and plaques with follicular swelling and ecchymosis (Fig. 13A). Anogenital disease tends to be characterized by flatter lesions of atrophic, whitened epithelium, which may become confluent extending around the vulvar and perianal skin in a figure of eight configuration (the “keyhole” distribution, cigarette paper wrinkling rather than white) (Fig. 13B). There may also be bullae, erosions, and ulceration. The sites

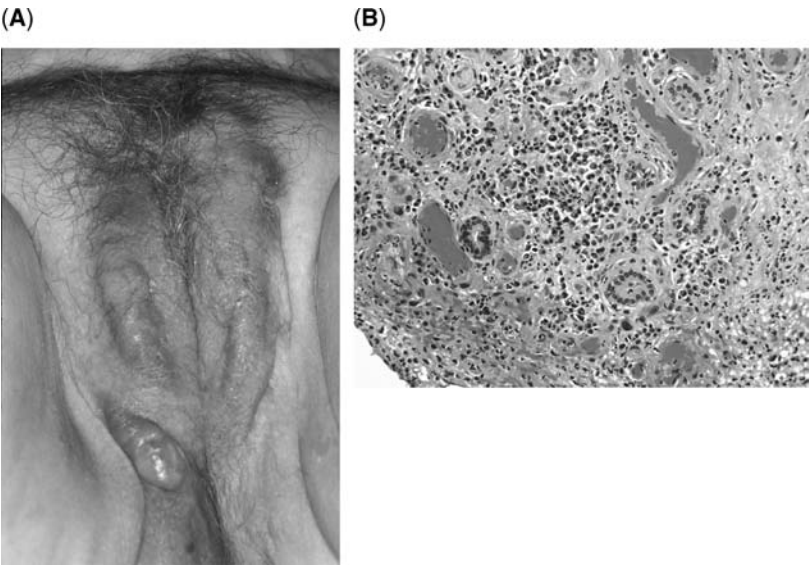


Figure 12 (A) Hidradenitis suppurativa showing inflamed nodules, abscesses, and large linear sinus tracts. (B) Hidradenitis suppurativa—the inflammation frequently involves the sweat glands.

Table 7 Hidradenitis Suppurativa

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Hidradenitis suppurativa	Painful discharge	Pustules, nodules, and abscesses. Linear sinus tracts	Crohn's disease	Long-term oral tetracyclines Antiseptic washes and weight reduction; oral retinoids Surgical excision to lay open sinus tracts, and excision and grafting for extensive disease poorly controlled with medical treatment

most commonly affected are the inner aspects of the labia majora, labia minora, clitoris, and clitoral hood. Less commonly lesions occur in the genitocrural folds. Vestibular involvement is rare and vaginal lesions do not occur, as LS seems to spare noncornified stratified squamous epithelia, i.e., mucosal epithelium. Perianal lesions occur in approximately 30% of female patients in contrast to men who do not seem to develop perianal involvement. Extragenital lesions occur in some women with vulvar disease. The extragenital areas may be truncal, at sites of pressure, upper back, wrists, buttocks, and thighs. The Köebner phenomenon has also been reported at sites of radiotherapy, scar tissue, and vaccination sites. Facial, scalp, and nail involvement (27) have all been reported. Lesions of LS in the oral cavity are extremely rare and many of the reports of oral involvement in the literature have often not been confirmed histologically and many have probably been examples of LP (28). It is not uncommon for patients with vulvar LS to have coexistent oral LP.

LS is a scarring dermatosis and the changes that can occur on the vulva include loss of the labia minora, and sealing over of the clitoral hood, burying the clitoris. Introital narrowing because of anterior and posterior labial fusion sometimes results in a tiny opening into the vestibule. Milia may occur.

The classical histology is a thinned epidermis with flattening of the rete pegs. The underlying dermis is hyalinized (homogenized appearance). Below the hyalinized area is a lymphocytic mixed infiltrate (Fig. 13C). In some cases the epidermis is not thin but thickened, i.e., with squamous cell hyperplasia.

The differential diagnosis includes vitiligo, mucous membrane pemphigoid, LP, and morphea as they may present with a similar clinical appearance. There can be clinical and histological overlap between morphea, LP, and LS.

The incidence of SCC developing on LS in clinical practice is of the order of 4% or less.

The histological patterns associated with SCC arising on LS include epithelial hyperplasia and both differentiated and undifferentiated intraepithelial neoplasia.

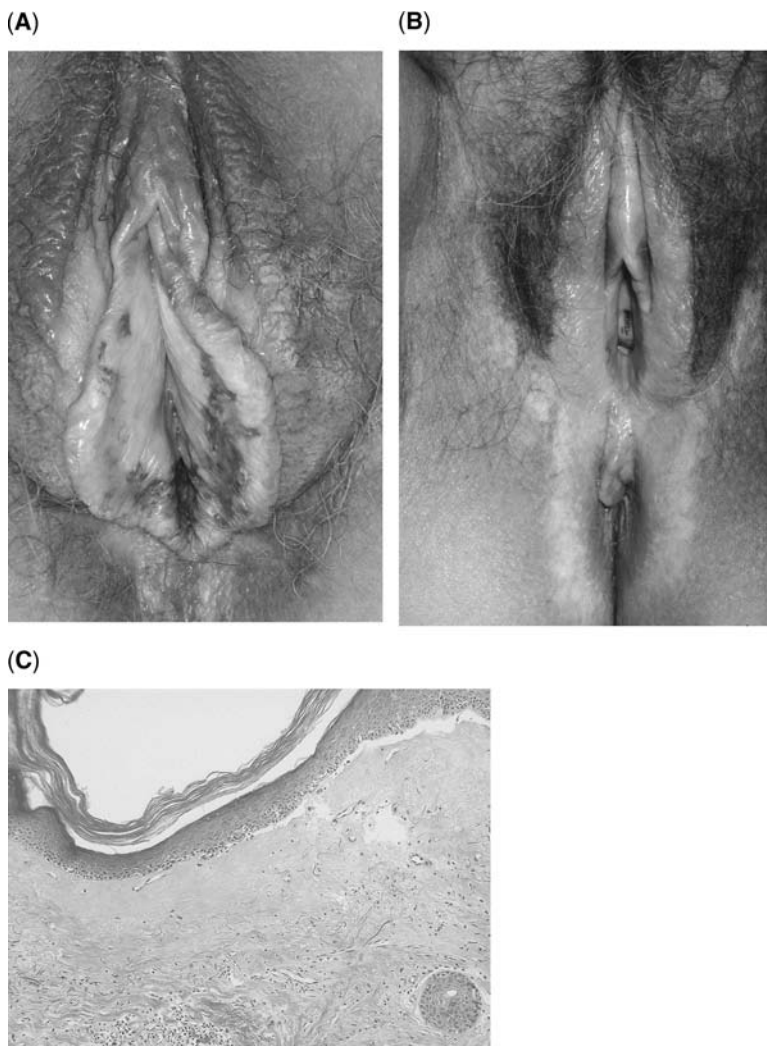


Figure 13 (A) Lichen sclerosus showing white wrinkled skin on the inner aspects with sheets of ecchymosis on the inner labia minora. (B) (*See color insert*) Lichen sclerosus involving the vulva and perianal skin with extension into the genitocrural folds, resulting in loss of the labia minora and sealing over of the clitoral hood. (C) (*See color insert*) Lichen sclerosus—there is thinning of the epidermis with loss of rete pegs and dermal homogenization. Dermal inflammation beneath the area of dermal homogenization is variable and is minimal here.

Verrucous carcinoma has also been described in association with LS. More rarely, vulvar basal cell carcinoma (29) and melanoma (30) have been reported occurring in association with LS. The validity of the case report of an association with malignant melanoma and LS was questioned but the original authors upheld their view.

Treatment: The current recommended treatment for uncomplicated LS is a potent topical corticosteroid, e.g., clobetasol propionate (31). There are no randomized controlled trials providing evidence for any particular corticosteroid or treatment regimen being more effective than any other. The regimen recommended by the author for a newly diagnosed case is initially clobetasol propionate once a night

for four weeks then alternate nights for four weeks and for the final month twice a week. A 30 g tube of clobetasol propionate should last 12 weeks and the patient is then reviewed. The clobetasol propionate is then continued and used as and when required. Most patients seem to require 30 to 60 g annually. Some patients will go into complete remission requiring no further treatment. Others will continue to have flares and remissions and they are advised to use clobetasol propionate as required. A soap substitute is also recommended, and an information sheet on LS and the instructions for the use of the topical steroid. In the past topical testosterone was used with an improvement in the clinical appearance and diminution of symptoms. Clobetasol dipropionate is a more effective treatment and has now replaced testosterone in the treatment of LS. Surgical excision is not necessary in the management of most LS and it should be used exclusively for the management of functional problems because of postinflammatory scarring (32,33), premalignant lesions, and malignancy (Table 8).

Aphthae

Benign aphthae of the vulva may or may not occur with concomitant oral lesions. The age of onset is in childhood, by about the age of six, and there may be a family history. The lesions are usually multiple and small. Less commonly, the lesions are solitary or few but larger, referred to as giant aphthae. Herpetic infection has to be excluded and there is often a premenstrual exacerbation once the menarche is reached. The etiology remains unknown. The lesions are superficial and painful with a yellow base surrounded by a red areola (Fig. 14). They are distributed most frequently on the labia minora and heal quickly.

Many eponymous names have been assigned to acute vulvar ulcers, many of which are probably examples of benign aphthae, e.g., Sutton’s ulcer.

Lipschutz’s ulcer, which occurs in young women, is a separate entity. This is usually one large deep painful ulcer that develops very rapidly and is covered with an adherent slough. The ulcer is sited most frequently in the inner aspect of one of the labia minora. Occasionally, two ulcers develop at apposing sites bilaterally (Fig. 15). The ulcer heals spontaneously over several weeks leaving some scarring. The Lipschutz-type ulcer is sometimes associated with a systemic infection such as infectious mononucleosis (34–36), typhoid, or paratyphoid fever. Healing is spontaneous but may take several weeks and leaves some scarring. Differential diagnoses include Herpes simplex infection with type 1 or 2, erythema multiforme, and Langerhans cell histiocytosis.

Table 8 Lichen Sclerosus

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Lichen sclerosus	Severe itch and, if ulcerated or fissured, pain; dyspareunia	White wrinkled epithelium with ecchymoses fissures in the interlabial sulci; scarring	Lichen planus, morphea, and mucous membrane pemphigoid	Potent topical steroid



Figure 14 (See color insert) Benign aphthae with erythematous halo and slough-covered central ulceration.

Treatment: This includes symptomatic treatment with analgesics either oral or topical. Astringent soaks with either potassium permanganate solution 1:10,000 or Monsel's solution followed by a topical corticosteroid and/or topical tetracycline have been used but may exacerbate symptoms.



Figure 15 (See color insert) Lipschutz' ulcer. There are two large and deep ulcers apposed on either side.

Table 9 Aphthae

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Aphthae	Pain	Central slough-covered ulcer with erythematous halo	Herpes simplex, Behçet's syndrome erythema multiforme and blistering disease	Moderate to potent topical steroid and tetracycline mouth washes

In very severe ulceration that may occur with the Lipschutz ulcer, a short course of oral steroids may be required. Testing for herpes virus is mandatory, as a positive result will lead to specific therapy (Table 9).

Behçet's Syndrome

This is a syndrome of recurrent oral ulceration accompanied by two of the following: genital ulceration, eye lesions including anterior uveitis and retinitis, other cutaneous lesions, i.e., erythema nodosum, sterile pustules, erythema multiforme, and pustulation at sites of trauma (pathergy). It is a multisystem disorder (37) and there may be gastrointestinal, neurological, psychiatric, rheumatological, cardiological, and pulmonary involvement. Vascular complications include superficial and deep vein thromboses, arterial occlusions, and aneurysms (Fig. 16). Vulvar ulcers occur less frequently than the oral ulceration and they are clinically similar to benign aphthae although they may be larger and or more numerous and tend to last longer. They heal with scarring. Diagnosis is sometimes difficult and often only made as the clinical signs and complications evolve over a period of time. The geographic distribution of cases suggests either local endemic agent or physician overacceptance of the diagnosis.

Treatment: Topical steroids with or without a topical antibiotic can be used for minor vulvar ulceration. Severe ulceration may require an oral steroid or colchicine and immunosuppressants. Thalidomide is reserved for recalcitrant disease.

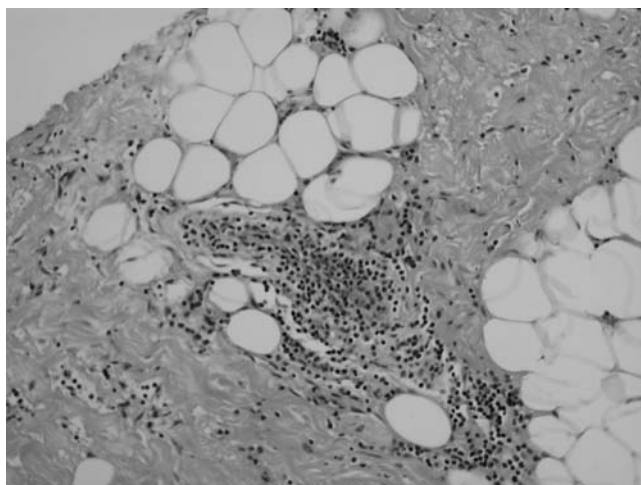


Figure 16 Behçet's disease—the lesions are characterized by vasculitis and perivasculitis deep to the ulcerations.

Table 10 Behçet’s Syndrome

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Behçet’s	Pain	Ulceration and pustulation	Aphthae	Thalidomide Potent topical steroids with or without a topical antibiotic, oral steroids, and colchicine

It is important to have an eye assessment, because ocular complications are common. Anticoagulants are indicated for thrombotic disease. It is important to have a multidisciplinary team involved in the management of patients with Behçet’s syndrome (Table 10).

EROSIVE, ULCERATIVE, AND BULLOUS DERMATOSES

Chronic Ulcerative and Bullous Diseases

Any chronic solitary ulcer of the genital mucosa must be considered malignant or infective until proven otherwise. Generalized ulceration of the vulva can be because of an underlying bullous condition but because of the friction and forces at the site, blisters do not often remain intact and erosions and ulcers are seen instead. The differential diagnosis of chronic ulceration can come under any of the headings listed below.



Figure 17 (See color insert) Hailey–Hailey disease. There is erythema with maceration in the genitocrural fold and tiny erosions.

Genetic

Congenital epidermolysis bullosa is a rare disorder of the skin, which is characterized by blistering and scarring of the skin in response to friction or trauma. The two types that involve the vulvar and vaginal area are dystrophic and functional epidermolysis bullosa.

Hailey–Hailey disease (benign familial pemphigus) and Darier’s disease may also be responsible for chronic recurring erosions and ulceration of the vulvar skin and genitocrural folds (Fig. 17). Sometimes turbid intact vesicles are seen. The diagnostic histological finding is acantholysis of the epidermal cells. Hailey–Hailey and Darier’s disease affect other sites as well as the vulva. Darier’s disease is characterized by notching of the nails and white longitudinal lines. Hailey–Hailey disease does have the white lines but not the notching but vaginal lesions have been described in Hailey–Hailey diseases but not in Darier’s disease. There appears to be a distinct clinicopathological entity, genital papular acantholytic dyskeratosis, that affects the vulvar area only (38,39). It may be a forme fruste of Hailey–Hailey or Darier’s disease. Exacerbations may follow friction, infection, irritants, and herpes simplex infection.

External Trauma

Nymphohymeneal Tear. This is usually because of a tear around the nymphohymeneal sulcus and most frequently occurs after sexual intercourse (Fig. 18). The tear will heal spontaneously but can recur. These tears tend to occur around the nymphohymeneal sulcus usually in the posterior segment in the 5 and 7 o’clock positions. Those that do not heal can be excised radially. Recurrent superficial tears at the fourchette may sometimes occur in celibate women.



Figure 18 Nymphohymeneal tear healing at 7 o’clock in the inner aspect of the vestibule and a fresh lesion just above at 8 o’clock.



Figure 19 (*See color insert*) Erythema multiforme—characteristic targetoid lesions. *Source:* Image courtesy of W. Clark Lambert, MD, PhD., UMDNJ–New Jersey Medical School, Newark, New Jersey, U.S.A.

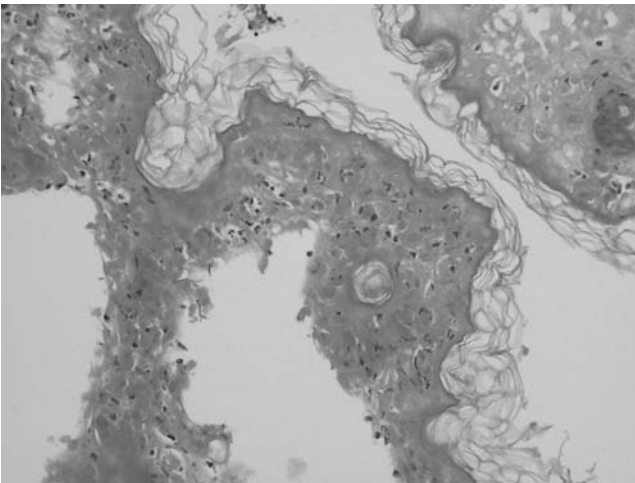


Figure 20 Stevens–Johnson syndrome. This superficial biopsy of a blister shows the characteristic epidermal necrosis.

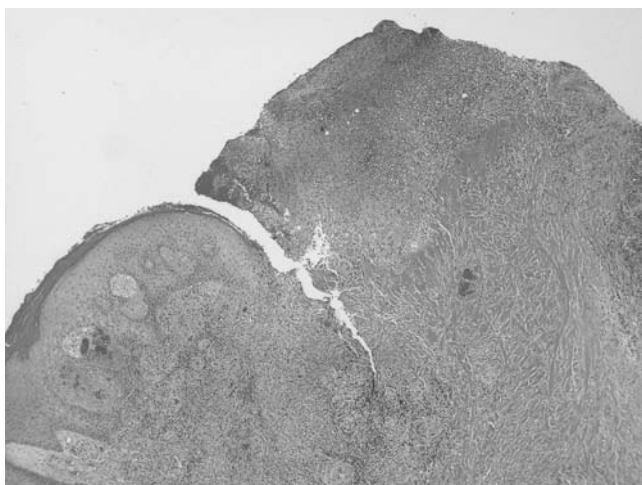


Figure 21 Pyoderma gangrenosum—characteristic ulcer and heavy inflammatory infiltrate.

Dermatitis artefacta and radiation damage following treatment of a gynecological malignancy may also be a cause of chronic ulceration.

Drugs

These are slightly unusual to be the sole cause of a problem in the anogenital area alone and genital involvement occurs as part of a generalized skin eruption.

Erythema multiforme may produce vulvar ulcers and erosions. The etiology is often herpes simplex but many are drug induced. The lesions are usually aphthous-like ulcers and there is usually oral involvement at the same time. The typical target-like lesions may be seen at other nongenital sites (Fig. 19).

Stevens–Johnson syndrome (Fig. 20) and toxic epidermal necrosis is a severe problem and is often drug induced. Some of the drugs involved include phenytoin, trimethoprim, sulphonamides, and nonsteroidal anti-inflammatories. The onset is acute with systemic symptoms. Shallow ulcers, erosions, and flaccid

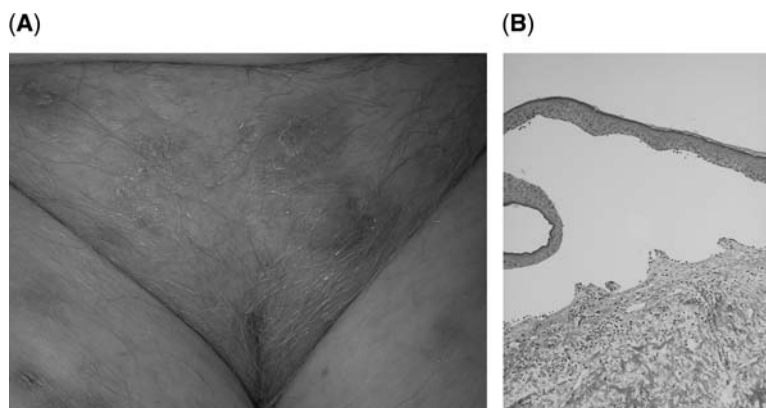


Figure 22 (A) (See color insert) Bullous pemphigoid. Erythematous lesions with erosions and flaccid blisters. (B) Pemphigoid—characteristic subepidermal bulla and eosinophilic-rich dermal infiltrate.

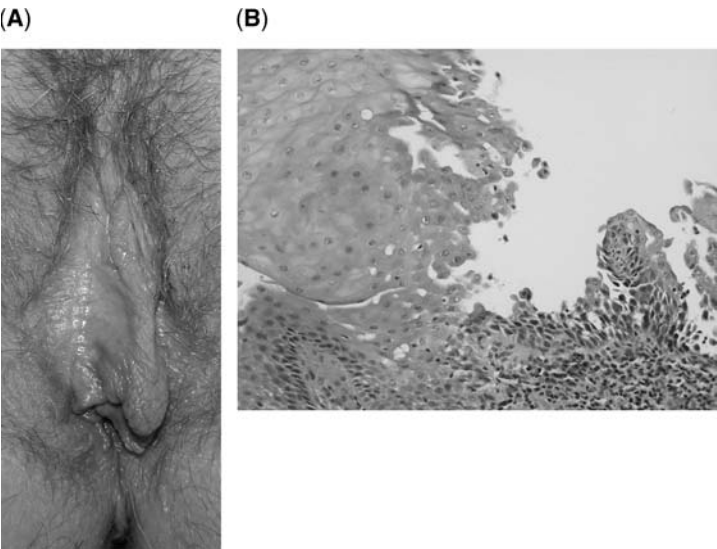


Figure 23 Pemphigus. **(A)** (*See color insert*) Erosions on right side of vulva. **(B)** Characteristic intraepidermal bulla, most prominent in the deeper aspect of the epithelium.

blisters develop on the inner aspects of the vulva and vagina. This may rapidly lead to adhesions and vaginal stenosis. The other mucous membranes are similarly affected, particularly the eyes and mouth. The lesions on the nonmucosal sites start as an indurated erythema and then blister, leaving large expanses of denuded skin.

Fixed drug eruption (FDE) may present as a bullous lesion (see below).

Malignancy

The two commonest malignant ulcers of the vulva are SCC and basal cell carcinoma. Melanoma may also present as an amelanotic ulcerating nodule. Langerhans cell histiocytosis may present with vulvar and vaginal ulceration.

Infection

Chronic infective ulcers occur in tuberculosis, actinomycosis, and other deep mycoses. The late stages of lymphogranuloma venereum (chlamydia) cause ulceration and scarring. Patients who are immunosuppressed may have chronic ulceration with herpes simplex and cytomegalovirus.

Table 11 Lymphangiectasia

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Lymphangiectasia	Itch, wetness because of lymphorrhea	Shiny skin-colored micropapules or pseudo-vesicles	Lymphangioma circumscripta	Potent topical steroid ointment or CO ₂ laser

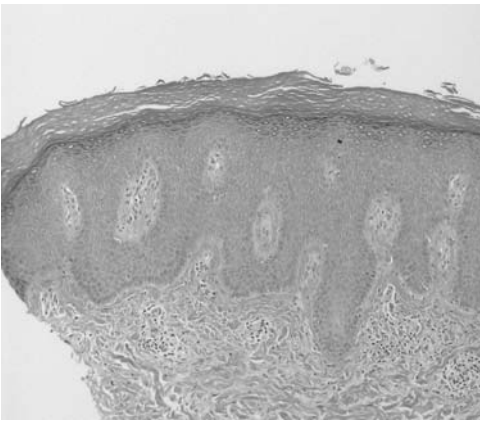


Figure 24 Lichen simplex (lichen simplex chronicus, squamous cell hyperplasia)—there is hyperkeratosis and acanthosis with fusing of rete ridges.

Inflammatory

LS, LP, and lupus erythematosus can all cause chronic ulceration. Vulvar and vaginal lesions are very rare in systemic lupus erythematosus. Hidradenitis suppurativa and Crohn’s disease can sometimes be difficult to distinguish and they can occur together.

Pyoderma gangrenosum (Fig. 21) may occur in association with inflammatory bowel disease, rheumatoid arthritis, and hematological malignancies. Vulvar pyoderma gangrenosum can often accompany Crohn’s disease and it can be difficult differentiating this from a fistulous tract from the bowel. The lesion may be solitary and large or occasionally multiple and small. The initial lesion may be a hemorrhagic vesicle or bulla.

Autoimmune Bullous Diseases

The mucocutaneous autoimmune blistering disorders can affect the vulva and vagina. The integrity of the cellular adhesion of the epidermal cells and/or the basement membrane zone is damaged by the antibody attack and the various blistering diseases that occur are classified according to the site of the target antigen. Several of the autoimmune bullous diseases’ effect can affect the vulva. Pemphigoid (Fig. 22A and B), linear IgA disease, and pemphigus (Fig. 23A and B) may all present with vulvar and vaginal ulceration.

Treatment: The underlying cause, be it drug, dermatosis, or infection needs to be identified and managed. Microbiological studies to exclude bacterial or viral infection must be carried out and a detailed drug history taken, not forgetting over-the-counter medicines. General measures include potassium permanganate 1:10,000 soaks or Burow’s solution, topical antibacterial such as silver sulfadiazine, and oral or topical analgesics.

Table 12 Lichen Simplex

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Lichen simplex	Severe itch	Pale lichenified skin; no scarring; usually unilateral	Eczema	Potent topical steroid

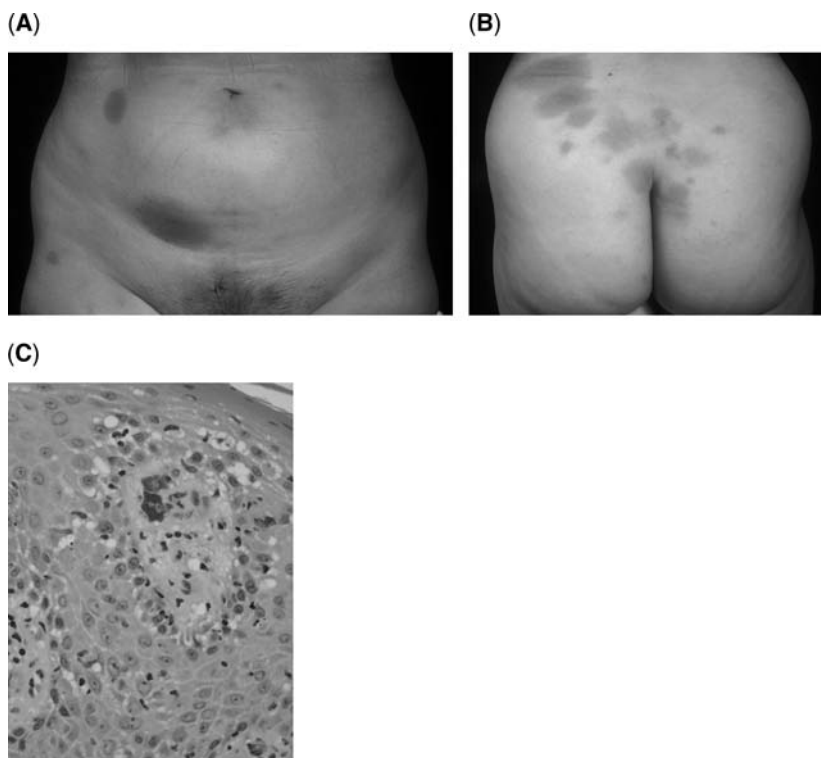


Figure 25 (A and B) Indurated erythematous and discolored lesions of a fixed drug eruption because of fluconazole. (C) (*See color insert*) Fixed drug eruption—vacuolization of the basal layer and pigmentary incontinence are seen.

MISCELLANEOUS

Lymphangiectasia

Vulvar lymphangiectasia is a result of dilatation of superficial lymphatics secondary to obstruction of previously normal deep lymphatics (40). It is most frequently seen

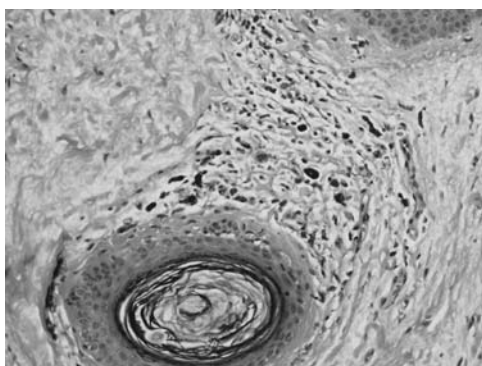


Figure 26 (*See color insert*) Postinflammatory hyperpigmentation—pigment incontinence is seen.

Table 13 Fixed Drug Eruption

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Fixed drug eruption	Itch	Usually solitary urticated erythematous patch that leaves an area of hyperpigmentation; occasionally multiple lesions; can be bullous	Lichen planus; dermatitis artefacta and erythema multiforme	Stop the medication

following surgery or radiation for vaginal or cervical malignancy. It may also be a feature of Crohn’s disease (Figs. 9 and 10).

Treatment: This is sometimes required if there is marked lymphorrhea, leaving the patient permanently wet, and CO₂ laser can give long-term symptomatic relief (41) (Table 11).

Lichen Simplex

Lichen simplex is used to describe the skin changes seen secondary to scratching or rubbing in response to the symptom of itch. The itch may be because of a low-grade dermatitis such as psoriasis or seborrheic eczema but often is a sensory abnormality alone. The lesions of lichen simplex tend to be in one isolated area, usually on the labia majora or mons pubis. The change is characterized by a well-defined pale gray or white surface with an accentuation of the normal rhomboidal markings. The histological changes of lichen simplex include hyperkeratosis, acanthosis, a prominent granular layer, and lengthened rete ridges (Fig. 24).

Treatment: The treatment is the nightly application of a potent topical steroid to try and break the itch scratch cycle. A soap substitute should be introduced and possible irritants avoided. If the problem continues despite these measures, patch testing should be performed to exclude the possibility of an unsuspected allergen (Table 12).

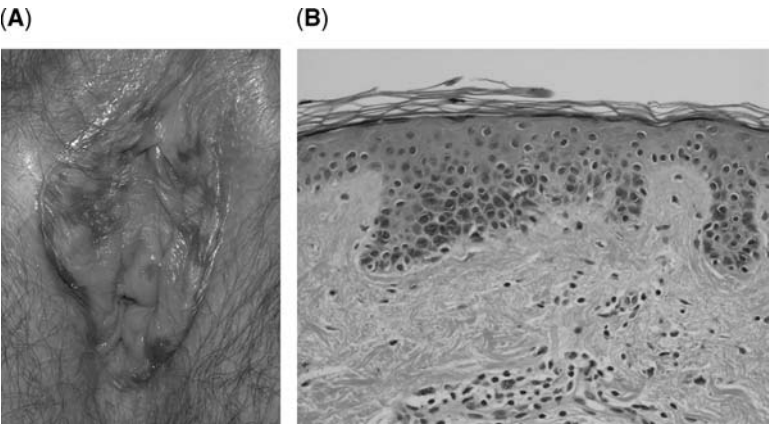


Figure 27 (A) Melanosis. Multiple pigmented areas are seen. (B) Melanosis (lentigo)—there are increased numbers of melanocytes and an increase in the amount of melanin.

Table 14 Vulvar Melanosis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Vulvar melanosis	None	Brown, gray, black pigmented macules	Postinflammatory hyperpigmentation following lichen planus, VIN	None, but requires monitoring

Abbreviation: VIN, vulvar intra-epithelial neoplasia.

Fixed Drug Eruption

FDE appears to be an extremely rare occurrence on the anogenital skin in females, whereas it is reasonably well documented in males. The author has only seen one case, which involved the mons pubis, buttocks, and nongenital sites because of fluconazole (Fig. 25A and B). The patient was treated for recurrent “thrush” with oral fluconazole and developed urticated erythematous plaques on the trunk and anogenital skin. There were no further problems on discontinuation of the repeated doses of fluconazole.

Postinflammatory pigmentation is often a striking feature of a FDE. Pigmentary changes can be the sequelae of inflammatory conditions of the vulva and may result in hypopigmentation or hyperpigmentation (Fig. 26). The hyperpigmentation may be because of either hemosiderin, which results in a reddish-brown discoloration, or *melanin*. The hemosiderin deposition is a result of extravasation of red blood cells and is seen in capillaritis, urethral caruncles, LS, Zoon’s vulvitis, and chronic vulvar purpura. Melanin pigmentation is most frequently seen following inflammatory conditions where there is a disruption of the dermoepidermal junction and the melanin pigment has dropped down into the upper dermis. It is commonly seen with LP and very occasionally with LS (Table 13).

Vulvar Melanosis

The term vulvar melanosis is used when there is extensive macular pigmentation affecting the vulvar skin only (Fig. 27A and B) with the histological changes of basal hypermelanosis and a slight increase in the number of melanocytes. The etiology is unknown and the condition runs a benign but prolonged course over many years. It is

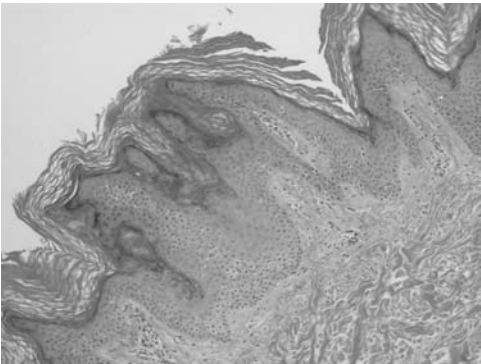


Figure 28 Acanthosis nigricans—marked hyperkeratosis and papillomatosis. Increased pigmentation is often prominent as well.

Table 15 Necrolytic Migratory Erythema

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Necrolytic migratory erythema	Weight loss, itch, and painful rash on lower abdomen and genital area; sore mouth	Erythematous patches that expand out with an eroded and scaly border. Glossitis, angular cheilitis	Tinea infection, impetiginized psoriasis or eczema	Treating any underlying glucagonoma. Correction of nutritional deficiencies

essential to have a confirmatory biopsy, because the clinical findings are frequently indistinguishable from atypical lentiginous dysplasia or even malignant melanoma (42,43).

Treatment: There is no treatment and the best management is baseline photographic documentation for self-monitoring and physician follow-up. Biopsies should be performed for any unusual changes (Table 14).

Acanthosis Nigricans

This condition is usually related to insulin resistance and rarely with malignancy. Initially, the appearance is of a dark and velvety thickening of the skin in the genitocrural folds and upper inner thigh, which later becomes warty. Skin tags may also occur (Fig. 28).

Necrolytic Migratory Erythema

This rare dermatosis occurs most frequently on the genital skin and lower abdomen. The distinctive eruption consists of an erythema with erosions, vesiculation, and bulla formation. The rash extends outward with healing and crusting at the outer edge. Postinflammatory pigmentation is common. There is also an associated weight loss, glossitis, and angular cheilitis. The patient may also have diabetes. Histologically, there is marked epidermal necrolysis and a mild dermal lymphocytic infiltrate. It is nearly always associated with an underlying pancreatic glucagonoma. The dermatosis resolves with treatment of the glucagonoma and correction of nutritional deficiencies secondary to malabsorption (Table 15).

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4

Vulvovaginal Infections

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VIRAL INFECTIONS

Varicella Zoster Virus

Varicella zoster virus (VZV) is a member of the herpes virus group. It persists in the body as a latent infection after the primary infection. Primary infection with VZV results in chicken pox (varicella). Herpes zoster (shingles) represents a one-time reactivation. VZV enters through the respiratory tract and conjunctiva.

The initial infection results from transmission through the respiratory tract from inoculation through respiratory tract secretions, respiratory contact with airborne droplets, or by direct contact or inhalation of aerosols from vesicular fluid of skin lesions. By the time the rash appears, the virus has cleared from the respiratory tract and transmission to others is unlikely. The rash of varicella is generalized and pruritic, with individual lesions advancing from macules to papules to vesicular lesions before crusting (Fig. 1). The rash first appears on the scalp and progresses to the trunk and extremities. The majority of lesions remain on the trunk in a centripetal distribution. Lesions can also be seen on the mucous membranes of the oropharynx, respiratory tract, vagina, conjunctiva, and cornea. Although mucous membrane lesions also develop as vesicles, the fragile mucous membrane blister roof, lacking a stratum corneum, is shed almost as soon as it forms, leaving round erosions. Vaginal involvement is manifested as a vaginal discharge, often purulent.

Keratinized skin lesions begin as pink papules that develop a central vesicle approximately 2 to 4 mm in diameter. Classically, these become pustular and develop a central crust, leaving an annular blister. Lesions evolve over several days and exhibit all stages of development simultaneously. Systemic signs of varicella are generally self-limited and mild. These consist of malaise, itching, and fever up to 102°F for two to three days. Adults may experience a more severe clinical course. Recovery from primary varicella usually results in lifetime immunity from another generalized outbreak of varicella, but not necessarily from reactivation of latent infection.



Figure 1 Varicella is characterized by discrete papules, vesicles, pustules, and crusts; the genital and diaper areas classically are more prominently affected than most other skin surfaces.

Herpes zoster (shingles) occurs when latent VZV resurfaces. Factors associated with recurrent disease include aging, immunosuppression, intrauterine exposure, and varicella infection at an early age. The eruption occurs unilaterally in the distribution of a dermatome supplied by a dorsal root or extramedullary cranial nerve sensory ganglion. Clinically, this is often seen on the trunk or the area of the fifth cranial nerve, but herpes zoster can appear on the buttock, perineum, and vulva (Fig. 2). Typically, two to four days prior to visible eruptions, patients report pain and paresthesia in the involved area. This is followed by discrete urticarial plaques scattered along a dermatome. Small, clustered blisters appear on the plaques, coalescing into larger bullae that may become hemorrhagic.

The differential diagnosis of varicella includes folliculitis, primary herpes simplex virus (HSV) infection or eczema herpeticum, and bullous impetigo. The diagnosis of VZV infection is generally easily made on the basis of the morphology of the skin findings. The virus can be cultured from mononuclear cells of an infected person from five days before to one to two days following the appearance of a rash. Specimens are collected from crusts or by unroofing a fluid-filled vesicle and rubbing the base with a polyester swab. A number of molecular assays for varicella antibody are available.

Complications of varicella infection include secondary bacterial infections, pneumonia, central nervous system manifestations including aseptic meningitis and encephalitis, and Reyes syndrome from VZV and aspirin exposure in young children.



Figure 2 This woman with herpes zoster shows the characteristic dermatomally distributed urticarial plaques with closely set vesicles.

In addition, complications from herpes zoster can include postherpetic neuralgia, herpes zoster ophthalmicus, and facial nerve involvement including Ramsey Hunt Syndrome. Maternal varicella may result in infection of the neonate with a fatality rate as high as 30% (1). Primary varicella infection in the first 20 weeks of gestation can be associated with a variety of abnormalities, collectively referred to as congenital varicella syndrome.

The treatment of varicella and herpes zoster with antiviral medication in immunocompetent patients is only beneficial when begun in the first two or three days. Varicella in an immunocompetent adult is treated orally with acyclovir 800 mg four times a day for five days (children receive 20 mg/kg up to the adult dose). The therapy of herpes zoster in an immunocompetent patient includes valacyclovir 1 g three times a day for one week, famciclovir 500 mg every eight hours, or acyclovir 800 mg every four hours. Immunosuppressed patients with varicella and those with complicated herpes zoster are generally admitted to the hospital for intravenous acyclovir. There are clinical trials that suggest a decrease in the likelihood or severity of postherpetic neuralgia when antiviral agents are used early in the course of herpes zoster, and other trials that suggest no benefit (2). In practice, most patients, especially the elderly who are at greatest risk for long-lasting pain, are treated with antiviral agents (3).

Immunization against varicella is now standard of care, and the efficacy is good but not perfect (4). There is concern that vaccination may be less effective than natural immunity, resulting in a higher risk of postherpetic neuralgia, but this has not been definitively proven (5). However, newer information has shown that immunization of adults decreases the incidence and severity of herpes zoster and postherpetic neuralgia (Table 1) (6).

Herpes Simplex Virus

HSV infection is a member of the herpesviridae family. Two serotypes of HSV have been identified: HSV-1 and HSV-2. HSV-1 most often affects the mouth and is usually transmitted in childhood by contact with infected saliva. HSV-2 is generally

Table 1 Varicella Zoster Virus Infections

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Varicella (primary infection)	Pruritus, pain, fever, malaise	Vesicular lesion with erythematous base	Eczema; folliculitis; herpes simplex; hand, foot, and mouth disease; rickettsialpox; impetigo	If immunosuppressed: varicella zoster immunoglobulin within 96 hr of exposure for naïve patient; otherwise, acyclovir, valacyclovir, famciclovir within 48–72 hr of rash
Herpes zoster (reactivation of latent infection)		Pink, urticarial plaques in unilateral dermatomal distribution, with central clustered, coalescing vesicles	Erysipelas, herpes simplex, contact dermatitis, folliculitis, insect bites, candida, drug eruptions	Supportive and local care; analgesics, cool/wet compresses, colloidal oatmeal baths Oral antiviral medications within 48–72 hr

associated with anogenital infection, and it usually is transmitted from anogenital or oral–genital sexual contact or transmission from a mother to her newborn. However, 14% to 47% of genital herpes results from HSV-1 (7). Thirty to fifty percent of pregnant women with a primary HSV outbreak transmit the disease to their newborn (8).

Transmission generally occurs from skin-to-skin contact and introduction of the virus into the basal cell layers of susceptible mucosal surfaces. Following the primary infection, the virus is not eliminated, but exists in a latent form in nerve cell ganglia. The trigeminal ganglia are usually involved following oral HSV infection, and the virus is harbored in the sacral nerve root ganglia, S2–S5, following genital infection.

Often, the initial infection with HSV is subclinical and asymptomatic. However, when present, this primary outbreak in the genital area is characterized by local pain, itching, and vaginal or urethral discharge. This is followed by the development of scattered painful vesicles on an erythematous base with shallow, round erosions (Fig. 3). On keratinized skin, these may be somewhat more long lived and progress to crusts. Fever, painful lymphadenopathy, headache, myalgia, herpetic urethritis, or cervicitis may also develop. Lesions generally heal in 8 to 10 days. The primary outbreak is usually eventually followed by recurrent episodes when the latent virus reactivates and affects overlying skin. These recurrences occur with variable frequency, duration, and severity. Generally, recurrent episodes exhibit clusters of vesicles or coalescing erosions, with mild or no pain and shorter duration (Fig. 4). Constitutional symptoms are mild or absent. Because the initial infection is often subclinical, the first recognized episode of HSV infection frequently exhibits the pattern of a recurrent outbreak and may occur long after the original exposure to the virus.



Figure 3 This photograph shows the scattered vesicles and round erosions that are classic for a primary herpes simplex infection.

Acute herpetic gingivostomatitis represents the primary HSV infection of the mouth. This occurs almost exclusively in children six months to five years old, and present with the abrupt onset of vesicular lesions on the oral mucosa, tongue, perioral skin, and lips. The vesicles quickly erode and develop coalescing erosions



Figure 4 Recurrent herpes simplex virus infection exhibits grouped, coalescing vesicles that often falsely appear pustular on dry, keratinized skin after several days; these become almost immediately erosive on modified mucous membranes.

on mucous membrane and crusts on keratinized skin. The gingivae are swollen, erythematous, and friable. These children have high fevers 102°F to 104°F, anorexia, dysphagia, and listlessness.

Reactivation and replication of latent virus can be induced by many factors including fever, trauma, stress, sunlight, and menses. Reactivation is most severe in immunocompromised patients. Recurrent genital outbreaks from HSV-2 are more frequent than from HSV-1.

Even in the absence of clinical recurrences, patients shed the virus asymptomatically and intermittently into the genital tract. Most HSV infections are transmitted during asymptomatic shedding. The HSV shedding rate has been reported as 15.4% of days by culture and 40.2% of days by polymerase chain reaction (PCR), with the subclinical shedding rate being 6.6% of days by culture and 27.1% of days by PCR (9). Shedding was decreased but not eliminated by chronic suppression with oral acyclovir and valacyclovir therapy (9).

The transmission of HSV from an infected mother to the neonate occurs primarily when the mother is experiencing the uncommon event of an active primary HSV infection during labor. The risk in women with recurrent disease or asymptomatic shedding is very low. However, neonatal HSV infection is very often devastating, producing severe brain damage, eye disease, skin lesions, and, often, death. Fortunately, in the past few years, the morbidity and mortality have improved substantially, although neonatal HSV remains a serious disease. The mortality has decreased from 85% to 29% in the past 30 years, and the proportion of patients with disseminated disease who are developing normally at one year has increased to 83% from 50% (10).

HSV infection of anogenital skin is sometimes confused with candidiasis, folliculitis, impetigo, and allergic contact dermatitis. The diagnosis of HSV is generally made by the onset and morphology, and confirmed by laboratory testing because this diagnosis frequently produces denial and depression. Cultures are widely available but notoriously yield false-negative results. A viral culture is performed by a vigorous swab of a vesicle that has been unroofed. The PCR evaluation is extremely sensitive but is less widely available. Swabs frequently must be mailed to an academic medical center or large commercial laboratory. A biopsy from the edge of an erosion or a sample of an intact vesicle is very sensitive test for the herpes virus but does not differentiate HSV from the VZV; that differentiation is made upon the setting. Serologic assays are often used for diagnosing recurrent disease or past exposure but do not indicate whether the current eruption is because of HSV infection.

The treatment of a genital HSV infection requires careful and caring patient education and support. Pain control and local care to include soaks and treatment of secondary infection is especially important for a primary herpetic outbreak. Occasionally, edema and dysuria require insertion of a urinary catheter. Otherwise, the use of any of the antiviral therapies for HSV infection can shorten outbreaks if given early in the course. A 10-day course of acyclovir 200 mg five times a day, valacyclovir 1 g b.i.d., or famciclovir 125 mg b.i.d. is indicated for a primary infection, and five day course of acyclovir 200 mg five times a day, valacyclovir 500 mg b.i.d., or famciclovir 125 mg b.i.d. for recurrent disease. Immunosuppressed patients sometimes require higher and/or longer dosing, or occasionally intravenous therapy. Vaccines are being investigated.

Patients who experience frequent recurrences, very severe recurrences, or who have seronegative partners may benefit from daily suppressive therapy both to avoid recurrences and to minimize (but not eliminate) transmission risk. These doses are

Table 2 Herpes Simplex Virus

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Herpes simplex virus (HSV), primary infection	Fever, lymphadenopathy, malaise, headache (may be asymptomatic)	Painful scattered vesicles and round erosions often affecting both mucous membrane and keratinized skin of the genitalia. (May be subclinical)	Herpes zoster; candidiasis; folliculitis; allergic contact dermatitis; hand, foot, and mouth disease	Acyclovir, valacyclovir, famciclovir
HSV, recurrent infection	Itching or pain followed by skin lesions, constitutional symptoms mild or absent	One or two areas of clusters of vesicles or round, coalescing erosions	Herpes zoster, candidiasis, folliculitis, allergic contact dermatitis, fixed drug eruption	If mild or late, no therapy; otherwise, acyclovir, valacyclovir, famciclovir

acyclovir 400 mg twice a day, valacyclovir 500 or 1000 mg each day, or famciclovir 250 mg twice daily (Table 2).

Human Papillomavirus

Human papillomavirus (HPV) belongs to the Papovaviridae family of double-stranded DNA viruses. Transmission of genital HPV occurs through skin-to-skin contact. There are more than 200 HPV types identified by PCR techniques. Different HPV types have preferences for different body tissues, with some types preferentially affecting the mucosa, others affecting thinner keratinized skin such as lower legs or dorsal hands, and still others found primarily on palms and soles.

Common, plantar, and flat warts are examples of extragenital skin lesions. Genitomucosal lesions can be associated with significant clinical disease. HPV types 6 and 11 are most often associated with benign disease or low-grade cervical intraepithelial neoplasia. High-grade cervical intraepithelial neoplasia (CIN), cervical squamous cell carcinoma, vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia, penile cancer, and anal cancers are traditionally associated with high-risk HPV types 16 and 18. Although 50% of the reproductive age population exhibits signs of exposure to HPV infection, only 1% to 2% of the adult population actively manifests clinical genital warts (11,12). Identifiable risk factors for genital warts and cervical dysplasia include multiple sexual partners, sexual activity at an early age, history of other sexually transmitted diseases, age of first pregnancy, previous abnormal Pap smear, cigarette smoking, poor diet, poor hygiene and immunocompromised state. Patients with an immunocompromised state often have genital warts that are resistant to treatment. While infection with HPV is strongly linked to cervical dysplasia and invasive cervical cancer, other factors are important as well. Other factors such as immune status and environmental factors are important in the development of cervical neoplasia.

Most HPV infections are temporary and asymptomatic, although occasionally large warts can produce irritation from fissuring or itching. Genital warts can present as a single or multiple papules on the penis, vulva, vagina, cervix, or perineum, on any skin covered by a bathing trunk. Additionally, lesions can extend into the urethra or rectum. Lesions are flesh colored, hyperpigmented, or pink. Otherwise, the morphology varies from acuminate, or pointed (the classic condyloma acuminatum), to flat-topped, to verrucous, and to cauliflower appearance with a narrow or broad base (Fig. 5). The lesions vary in size and often coalesce with fusion at the base. Flat, pigmented lesions are the warts that most often exhibit vulvar intra-epithelial neoplasia (VIN) 3 on biopsy, although naturally darkly complexioned patients regularly exhibit benign hyperpigmented warts.

Most lesions are self-limited in the immunocompetent patient and often resolve spontaneously. During pregnancy, lesions may increase in size and number. Patients with condylomata acuminata have an increased risk of HPV-associated cervical pathology. Persistent HPV can be associated with increased age or HPV types 16 and 18. Although genital HPV lesions acquired perinatally can appear in children up to about three years of age, sexual abuse should be considered and children at risk should be evaluated.

Cervical dysplasia is generally not visualized on examination. Evidence of moderate-to-severe dysplasia may be evident on colposcopy by punctuation or mosaicism, or acetowhite changes after treatment with acetic acid.

Mollusca contagiosa, nevi, sebaceous hyperplasia, vulvar papillomatosis, and epidermal cysts are lesions most often mistaken for genital warts. Genital warts are generally diagnosed by physical examination alone, but a biopsy to confirm

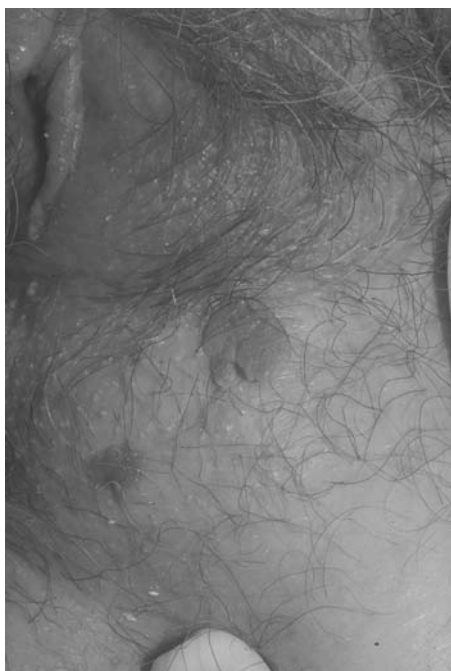


Figure 5 Genital warts can exhibit any of several morphologies. These papillomatous and flat lesions are characteristic, and the hyperpigmented nature in a light-complexioned patient should raise the suspicion of vulvar intraepithelial neoplasia, which was not present in this woman.

the diagnosis is indicated in atypical cases, and reveals the presence of koilocytes in the superficial malpighian and granular layer.

Cytologic findings on pap smear often guide the management of patients with cervical dysplasia. HPV DNA testing using hybrid capture techniques can be performed at the time of a pap smear to look for specific HPV high-risk types.

The management of genital warts includes patient education regarding the nature of genital warts, transmission, and treatment issues, as well the increased risk of cervical carcinoma. Although in the past many clinicians sought evidence for HPV in male partners to prevent reinfection, newer evidence does not indicate that a careful search is fruitful or helpful (13). Frequent Papanicolaou smears are indicated, and warts suspicious for vulvar intraepithelial neoplasia should be biopsied. There is no ideal therapy for anogenital warts, as evidenced by the very large number of treatments and treatment regimens (14). Treatments for genital warts include destructive therapies performed in the office, such as cryotherapy, excision, podophyllum resin, trichloroacetic and bichloroacetic acid, and laser (14). Home therapy with podofilox or the immune enhancer imiquimod can also be used. Because imiquimod exerts its effect at least partly by enhancing the immune system, recurrences are fewer (15). Local injections of alpha interferon are useful in some. However, recurrence following treatment is usual, and several courses of therapy are often required for definitive removal. Patients who are immunosuppressed present greater difficulties because elimination of the virus depends upon an intact immune system. Those patients with HIV treated with highly active antiretroviral medications respond much better to therapy for their genital warts than those not on medication for HIV (16).

Vaccines are under investigation, with one showing a beneficial effect for HPV 18 in women. Some reviews suggest that many are late in investigation showing promise as safe and effective prevention, while other reports describe safety but no evidence for efficacy (Table 3) (17,18)^a.

Molluscum Contagiosum

Molluscum contagiosum is a benign lesion produced by a virus that is a member of the Poxviridae family. Transmission occurs by direct skin contact with an infected individual, and when occurring on anogenital skin, it is generally sexually transmitted. However, genital mollusca in a child do not suggest sexual contact.

Most often, molluscum contagiosum is an asymptomatic infection, although when the immune system mounts an inflammatory reaction itching can occur. Molluscum contagiosum in adults primarily affects the genital, perianal, groin, upper thigh, and lower abdomen. The eruption is characterized by multiple pearly lesions, at least some of which show umbilication (Fig. 6). Often these are shiny and appear nearly vesicular, leading to the lay term “water warts.” The central umbilication contains a white, cord-like core. The lesions vary in size but are generally 1 to 3 mm. Histologically, molluscum bodies are cytoplasmic inclusion bodies within keratinocytes that contain large numbers of mature virions. The papule consists of acanthotic epithelium with hyperkeratosis. In the immunocompetent host, they often resolve without treatment within one to two years. Immunocompromised individuals may have lesions that are unusually large, numerous, and resistant to treatment.

^a Editor's note: Two multivalent vaccines against HPV have recently been approved by the FDA and marketed.

Table 3 Human Papillomavirus Infections

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Genital warts	Usually asymptomatic	Acuminate, flat-topped, verrucous, or cauliflower skin-colored, pink, or hyperpigmented papules	Vulvar/vestibular papillomatosis, sebaceous hyperplasia, nevi, condylomata, molluscum contagiosum, vulvar intraepithelial neoplasia, acrochordons, fibroepitheliomas, verrucous carcinoma	Cryotherapy, excision, podophyllum resin, trichloroacetic or bichloroacetic acid, 5-fluorouracil injection, laser, electrosurgery, podofilox, imiquimod, α -interferon
Vulvar intraepithelial neoplasia	Usually asymptomatic but can produce irritation, burning or itching	Vulvar intraepithelial neoplasia lesions vary in clinical appearance, acetowhite changes with acetic acid		Cryotherapy, imiquimod, laser, local excision to vulvectomy



Figure 6 Although the central dell seen on these mollusca contagiosa are classic, most lesions are dome shaped and the dell can be difficult to identify.

Table 4 Molluscum Contagiosum

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Molluscum contagiosum	Generally asymptomatic; occasionally may be pruritic or painful	Well-demarcated, dome-shaped, white, pink, or skin-colored glistening papules. Some with central umbilication; white central core	Condylomata acuminata, varicella, herpes simplex, milia, nevi, basal cell carcinoma, folliculitis, keratoacanthoma	Observation, cryosurgery, expression of the core either by light curettage or with a needle, podophyllin and podofilox, cantharidin, potassium hydroxide, imiquimod, cidofovir, tretinoin

Conditions that can resemble mollusca contagiosa include genital warts, folliculitis, dermal nevi, milia, and sebaceous hyperplasia. The diagnosis is generally made clinically. However, when the presentation is atypical, the diagnosis can be made when the white central core is expressed and examined microscopically to visualize brick-shaped inclusion bodies. Treatment includes observation, destruction by cryotherapy or cantharidin, and expression of the white molluscum body. More recently, open trials have suggested that topical imiquimod cream applied overnight three nights a week is beneficial, and a controlled trial of 23 children showed that imiquimod used for 12 weeks cleared one-third of patients receiving active medication as compared to one of eleven placebo patients (19). Irritation was tolerable (19,20). Other, less common therapies include podophyllum resin, potassium hydroxide, podofilox, and trichloroacetic and bichloroacetic acid. Mollusca contagiosa are a more recalcitrant problem in the immunosuppressed, and these have been shown to respond well to antiretroviral therapy in women with concomitant mollusca contagiosa and HIV (Table 4) (21).

BACTERIAL INFECTIONS

Syphilis

Syphilis is a systemic, sexually transmitted disease caused by *Treponema pallidum*. This infection initially is manifested by an ulcer at the inoculation site, but secondary skin disease and constitutional symptoms can ensue, followed by latency and late, grave disease. The signs and symptoms vary remarkably, depending upon the stage of the disease. The incidence of syphilis has increased substantially recently, and many clinicians are uncomfortable with dealing with the diagnosis of syphilis, especially obtaining samples for darkfield microscopy and interpreting the preparations.

The incubation period varies from about one week to three months, with an average of three weeks. One or a few small papules occur, and erode into a chancre, an ulcer that classically is painless, with raised, indurated borders and a clean base.

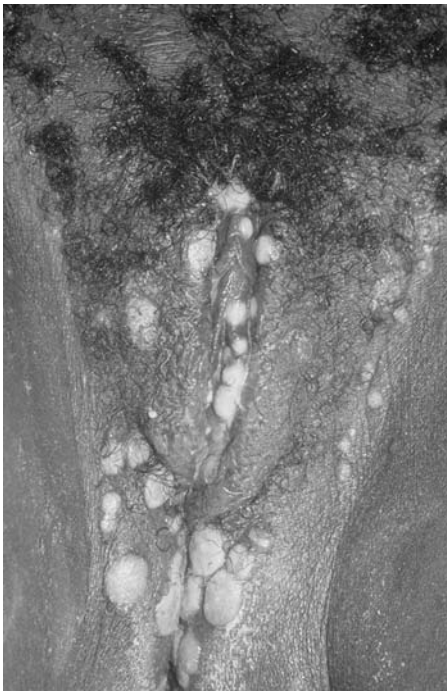


Figure 7 Condylomata lata are characterized by well-demarcated, white, flat papules when occurring on moist skin, and skin-colored on dry skin.

Local lymphadenopathy follows, and the ulcer resolves even without treatment in several weeks. Most patients then develop latent disease, but about a quarter-progress to secondary syphilis. This stage is manifested by some or all of the following: generalized lymphadenopathy, flat, skin-colored (dry keratinized skin) to moist white (mucous membrane and modified mucous membrane skin) papules of the genital skin (condylomata lata), white mucous patches of the mouth, patchy hair loss, and generalized scaling, inflamed, well-demarcated papules that show a predilection for the palms and soles (Fig. 7). This stage also resolves with or without treatment. Latent infection can ensue, followed much later by tertiary syphilis, manifested by gummas that can be life threatening.

The differential diagnosis of primary syphilis is any ulcerative genital disease, including aphthous ulcers, ulcerative HSV in an immunosuppressed host, chancroid, granuloma inguinale, and lymphogranuloma venereum (LGV). The differential diagnosis of secondary syphilis primarily includes pityriasis rosea and guttate psoriasis. The diagnosis of a chancre is made by a darkfield examination of exudate from the surface of the ulcer, performed at an experienced laboratory. Serology is negative initially. The diagnosis of secondary syphilis is made on the basis of positive serology.

Patients found to have syphilis should be evaluated for infection with the human immunodeficiency virus, because an association has been noted.

First-line treatment of syphilis is intramuscular (IM) benzathine penicillin 2.4 million units in a single dose. This is the current CDC guideline for 1° or 2° syphilis. At least one recent study shows that the combination of penicillin and 1 g of azithromycin orally is superior to penicillin alone in patients with high-serology titers, whether or not associated with HIV (22). The treatment of syphilis during pregnancy

Table 5 Syphilis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy: primary and secondary
Primary syphilis	Usually asymptomatic	Painless indurated genital ulcer with clean base	Herpes simplex virus in immunosuppressed patient, chancroid, granuloma inguinale, lymphogranuloma venereum	Benzathine penicillin 2.4 MU IM, 2 wk of tetracycline or erythromycin 500 mg q.i.d., or doxycycline 100 mg b.i.d.
Secondary	Fever, malaise	Generalized, well-demarcated, pink, scaling papules, white mucous patches, alopecia	Pityriasis rosea, guttate psoriasis	Same as above

Abbreviation: MU IM, million units intramuscularly.

is controversial (23). Benzathine penicillin 2.4 MU IM weekly for three weeks has been used, and a recent trial suggests that one dose is effective (24).

Following treatment for syphilis, serology should be followed to ensure (in the case of primary syphilis) that it remains negative, or (in the case of secondary disease) that the titers decrease at least fourfold. Those who are allergic to penicillin can be treated with tetracycline or erythromycin 500 mg q.i.d., or doxycycline 100 mg b.i.d. for two weeks. Treatment in pregnancy for penicillin-allergic patients requires special consideration because of potential impact on the fetus. Bacteriostatic rather than bacteriocidal therapy such as doxycycline should be avoided in immunosuppressed patients (Table 5).

Granuloma Inguinale

Granuloma inguinale is a chronic, progressive, sexually transmitted bacterial infection, caused by *Calymmatobacterium (Klebsiella) granulomatis*. The disease is prevalent in tropical and subtropical areas, and it is rarely seen in the United States. The incubation period is 8 to 12 weeks.

Clinically, the disease is characterized by an initial papule in the anogenital area that necroses to form an ulcerative mass with rolled edges of red granulation tissue. This tissue is highly vascular and bleeds easily with contact. Multiple ulcers may coalesce because of autoinoculation at adjacent sites. The ulcers spread and proliferate over the course of years to form large vascular granulomatous masses. If untreated, these lesions result in destruction of the genital tissue. The lesions can spread from the genital area to the thighs and lower abdomen. The course of the disease is divided into three stages. The exuberant stage involves a mass of granulation tissue. In the ulcerative stage, bacteria erode the skin to form shallow, foul-smelling ulcers. The cicatricial stage is marked by scarring and keloid formation. Patients with granuloma

Table 6 Granuloma Inguinale

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Granuloma inguinale	Painless	Granulomatous ulcers, scarring, depigmentation, disfigurement	Chancroid, chancre, lymphogranuloma venereum, anogenital amebiasis, elephantiasis, genital cancer, fungal infection	Recommended treatment: doxycycline or trimethoprim-sulfamethoxazole. Alternative treatment: ciprofloxacin, erythromycin, azithromycin

inguinale are susceptible to superinfection by other bacteria and sexually transmitted diseases, especially syphilis. Open genital ulcers are a nidus for contracting AIDS.

Other diseases in the differential diagnosis in the early ulcerative stages include other sexually transmitted ulcers, including syphilis and chancroid. Later disease with scarring and granulation tissue can be confused with hidradenitis suppurativa, Crohn’s disease, and genital malignancy. The diagnosis is usually made by punch biopsy. Donovan bodies are diagnostic and appear as intracytoplasmic inclusion bodies in hystiocytes. Complications of infection include permanent genital destruction and scarring, blockage of the urinary tract from stenosis, genital depigmentation, permanent genital swelling from lymphatic scarring, and even death. Affected areas are at increased risk of developing genital cancer.

Therapy consists of doxycycline 100 mg b.i.d. or trimethoprim-sulfamethoxazole DS b.i.d. for three weeks (8). Alternative medications include erythromycin, ciprofloxacin, and azithromycin (Table 6).

Lymphogranuloma Venereum

LGV is primarily an infection of the lymphatics and lymph nodes caused by *Chlamydia trachomatis* serotypes L1, L2, and L3. LGV is a rare disease that is more frequently seen in men than in women. Transmission is by sexual contact, primarily with asymptomatic female carriers.

The incubation period is 3 to 30 days after inoculation. Constitutional symptoms may be present, and the anorectal syndrome is more common in females and homosexual males, consisting of pruritus, pain, and tenesmus. LGV presents on the genitalia as a painless papule, shallow ulcer, herpetiform lesion, or urethritis. This lesion heals in approximately one week. The second stage begins within two to six weeks after the initial lesion and is referred to as the inguinal stage. During this stage, inguinal lymph nodes swell and form painful, firm nodes that enlarge. Bacteria travel through the regional lymphatics producing unilateral lymphangitis, referred to as buboes. These nodes may rupture or form hard masses. A classic sign of LGV is the “groove sign of Greenblatt,” formed by Poupart’s ligament crossing over enlarged femoral lymph nodes. Inguinal and femoral lymphadenopathy is seen in approximately 20% of infected females and is often unilateral (25). The rectum, cervix, and vagina are more commonly affected in females. These areas drain into

Table 7 Lymphogranuloma Venereum

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Lymphogranuloma venereum	Painful, enlarged lymph nodes	Chronic lymphangitis, esthiomene, buboes	<i>Initial stage:</i> syphilis, chancroid, genital herpes <i>Inguinal stage:</i> syphilis, chancroid, genital herpes, incarcerated inguinal hernia, inguinal lymphadenopathy <i>Anorectal stage:</i> Crohn's disease, trauma, malignancy <i>Elephantiasis:</i> tuberculosis, filariasis, fungal, parasites, granuloma inguinale	Recommended treatment: doxycycline. Alternative treatment: erythromycin, lymph node drainage or aspiration may be indicated

the iliac or perirectal nodes and may present as lower back or abdominal pain. Involvement of the iliac lymph nodes can result in pelvic adhesions. Complications include rectal strictures, stenosis, perianal abscesses, fistulas, proctocolitis, and perianal outgrowths of lymphatic tissue. If untreated, the disease can progress to genital elephantiasis, chronic lymphatic obstruction, worsening strictures and fistulas, or a “frozen” pelvis.

Other diseases to be considered in the differential diagnosis include, in those patients who recognize the early, subtle erosion or ulcer, HSV, chancre, or chancroid. Later disease can be confused with any cause of lymphadenopathy, an incarcerated inguinal hernia, or malignancy. The diagnosis is made by complement fixation, immunofluorescence, or isolation of the organism from aspiration of an infected bubo or rectal swab when proctocolitis is present.

The treatment is doxycycline 100 mg b.i.d. or erythromycin 500 mg q.i.d. for 21 days (8) (Table 7).

Chancroid

Chancroid is a sexually transmitted disease caused by inoculation of *Haemophilus ducreyi* through genital breaks in the skin. Chancroid is rare in the United States but common in Africa and some parts of Asia. It is more common in men than in

women and associated with lower socioeconomic groups. Chancroid is commonly associated with coexisting syphilis or HIV.

Within four to seven days after exposure, a tender papule arises. Within another one to two days, the lesion becomes pustular or ulcerates (Fig. 8). The ulcer is extremely painful and surrounded by erythema, and it is often foul smelling. Lesions can be solitary or by autoinoculation form multiple lesions that can coalesce into “kissing” lesions or giant ulcers. Within one or two weeks, inguinal lymphadenopathy develops in approximately 50% of patients and is usually unilateral. The lymphadenitis may become suppurative and rupture. If untreated, extensive ulceration, necrosis, genital and perineal edema, and rectovaginal fistulae can result.

The differential diagnosis includes all sexually transmitted ulcerative diseases, including HSV infection in an immunocompromised patient, as well as aphthae, Crohn’s disease, and hidradenitis suppurativa. The diagnosis of chancroid is likely if the patient has one or more painful genital ulcers and the presence of painful regional lymphadenopathy and there is no evidence of *T. pallidum* or HIV in the ulcer exudate. The diagnosis is difficult to confirm because the appropriate culture media for *H. ducreyi* is generally not available. Even in the best circumstances, *H. ducreyi* isolation has a sensitivity no more than 80%. Gram-stain evaluation classically shows coccobacilli in groups, described as “schools of fish,” or in parallel, described as “railroad tracks.”

Antimicrobial resistance is becoming more prominent with *H. ducreyi*. Antibiotic therapies include azithromycin 1 g orally or ceftriaxone 250 mg IM once, ciprofloxacin 500 mg b.i.d. for three days, erythromycin 500 mg t.i.d. for seven days, or amoxicillin/clavulanic acid 500/125 t.i.d. for seven days (Table 8) (26).



Figure 8 (See color insert) Despite the careful descriptions of differing morphologies of ulcers in the various ulcerative sexually transmitted diseases, the ulcers often appear discouragingly similar. This lesion of chancroid cannot be diagnosed on morphology alone, but rather on clinical suspicion and laboratory investigation.

Table 8 Chancroid

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Chancroid	Painful genital ulcers and painful regional lymphadenopathy	Genital ulcer, with surrounding erythema and erythematous, suppurative buboes	Genital herpes, primary syphilis, lymphogranuloma venereum, granuloma inguinale, trauma	Azithromycin or ceftriaxone, ciprofloxacin, or erythromycin base

Tuberculosis

Tuberculosis (TB) is a leading cause of death among adults worldwide. Initially, pulmonary infection is the most common site of primary disease. Extrapulmonary TB may spread by hematogenous, lymphatic, or local routes. Genital TB arises primarily from hematogenous spread after primary infection. Genital TB is nearly always pelvic disease rather than vulvar or vaginal.

Primary TB is transmitted by infected airborne particles and usually results in mild pneumonic illness that frequently is unnoticed. Following initial infection, a latent phase ensues. By the time genital disease arises, the primary infection site has healed. Rarely, primary infection by sexual transmission or contact may occur. The fallopian tubes are infected in almost 100% of genital tract cases. This is followed by the endometrium in approximately 50% of cases, the ovaries in about 20% of cases, the cervix in 5% of cases, and the vulva and vagina in less than 1% of cases (27). Clinically, patients with genital disease present with infertility, pelvic pain, or abnormal uterine bleeding. Menstrual irregularities occur secondary to direct effects on the endometrium as well as an antagonistic effect on gonadotrophic function. Generally, both fallopian tubes are severely affected. In the endometrium, significant scarring disease may mimic Asherman's syndrome. On the vulva, TB manifests as a chronic painful ulcer that spreads slowly, leaving behind scar tissue. Cutaneous TB is most often manifested by scrofuloderma (64.9%) or lupus vulgaris (21.5%) (28). Adenopathy is often present. In advanced disease, vulvar edema from scarred lymphatics or genital fistulas may present.

Diseases that could be confused with vulvar TB include hidradenitis suppurativa, late granuloma inguinale, chancroid, or Crohn's disease. Useful diagnostic tests for genital disease include hysterosalpingogram, pelvic ultrasound, laparoscopy, and hysteroscopy. Isolation of *Mycobacterium tuberculosis* from endometrial tissue, peritoneal fluid, menstrual fluid, or ulcer exudate provides definitive diagnosis but is difficult to observe because of low bacterial counts in these samples. Acid-fast staining shows red-stained bacilli. Tissue biopsies classically show granulomatous changes, central caseation, surrounding epithelioid cells, and Langerhans giant cells. Culture growth takes four to eight weeks. The tuberculin skin test (Mantoux test) is neither sensitive nor specific for genital TB.

Patients should undergo drug treatment prior to any surgical interventions. Despite treatment, pregnancy outcomes after active genital TB are poor and include increased infertility, ectopic pregnancies, and spontaneous abortions. In vitro fertilization may be promising for infertile couples in specific cases (Table 9).

Table 9 Genital Tuberculosis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Genital tuberculosis	Infertility, pelvic pain, abnormal uterine bleeding, painful vulvar ulcers, and adenopathy	Chronic painful ulcers and adenopathy, occlusion of fallopian tubes, pelvic and endometrial scarring	Tubo-ovarian abscess, pelvic endometriosis, ovarian cyst, pelvic inflammatory disease, mycotic infection, enterobiasis, carcinoma	Rifampin, isoniazid hydrochloride (INH), pyrazinamide, and ethambutol or streptomycin for 2 mo followed by two drugs, i.e., INH and rifampin for 4 mos

Abbreviation: INH, isoniazid hydrochloride.

Bacterial Vaginosis

Bacterial vaginosis is polymicrobial in origin and caused by changes in the normal vaginal flora. It primarily affects reproductive-age women and is associated with sexual activity, although transmission is not fully understood. Risk factors include multiple sexual partners, a new sexual partner, non-white race, previous pregnancy, intrauterine device, and use of douches. There is a reduction of hydrogen peroxide-producing lactobacilli and an increased growth of *Gardnerella vaginalis* and gram-negative anaerobes such as *Mycoplasma hominis*, Prevotella species, Peptostreptococcus species, Bacteroides, and Mobiluncus. An increased production of amines and alkalization of the vaginal discharge create the characteristic fishy odor.

Clinically, patients complain of an increased volume of foul-smelling vaginal discharge that is off-white, thin, and homogenous. Many women remain asymptomatic. Uncommonly, patients describe accompanying irritation. Vaginal secretions are characterized by a lack of lactobacilli with a resulting alkaline pH, as well as normal number of white blood cells (hence the term “vaginosis” rather than “vaginitis,” denoting the lack of inflammation). The characteristic fishy odor is especially noticeable in the presence of an alkaline substance, such as semen or 10% KOH added to vaginal fluid (the “whiff” test). Another hallmark is the presence of clue cells, epithelial cells studded with bacteria that obscure the sharp margins of the cell, leaving ragged borders.

The differential diagnosis includes any cause of vaginitis, including candidiasis, atrophic vaginitis, bacterial vaginitis, desquamative inflammatory vaginitis, trichomonas, and erosive skin diseases such as lichen planus. The diagnosis is made by the presence of a noninflammatory thin vaginal discharge that adheres to the vaginal wall, a vaginal pH more than 4.5, a positive whiff test, the presence of clue cells on wet mount, and a lack of lactobacilli and signs of inflammation.

Bacterial vaginosis facilitates transmission of HIV and other sexually transmitted diseases (29). In addition, vaginal shedding of HIV is increased in the presence of bacterial vaginosis (30). Several studies have shown that bacterial vaginosis is associated with an increase in premature labor, low-birth-weight infants, and chorioamnionitis. Bacterial vaginosis has also been linked with pelvic inflammatory disease, endometritis, posthysterectomy vaginal cuff cellulitis, and postpartum fever. Currently, there is no recommendation to treat male sexual partners.

Table 10 Bacterial Vaginosis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Bacterial vaginosis	Foul-smelling discharge	Increased thin adherent discharge, clue cells seen under microscope	Trichomonas vaginitis, atrophic vaginitis, vulvovaginal candidiasis	Oral metronidazole, topical metronidazole gel, 2% clindamycin cream

The therapy of bacterial vaginosis includes oral metronidazole 500 mg b.i.d. for a week or 2 g once, or clindamycin cream 2% h.s. at bed time daily for 7 days, or orally 300 mg b.i.d. for three to five days. Recurrence is common, and more prolonged suppression is sometimes useful (Table 10).

Staphylococcus aureus

Staphylococcus aureus genital skin infections vary in appearance and severity. The staphylococcal bacterium is characterized by gram-positive cocci in clusters under the microscope. Bacteria often gain access to underlying tissue through abrasions, burns, bites, cuts, fissures, or surgical incisions. Both community-acquired and hospital-acquired staphylococcal infections have continued to rise.

Genital staphylococcal infections are most often manifested as impetigo (superficial epidermal infection), folliculitis (superficial infection of follicular epithelium), furunculosis (deep suppurative infection of follicles, often with limited surrounding cellulitis), and cellulitis (infection of soft tissue.) Fairly often, one or more of these morphologies are present concomitantly.



Figure 9 Staphylococcal impetigo typically shows very superficial and fragile blisters manifested clinically by round erosions with peeling of the periphery, which represents the remnants of the blister roof.

Impetigo primarily affects children and there is no predilection for the genital skin. These lesions are characterized by very superficial vesicles produced by a staphylococcal toxin. The vesicle ruptures and leaves behind a superficial erosion and the development of a yellow crust surrounded by a base of erythema when occurring on keratinized skin (Fig. 9). The lesions are multiple and of varying duration.

Patients with folliculitis present with painful red papules overlying a hair follicle (Fig. 10). Folliculitis can be exacerbated by friction, shaving, or other trauma to the pubic hair-bearing area. These lesions sometimes enlarge to form furuncles, which are painful, red nodules measuring 1 to 2 cm (Fig. 11). The center of the lesion is filled with purulent material that releases by rupture or surgical incision. Carbuncles represent coalescing furuncles. Constitutional symptoms of fevers, generalized malaise, and chills are uncommon unless significant cellulitis is present.

Cellulitis consists of soft-tissue infection, usually accompanied by fever and other constitutional symptoms. Affected areas are painful, firm, edematous, and red, often with a peau d'orange appearance (Fig. 12). The area is sometimes purulent with abscess formation. This often occurs as extension from furunculosis or inoculation following trauma such as surgery, and it is more common in immunosuppressed patients and those who are diabetic. Uncommonly, extension of infection to deeper tissues and progression to polymicrobial disease represent soft-tissue necrotizing infection (Fournier's gangrene), often with anaerobic and gram-negative organisms.

Staphylococci produce many toxins such as cytotoxin, pyrogenic toxin, toxic shock syndrome toxin, and exfoliative toxin that characterize their destructive course. Toxic shock syndrome was first described in the 1980s associated with the introduction of extra superabsorbent tampons. Clinical manifestations are most often caused

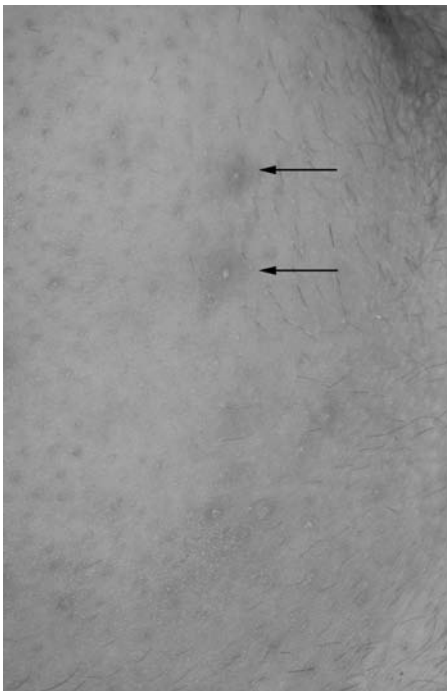


Figure 10 Bacterial folliculitis is almost always staphylococcal and exhibits scattered red papules and pustules; sometimes a hair can be visualized in the center of a lesion.

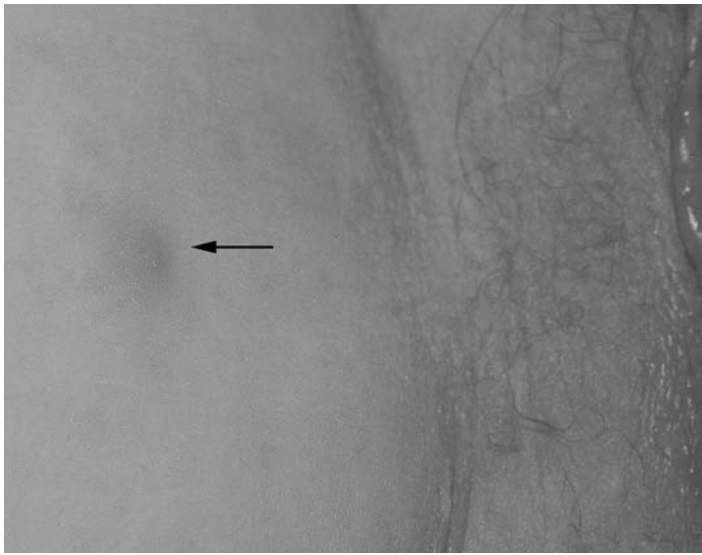


Figure 11 Furunculosis represents deep follicular infection that extends to surrounding tissue, producing a firm, tender red nodule.

by toxic shock syndrome toxin produced by *S. aureus*. Initial signs of infection may include myalgias, fevers, vomiting, and diarrhea. Patient status can decline within a matter of hours into hypovolemic shock and a dark red sunburn rash. On exam, vaginal inflammation and vaginal discharge are present. Local cultures



Figure 12 Cellulitis is characterized by diffuse inflammation and pain, often associated with systemic signs of infection; darkly complexed patients often do not exhibit redness as a sign of inflammation, and instead the skin can be normal in color or apparently hyperpigmented.

and blood cultures are positive. Recently, nonmenstrual toxic shock syndrome has been defined in the literature and is associated with worsened renal and neurologic impairment.

The therapy of staphylococcal skin infections consists of antibiotics. Localized impetigo or folliculitis can be treated successfully with mupirocin ointment, but most skin infections are more widespread or deeper, responding best to systemic therapy. Essentially all *S. aureus* is resistant to penicillin, but until recently cephalexin, methicillin, oxacillin, and erythromycin were nearly always effective for these infections, especially when community acquired. Now, however, community-acquired methicillin-resistant disease has become common, in both urban and rural setting, sometimes accounting for the majority of infections and producing more severe disease than susceptible forms (31,32). Trimethoprim-sulfamethoxazole and vancomycin are usually effective for these patients, although resistance to these occurs at times. Fortunately, linezolid is a new antibiotic that is usually effective for methicillin-resistant *S. aureus* and available for oral administration (33). Unfortunately, there are now reports of resistance to linezolid from Germany (34). The treatment of toxic shock syndrome involves supportive care, fluid replenishment, and the addition of parenteral beta-lactamase-resistant antistaphylococcal antibiotics and aminoglycosides (Table 11).

Table 11 Staphylococcal Infection

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Staphylococcal infection	Tenderness, burning, constitutional symptoms	Erythema, induration, purulent exudates, lymphadenopathy	<i>Folliculitis:</i> herpes simplex, varicella, candidiasis, dermatophytes, pseudomonas <i>Furuncle:</i> granuloma inguinale, hidradenitis suppurativa, lymphogranuloma venereum	Local sterile cleansing, possible debridement, possible incision, and drainage First choice— β -lactamase-resistant antistaphylococcal antibiotics: cloxacillin, dicloxacillin, nafcillin, oxacillin (penicillin V for penicillin G-sensitive organisms) cephalexin, clindamycin Methicillin-resistant <i>Staphylococcus aureus</i> : depends upon sensitivities

Necrotizing Fasciitis (Deep Tissue Necrotizing Infection)

The term “necrotizing fasciitis” was first used by Wilson in 1952 to describe bacterial infection producing necrosis of the fascia and subcutaneous tissue with sparing of the underlying muscle. Over half of these infections occur on the perineum, where they are called Fournier’s gangrene (35). Common recent terminology that is less specific but includes serious destructive necrotizing infection is that of deep tissue necrotizing infection. These infections share common causes and treatment. The disease most often begins with a streptococcal infection in a breach in the skin in an immunosuppressed or diabetic patient, and perforating vessels are destroyed as the decomposition progresses, producing overlying ischemic necrosis. With the destruction of vessels, antibiotics cannot be delivered to the center of the necrotic and infected areas. The infection often becomes polymicrobial, with gram-negative organisms and anaerobic bacteria frequently playing a role. Gas-producing bacteria are fairly common, producing “gas gangrene.”

The mortality rates of necrotizing fasciitis range from 6% to 76%. Mortality rates increase with delayed diagnosis and delayed surgical debridement. On the vulva and perineum, the infection may follow trivial injury such as a vulvar biopsy or folliculitis. However, it is more often seen after episiotomy, vulvar surgery, or vulvar abscess formation. Immunocompromised conditions such as advanced age, diabetes mellitus, chronic renal failure, cancer, and illicit drug use are risk factors for this disease process. Classic diagnostic signs are not always present.

Early clinical signs and symptoms include poorly demarcated areas of intense skin pain and pallor. Blister or bulla formation represents the beginning of critical skin ischemia. Later signs include hemorrhagic bullae, skin anesthesia from nerve



Figure 13 (See color insert) Necrotizing fasciitis is characterized by hemorrhagic bullae because of ischemia from underlying infection that has destroyed the cutaneous vascular supply; resulting ulceration and hemorrhage can be seen in this patient who is in the healing phase.

damage, and skin gangrene (Fig. 13). Tissue crepitus may be palpable. Systemic manifestations may include high fever, hypotension, multiorgan failure, and systemic shock. Symptoms usually develop within hours or several days with rapid progression. Histologically, the bacteria proliferate within the superficial fascia and tissue necrosis is present. Enzymes and toxins produced allow for superficial spread of the bacteria. Angiothrombotic microbial invasion and liquefaction necrosis ensue.

The differential diagnosis includes cellulitis, which can sometimes be indistinguishable, brown recluse spider bite, and bullous pyoderma gangrenosum. A plain radiograph, computed tomography (CT), ultrasound, or magnetic resonance imaging may be helpful in diagnosis. Plain radiographs can show soft-tissue air in some patients. On CT, findings include deep fascial thickening, enhancement, and fluid and gas in the soft-tissue planes. Fine-needle aspiration or incisional biopsy may also be helpful for diagnosis when necrotizing fasciitis is suspected. A stab incision yields decomposed necrotic tissue rather than the inflamed and edematous tissue of cellulitis. During surgery, findings include a lack of tissue resistance, lack of bleeding of the fascia during dissection, and foul-smelling dishwater-colored pus. Laboratory values include an elevated white cell count, glucose, urea, and creatinine. Hypoalbuminemia, acidosis, and an altered coagulation profile may also be present.

The most important aspect of management is early diagnosis, antibiotics, and aggressive debridement (36). Methicillin-resistant *S. aureus* has been reported in community-acquired necrotizing fasciitis, so that this should be considered in the choice of an antibiotic (37). Hyperbaric oxygen has been suggested by some, but this has not been shown to be of use in other series (38). Polyspecific immunoglobulin may be beneficial adjunctive therapy (39). Management requires early diagnosis, immediate resuscitation, aggressive and repeated surgical debridement, hyperbaric oxygen, and broad-spectrum antibiotics (Table 12).

Erythrasma

Erythrasma is a superficial bacterial infection of skin folds that mimics tinea cruris. Caused by *Corynebacterium minutissimum*, this medically insignificant disease occurs primarily in men.

Usually, erythrasma is asymptomatic. Morphologically, it is characterized by well-demarcated, pink/tan, lightly scaling, or slightly crinkled plaques that, in the

Table 12 Necrotizing Fasciitis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Treatment
Necrotizing fasciitis (deep necrotizing soft-tissue infection)	Severe pain disproportionate to local findings, systemic shock	Erythema, swelling, blisters and hemorrhagic bullae, indistinct margins	Cellulitis, erysipelas, brown recluse spider bite, bullous pyoderma gangrenosum	Early diagnosis, resuscitation, surgical debridement, broad-spectrum antibiotics, with or without hyperbaric oxygen to affected tissues



Figure 14 (See color insert) Erythrasma resembles tinea cruris, but the color is often more tan than red, and there is no peripheral accentuation of scale.

genital area, occur on the proximal, medial thighs with sparing of the vulva proper (Fig. 14). Unlike tinea cruris, there is no accentuation of peripheral scale, and a microscopic examination of scrapings of the stratum corneum does not show fungal elements.

The differential diagnosis includes, in addition to tinea cruris, lichen simplex chronicus (eczema/localized atopic dermatitis) and psoriasis. The diagnosis is made by the absence of fungal elements on a microscopic examination, or by illumination with a Wood’s lamp, which produces a coral fluorescent color. The diagnosis is confirmed by response to therapy.

The treatment of erythrasma consists of erythromycin, either oral (500 mg) or topical application twice daily for one or two weeks, but topical erythromycin has the higher cure rate in the groin (40). Recurrence is common and chronic therapy is sometimes required (Table 13).

Bacterial Vaginitis

Bacterial vaginitis is an uncommon, but by no means rare, cause of vaginitis. Distinct from bacterial vaginosis, bacterial vaginitis can occur with group B Streptococcus with no apparent risk factors, and as a result of secondary infection with any of several bacteria, most often in a setting of a foreign body, atrophic vaginitis, or an erosive disease such as lichen planus (41–43).

Table 13 Erythrasma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Erythrasma	None	Pink-tan, lightly scaling plaques on proximal, medial thighs	Tinea cruris, psoriasis, eczema, candidiasis	Erythromycin 500 mg b.i.d. or topical erythromycin solution b.i.d. until clear

Bacterial vaginitis can occur in any age group, but group B Streptococcal infection is found primarily in the well-estrogenized vagina, and alpha hemolytic Streptococcus is seen most often in prepubertal girls, sometimes in association with perianal streptococcal dermatitis. Bacterial vaginitis is most often characterized by irritation, burning, and dyspareunia, although some patients describe itching. Women often report a yellow vaginal discharge, but odor is not prominent. Vestibular and vaginal erythema is usual, and a yellow or yellow/green vaginal discharge is present (Fig. 15). The vaginal pH is high, and a microscopic examination of a wet mount shows a high proportion of immature epithelial cells and a striking increase in neutrophils. Lactobacilli are generally absent. In the event of a group B Streptococcal infection, chains of cocci are often evident (Fig. 16).

The differential diagnosis includes atrophic vaginitis, the postpartum vagina, desquamative inflammatory vaginitis, trichomoniasis, and any disease causing vaginal erosions, such as erosive lichen planus and even a vaginal HSV infection. The use of a caustic chemical in the vagina, such as fluorouracil, can produce similar findings.

The diagnosis is made by the setting, a culture, and response to therapy. In the event of a secondarily infected underlying process, such as a foreign body, atrophic vaginitis, or erosive lichen planus, the response to therapy may be incomplete and short-lived until the underlying process is identified and corrected. Group B Streptococcus is more often a colonizer than a pathogen (42,43). However, in the setting of vaginal inflammation and symptoms, this organism can produce an inflammatory vaginitis.

The therapy of bacterial vaginitis consists of an oral or intravaginal antibiotic directed toward the causative organism as well as the correction of any underlying predisposing conditions. A bacterial culture should reveal the organism and its susceptibilities to antibiotics. In the case of group B Streptococcus, the patient can be treated with intravaginal clindamycin nightly for several weeks or with a penicillin



Figure 15 (See color insert) In uncommon cases, bacterial vaginitis can occur, extending to infect the skin and producing red, scaling, or exudative skin.

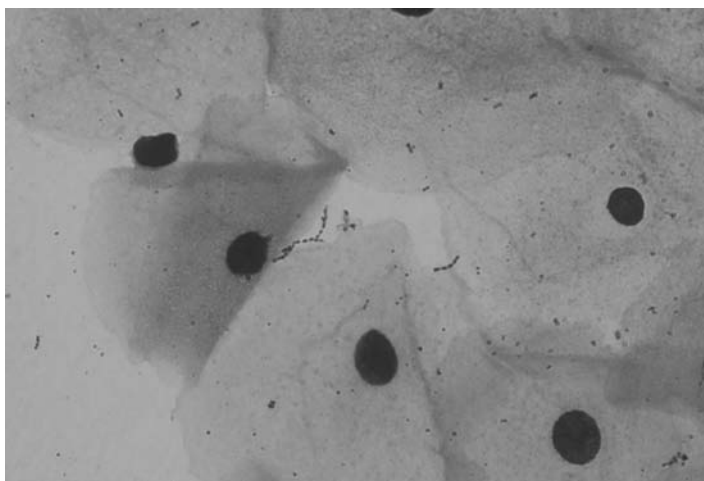


Figure 16 Group B streptococci are usually colonizers that produce no symptoms, but occasionally can cause irritation and fissuring that recurs immediately after cessation of therapy.

(penicillin V potassium, amoxicillin, or ampicillin) orally. Patients should be reevaluated while on medication for response of symptoms and vaginal inflammation to therapy. Nearly immediate relapse is extremely common. More prolonged therapy, sometimes several months, may be required. A positive culture is frequently seen in asymptomatic patients, with or without vaginal discharge.

For those patients whose cultures show other organisms, most often *S. aureus* or alpha hemolytic Streptococcus, an underlying process should be sought and treated in addition to antimicrobial therapy. The vagina should be examined for a foreign body (most often toilet paper or a retained tampon) and the vagina, oral mucosa, and vulva should be evaluated for signs of erosive disease such as lichen planus. A history normally makes the diagnosis of an accompanying atrophic vaginitis or postpartum vagina. Sometimes, an evaluation of the vagina after treatment of the bacterial infection better reveals any concomitant abnormalities (Table 14).

FUNGAL INFECTIONS

Candidiasis

Vulvovaginal yeast infections are very common, medically trivial but sometimes symptomatically miserable infections. Most women and many physicians rightly or wrongly attribute nearly all vulvovaginal symptoms to vulvovaginal candidiasis.

The majority of vulvovaginal yeast is produced by *Candida albicans*, but an increasingly large proportion of yeast infections involve *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, *Candida lusitanae*, *Saccharomyces cerevisiae*, or even less common organisms (44). Because the colon is a natural reservoir for yeast, occluded, moist, warm anogenital skin provides an ideal environment for infection, particularly in the setting of risk factors such as use of antibiotics, vigorous sexual activity, diabetes, incontinence, immunosuppression, and obesity.

The symptoms and clinical abnormalities of vulvovaginal candidiasis are extremely variable. *C. albicans* and *C. tropicalis* most often present with introital itching, and the less common widespread vulvar involvement produces more widespread itching. Other yeast forms generally only affect the vagina and vestibule, and produce

Table 14 Bacterial Vaginitis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Bacterial vaginitis	Introital irritation, dyspareunia, discharge	Erythema of the vestibule and vagina; vaginal secretions with increased white blood cells, immature cells	Atrophic vaginitis, desquamative inflammatory vaginitis	Topical or systemic antibiotics, evaluation for underlying factors

symptoms of burning, irritation, rawness, and soreness rather than itching. Women and infants who are estrogen deficient rarely experience vaginal yeast infections, although the anogenital skin can certainly exhibit *C. albicans* infections.

Most often, the physical examination only shows vestibular erythema. However, more severe infections exhibit more of the following vulvar abnormalities: erythema, edema of the modified mucous membranes, a superficial, shiny “glazed” texture, fissuring of skin folds, peripheral scale and peeling, and satellite red papules, pustules, and collarettes (circular scale that represents the edges of a desquamated blister roof) (Figs. 17 and 18). The vagina may or may not exhibit erythema. Although vaginal secretions are generally reported as a dry “cottage cheese” consistency, vaginal secretions are often normal clinically.

The differential diagnosis consists of several of the diseases characterized by itching, redness, and fissuring. Most common is lichen simplex chronicus (eczema/atopic dermatitis), often with intermittent, superimposed *Candida* infection. Lichen



Figure 17 (See color insert) Vulvovaginal candidiasis can produce redness, edema, and fissuring.



Figure 18 Candidiasis of dry, keratinized skin such as the labia majora and crural creases is manifested as very superficial and fragile pustules that rupture almost immediately, leaving desquamating collarettes.

sclerosus and irritant or allergic contact dermatitis are also common confusing processes. Often, patients with chronic symptoms of vulvodynia are misdiagnosed with vulvovaginal candidiasis, but vulvodynia should produce symptoms of irritation, rawness, or burning rather than itching.

The diagnosis can be suspected by the history and physical examination, but this should be confirmed by microscopic examination or culture. Vaginal secretions of patients with *C. albicans* or *C. tropicalis* infection examined on a wet mount or potassium hydroxide preparation shows branching hyphae/pseudohyphae with budding yeast. Lactobacilli are nearly always abundant, resulting in a normally acid vaginal pH. White blood cells can be either increased or normal in number. Otherwise, nonalbicans *Candida* infection shows only budding yeast, which can be more difficult to visualize microscopically. Therefore, negative microscopic evaluations should be followed up by culture. In addition, recalcitrant yeast infections should be reevaluated by culture as false-positive microscopic examinations because of artifacts are common and patients are sometimes labeled incorrectly as having resistant or recalcitrant yeast infections.

The treatment of vulvovaginal candidiasis is usually very easy. There are multiple therapies available, and all are quite effective for *C. albicans* and *C. tropicalis*. Topical and oral azoles all very effectively treat vulvovaginal *C. albicans* infections. Diflucan 150 mg by mouth is an effective treatment approved by the U.S. Food and Drug Administration (FDA), and trials have shown itraconazole 200 mg a day for three days to be beneficial as well (45). Patients with marked vulvar involvement may require more vigorous treatment, and those with substantial inflammation and fissuring sometimes experience burning with application of these creams. These patients often require several days of an oral azole or the application of soothing

nystatin ointment in addition to standard treatments for vaginal candidiasis. Although more is being written about resistant *C. albicans* in immunocompetent patients, these authors have not observed this phenomenon. All “resistant” yeast infections in immunocompetent women have been either nonalbicans *Candida* infection or a different underlying diagnosis altogether.

Nonalbicans *Candida* infections are frequently resistant to therapy (46). Generally, a course of any standard anticandidal therapy is prescribed. Those who fail this are usually given either boric acid vaginal capsules 600mg once or twice a day for two to four weeks or flucytosine cream (47). Nystatin vaginal tablets or ointment twice a day for two to four weeks is a time-honored and soothing treatment that occasionally is useful in nonalbicans *Candida* infections resistant to azoles. Gentian violet can be beneficial but irritating. Amphotericin intravaginally has been used with some success (48). Very often, the infection does not clear, but symptoms can be controlled with less frequent dosing.

Some patients experienced frequently recurrent vulvovaginal candidiasis. These patients can generally be managed with fluconazole 150 mg weekly (49), although a very rare patient requires every fourth day dosing. Medication is continued for three to six months. In some women, the fluconazole has broken this cycle and can be discontinued. Other patients require a longer course. Hepatotoxicity is not a major concern with weekly dosing, but some clinicians obtain liver function tests several times a year. Some women benefit from oral or topical therapy as a preventive at times of high-risk such as during antibiotic therapy, vigorous sexual activity, or before menses.

Although some clinicians and patients believe that diet, use of oral or vaginal lactobacillus supplements, and special disinfecting of underwear can minimize or treat vulvovaginal candidiasis, there are no data to support these beliefs (50,51). In addition, there is no evidence that vulvovaginal candidiasis produces systemic symptoms of depression, bloating, constipation, headaches, etc (Table 15).

Table 15 Vulvovaginal *Candida Albicans*

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Vulvovaginal <i>Candida albicans</i>	Vulvovaginal pruritus	Variable from no abnormalities on examination to vulvar erythema, edema, scale, collarettes, vaginal redness. Vaginal secretions sometimes white and clumped, always with fungal elements microscopically	Vulvar disease—psoriasis, lichen simplex chronicus/eczema, tinea cruris; Vaginal disease—bacterial vaginosis, bacterial vaginitis, desquamative inflammatory vaginitis, atrophic vaginitis, vulvodynia/vestibulitis (vestibulodynia)	Topical—any azole cream q.d.–b.i.d. to the vulva, cream or suppository hours one to seven nights, oral—fluconazole 150 mg PO once
Non-albicans <i>Candida</i>	Irritation, soreness, burning	Normal exam, budding yeast microscopically	Vulvodynia/vulvar vestibulitis (vestibulodynia)	Same as for <i>C. albicans</i> if resistant. Boric acid, nystatin, flucytosine, gentian violet, amphotericin

Tinea Cruris

Tinea cruris, a dermatophytosis infection of the anogenital skin, represents “ring-worm.” Also called “jock itch,” this is a disease much more common in men than in women. Primarily caused by *Epidermophyton floccosum*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*, tinea cruris often represents infection that has spread from the great toe nails (onychomycosis) or the feet (tinea pedis), also infections that are much more common in men. Obesity also predisposes to tinea cruris (52).

The predominant symptom of tinea cruris is that of itching. The rash occurs primarily on proximal, medial thighs, sometimes extending to the crural crease and hair-bearing labia majora. Because dermatophytes infect the stratum corneum of clinically hair-bearing skin, the modified mucous membranes are spared and the vagina is never affected. Classically, tinea cruris presents as well-demarcated, red, scaling plaques of the proximal, medial thighs, with the borders exhibiting more marked scale. Often, there is central clearing, and the infection progresses peripherally (Fig. 19). Sometimes, fungal organisms track down hair follicles, producing fungal folliculitis manifested by palpable red papules within the plaque. This is most marked in women with coarse terminal hair and this is almost universal in patients who have treated their tinea cruris with topical corticosteroids (Fig. 20).

The differential diagnosis of tinea cruris includes any red, scaling infection or dermatoses that can affect this area. Candidiasis, psoriasis, lichen simplex chronicus (eczema/localized atopic dermatitis), irritant or allergic contact dermatitis, and erythrasma are the most likely diseases requiring differentiation.

The diagnosis is made tentatively by the location and morphology, particularly when seen in the patient with fungal infection of the feet. The diagnosis is confirmed

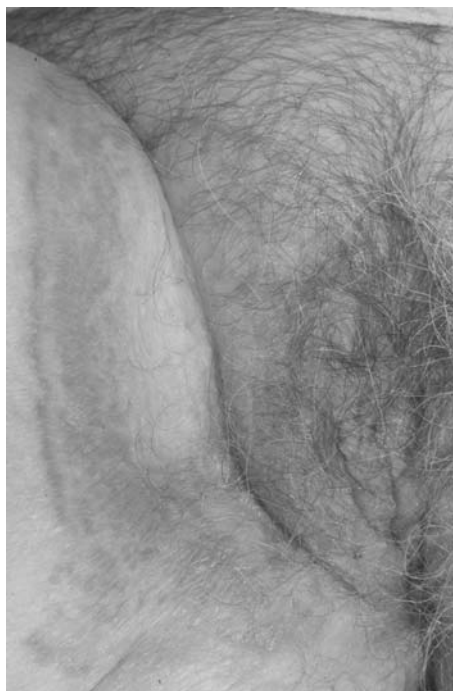


Figure 19 (See color insert) Classic tinea cruris shows a red plaque on the proximal, medial thighs with accentuation and scale at the periphery of the plaque.

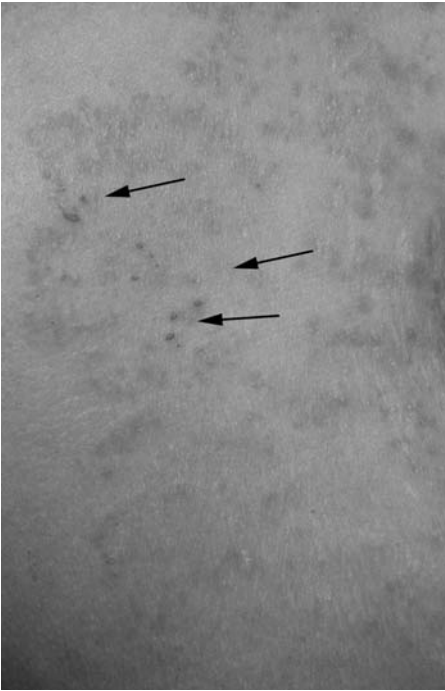


Figure 20 Tinea cruris that is treated with a steroid as well as a topical antifungal agent is less likely to completely clear, and this patient has developed an associated fungal folliculitis manifested by red papules within the plaque.

by a microscopic examination of scrapings of the stratum corneum, culture, or response to therapy.

The treatment of tinea cruris depends upon its extent. Those patients with limited disease and no signs of fungal folliculitis usually respond to any topical azole applied once or twice a day. Miconazole, clotrimazole, econazole, and ketoconazole are those most often marketed for this problem. However, any azole used for vulvovaginal candidiasis is also effective and often more inexpensively available over the counter. These include tioconazole and butoconazole. Topical terbinafine used once or twice a day is also effective (53). Nystatin is useless for dermatophytosis. Extensive disease, clinical fungal folliculitis, and disease in an area of marked terminal hair are best treated with an oral medication. Griseofulvin 500 mg twice daily, terbinafine 250 mg daily, fluconazole 100/200 mg a day, and itraconazole 200 mg a day are all highly effective and safe. A trial of itraconazole given as 200 mg on two or three occasions showed cure rates of 86% to 100% (54). Patients should be reevaluated after about two weeks for clinical cure. Recurrence is common when fungal infection of the feet is present. Early treatment of recurrent disease with a topical medication is generally effective. Alternatively, onychomycosis can be more definitively treated with standard doses of itraconazole or terbinafine (Table 16).

Pityriasis Versicolor

Pityriasis versicolor is a fungal infection of keratinized skin produced by several different kinds of *Malassezia* species (55). Also known by the misnomer, tinea

Table 16 Tinea Cruris

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Tinea cruris	Pruritus	Red, well-demarcated scaling plaques with accentuation of peripheral scale on proximal, medial thighs	Psoriasis, lichen simplex chronicus/eczema, candidiasis, erythrasma	Any topical azole cream or terbinafine. If fungal folliculitis is present, oral griseofulvin, fluconazole, itraconazole, terbinafine

versicolor, this is not a dermatophytosis, but rather an infection of yeast forms. Like tinea cruris, this is an infection much more common in men than in women.

Generally, pityriasis versicolor is asymptomatic. An occasional patient describes itching. Morphologically, this infection is characterized by almost macular, coalescing papules that exhibit very subtle and fine scale on close examination (Fig. 21). These papules can be pink, tan, or hypopigmented, hence the term “versicolor.” Pityriasis versicolor most often begins on the upper, central back and chest, and papules coalesce into larger plaques and then extend preferably to the proximal arms. Very occasionally, scattered papules extend as far as the lower abdomen and mons.

The differential diagnosis includes dermatoses with papulosquamous morphology. These include, primarily, secondary syphilis, tinea corporis, pityriasis rosea, and guttate psoriasis. The diagnosis is made by the identification of typical pityriasis versicolor on the trunk and confirmed by direct microscopic visualization of the hyphae/pseudohyphae and budding yeast within the stratum corneum of skin scrapings.

Treatment consists of either topical azoles as used for tinea cruris or a very short course of an oral azole such as ketoconazole 400 mg per week for two doses



Figure 21 (See color insert) Pityriasis versicolor is characterized by hypopigmented, pink, or tan (as seen here) well-demarcated flat papules with very subtle scale.

Table 17 Pityriasis Versicolor

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Pityriasis versicolor	Usually none; occasional mild irritation or pruritus	Pink, brown, or hypopigmented, well-demarcated, lightly scaling 2–10 mm papules coalescing into larger plaques centrally at times	Pityriasis rosea, secondary syphilis, guttate psoriasis, tinea corporis/cruris	Any topical azole cream applied one to two times a day until clear; if extensive, ketoconazole 100 mg/day for 5 days or fluconazole 300 mg/wk for 2 weeks

or fluconazole 300 mg twice, one week apart (56,57). Itraconazole given orally as a one-time dose of 400 or 200 mg a day for a week is effective as well (58). Selenium sulfide shampoos and lotions are frequently irritating and annoying in the anogenital area and generally should be avoided.

Pityriasis versicolor is frequently a recurrent condition, and patient should be advised that retreatment may be necessary in the future. Some patients benefit from once or twice monthly application of an azole cream to prevent recurrence. Oral itraconazole given intermittently has also been shown efficacious for the prevention of recurrent pityriasis versicolor (Table 17) (59).

PARASITIC INFECTIONS

Trichomonas

Trichomonas vaginitis is a sexually transmitted infection produced by the protozoan *Trichomonas vaginalis*. The organism is found not only in the vagina but also in the urethra and in Skene's glands and paraurethral ducts.

The primary symptom of *Trichomonas vaginitis* is severe pruritus, irritation, and, often, vulvar dysuria, accompanied by a grossly and microscopically purulent vaginal discharge. Sometimes, pelvic pain is present. The severity of disease varies widely, with some patients exhibiting fairly mild symptoms and signs. The infected male partner is usually asymptomatic. A physical examination reveals deep redness of the introitus, vagina, and cervix, classically but nonspecifically and unpredictably producing a "strawberry cervix." This finding is characterized by a red cervix covered with monomorphous, discrete, bright-red, tiny papules. Vaginal secretions are most often described as yellow and frothy. Microscopically, vaginal secretions show small (about the size of white blood cells), rapidly moving, teardrop-shaped, flagellate organisms that quickly lose motility and distinctive shape as they cool. In addition, very large numbers of neutrophils are present and lactobacilli are absent, resulting in a high vaginal pH.

The differential diagnosis includes all causes of purulent, inflammatory vaginitis. Desquamative inflammatory vaginitis, atrophic vaginitis, and the occasional

bacterial vaginitis (not vaginosis) produce vestibular and vaginal/cervical erythema and vaginal secretions with similar microscopic findings. However, the causative organism is absent. The diagnosis is made by the setting and the identification of the organism microscopically.

Treatment consists of oral metronidazole 500 mg twice a day for one week or 2 g orally in one dose. Topical medications are not sufficient because of the organisms protected within the urethra and paraurethral ducts. Sexual partners should be treated as well. *Trichomonas* resistant to metronidazole occurs occasionally, and those patients can be treated with tinidazole (Table 18) (60,61).

Scabies

Scabies is an excruciatingly pruritic skin infection produced by the mite, *Sarcoptes scabiei*. The mite is transmitted by close contact with an infected person, and infects the stratum corneum of the skin. The itching occurs after a week or two, as a result of the host immune response to the presence of the mite. Therefore, not all infected people may be symptomatic initially.

In addition to the intense itching, which is often the worst at night, patients present primarily with signs consistent with scratching. Redness, excoriations, and scale are usual. The classic specific lesion of scabies is the burrow, a 1 to 3 mm red, edematous linear papule or vesicle, most often located in the finger and toe web spaces, the ventral wrists, and on inframammary skin. However, in the axilla and on anogenital skin (most often, however, on the scrotum and penis) very itchy, red, excoriated, dermal nodules are characteristic (Fig. 22).

The differential diagnosis includes other very itchy skin diseases including lichen simplex chronicus (eczema/atopic dermatitis) and irritant/allergic contact dermatitis. The more discreet and specific nodules can be confused with folliculitis, furunculosis, and hidradenitis suppurativa, although scabetic nodules never drain.

The diagnosis is made by the history of intense pruritus, morphology, and distribution, and it is confirmed by demonstration of the organism (Fig. 23). A deep scraping/shave of a burrow often but certainly not always yields the microscopic identification of a mite, ova, or scybala (feces). Scraping a scabetic nodule of the anogenital skin is not useful. However, a punch biopsy is characteristic of an insect bite.

The treatment of scabies includes elimination of the mite, control of the inflammatory response, and avoidance of reinfection by treating other family members and

Table 18 Trichomoniasis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Trichomoniasis	Intense pruritus and burning, irritation	Introital, vaginal, and cervical erythema, "strawberry" cervix, purulent vaginal secretions that microscopically show white blood cells and trichomonads	Vaginal candidiasis, atrophic vaginitis, bacterial vaginitis, bacterial vaginosis, desquamative inflammatory vaginitis	Oral metronidazole 500 mg b.i.d. for 1 wk or 2 g once

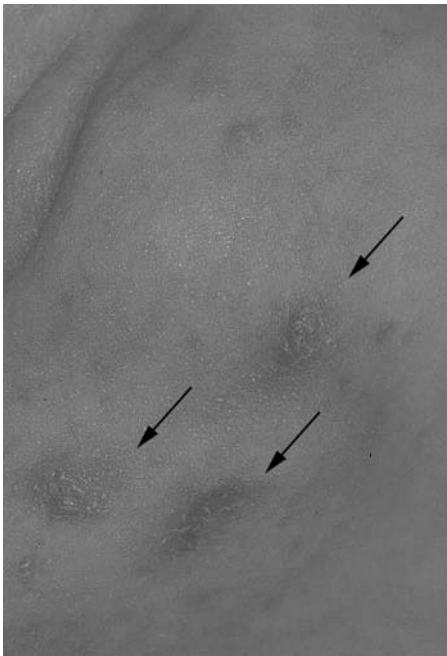


Figure 22 The pink papules with scale/crust are typical for scabies in skin folds and on the wrists.

fomites. The mite itself is treated with permethrin 5% applied overnight, and a second treatment one week later is often used but not generally needed. Lindane is no longer used for scabies due to concerns of neurotoxicity and local irritation, most common in infants (62,63). Alternatively, oral ivermectin is elegant and safe although not FDA approved (64). Scabies can be more difficult to eradicate in immunosuppressed patients, and the combination of topical and oral therapy is often necessary. Unfortunately, resistance to ivermectin has now been reported (65).

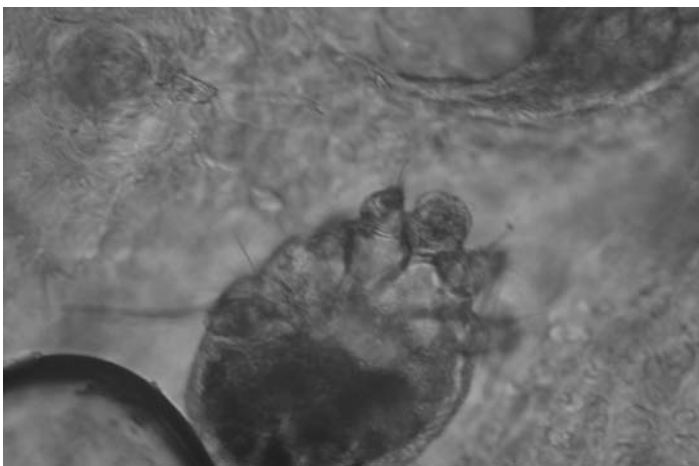


Figure 23 Identification of the mite, *Sarcoptes scabiei*, its feces, or ova proves the diagnosis of a scabies infestation.

Table 19 Scabies

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Scabies	Intense pruritus	Excoriations, burrows, inflamed dermal nodules	Eczema/lichen simplex chronicus, folliculitis, candidiasis	5% permethrin cream overnight or ivermectin orally

The short-term application of an ultrapotent topical corticosteroid such as clobetasol dipropionate ointment may help control itching. However, the thickened nature of scabetic nodules in the genital area precludes good penetration, and a few drops of triamcinolone acetonide 10 mg/cc often produce rapid symptomatic improvement. Finally, all clothing and linens used within 48 hours should be either washed with hot soapy water or bagged for several days to eliminate the mite. All those living in the same home or in close contact should be treated with permethrin or ivermectin. Persistence of disease is frequently reinfection rather than resistance (Table 19).

Pubic Lice

Pubic lice, *Phthirus pubis*, are small, macroscopic parasites that are generally sexually transmitted, annoying, and medically trivial. Fomites also are known to transmit lice. Also called “crabs,” these organisms localize to the pubic hair and eyelashes, and these are distinct from head lice.

The primary symptom of lice is itching. Physical findings are often very, very subtle. The 1 to 2 mm mites are nearly skin colored and attached to hair. Very close examination with magnification generally also reveals nits, light-colored oval eggs glued to the hairs. The skin is usually normal in appearance (Fig. 24). Modified mucous membranes and the vaginal epithelium are not affected.



Figure 24 (See color insert) Pubic lice are small parasites that cling to pubic hair, with nits appearing as teardrop-shaped eggs attached to hair shafts.

Table 20 Pubic Lice

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Pubic lice	None, or itching	Small tan parasites and nits attached to hair shafts	Lichen simplex chronicus, scabies	Lindane, pyrethrin, permethrin

The differential diagnosis includes any pruritic disease. The diagnosis is made by the visualization of the mite or nits.

The management of pubic lice includes a screen for other sexually transmitted diseases, as these have been reported to occur more often in patients with pubic lice (66). Treatment consists of the elimination of the lice, destruction of nits, and the treatment of fomites. Lindane applied topically overnight generally kills the lice and the nits, although the nits remain glued to the hair shaft. Alternatively, over-the-counter pyrethrin or permethrin are also effective, but resistance to pyrethrin has been reported (67). The nits can be left in place, removed by shaving the affected hair, or removed with a nit comb, a very fine comb often included with the medication. Resistance of pubic lice, like head lice, is becoming recognized (Table 20).

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5

Pigmented Lesions of the Vulva

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INTRODUCTION

Numerous pigmented conditions affect the vulva. These include common benign vulvar conditions with a variety of terminology, such as nevus, seborrheic keratosis, acanthosis nigricans (AN), lentigo simplex (lentigines), melanosis, condylomata, pigmented apocrine hamartoma, postinflammatory hyperpigmentation in association with lichen simplex chronicus, vulvar intraepithelial neoplasia (VIN), and angiokeratoma to name a few. Various medical conditions have hyperpigmentation as a sign, such as Cushing's disease, Addison's disease, discoid lupus erythematosus, LAMB syndrome (lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi) (1), LEOPARD syndrome (lentigines, electrocardiographic-conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and deafness) (2), Peutz-Jegher (3), and Bannayan-Riley-Ruvalcaba syndrome (4), as well as rarer conditions (5–10). Treatments for medical conditions or trauma can be associated with hyperpigmentation (radiation therapy, chemotherapeutic agents, antimalarials, and metals). While melanoma is the most common malignant process to be associated with hyperpigmentation, other vulvar precancers and cancers may have hyperpigmentation (Paget's disease, squamous cell carcinoma, verrucous carcinoma, and basal cell carcinoma) (11).

The prevalence of pigmented lesions on the vulva was investigated by Rock and Rock in 1990. They performed a yearlong prospective study evaluating pigmented lesions seen in a gynecology practice. Approximately 12% of patients

(37/301) had pigmented lesions or diffuse hyperpigmentation on examination. The majority of patients (84%) were unaware of the pigmentation (12). Many of the common conditions with vulvar pigmentation will be discussed. Management of these various conditions will also be discussed, including careful inspection of the vulva and total body surface, followed by biopsy of any suspicious lesion (13).

MECHANISMS OF HYPERPIGMENTATION

The cause of hyperpigmentation usually is related to the activity and presence of melanocytes. Embryologically, the melanocytes are derived from neural crest cells. They migrate into the basal layer of the epidermis. The melanocytes produce melanosomes (organelles that are transferred to keratinocytes). The melanosomes convert tyrosine to melanin, which is responsible for skin color. Various stimuli such as hormones or irritation increase the production of melanosomes resulting in hyperpigmentation (14).

CONDITIONS WITH PIGMENTATION

Acanthosis Nigricans

AN is a relatively common skin condition, which tends to occur in skin folds (axillae, under the breasts, and groin) or on the posterior neck. AN may occur on the vulva. It generally presents as a thickened, pigmented, velvety lesion (15). Often it is present on the crural folds. The distribution is often described as a butterfly distribution. It has been found in association with benign and malignant conditions. It may be associated with an underlying medical illness or cancer. There are different forms of AN, but often it is familial. It tends to occur in obese, hirsute, hyperandrogenic women. Grasinger et al. found 24/43 (55.8%) of patients with AN had it present on the vulva (15). AN can be subdivided into the following categories: AN with insulin resistance type A, AN with insulin resistance type B, benign AN, drug-induced AN, hereditary benign AN, malignant AN, and pseudoacanthosis nigricans (16).

Pathophysiology

AN is more common in individuals with darker skin pigmentation. It tends to present at puberty (17). In contrast to the benign form, there is no racial propensity with malignant AN (18). Multiple factors are known to stimulate keratinocytes and dermal fibroblasts to proliferate. The benign and malignant forms have differing pathophysiologies. In the benign form of AN, the stimulation factor is probably insulin or an insulin-like growth factor, which incites epidermal cell propagation. Hyperinsulinemia results in binding of insulin to insulin-like growth factor receptors on the keratinocytes and fibroblasts. This results in hyperplasia of the skin (19). In malignant AN (that is, AN associated with an underlying malignancy), the stimulating factor is hypothesized to be a substance secreted either by the tumor or in response to the tumor. Transforming growth factor is structurally similar to epidermal growth factor and may also be involved in AN. Exogenous medications also have been implicated as etiologic factors (18).

Histopathology

The diagnosis of AN is generally made clinically by the visual appearance, but at times biopsies are indicated. Histologic evaluation in all forms of AN demonstrates hyperkeratosis, papillomatosis, and irregular acanthosis (Fig. 1). Dermal papillae

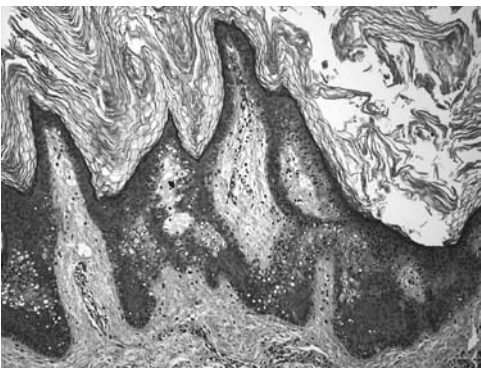


Figure 1 Acanthosis nigricans. Lesion demonstrates hyperkeratosis, papillomatosis, and irregular acanthosis.

extend upward in finger-like projections. Horn pseudocysts, as seen in seborrheic keratosis, may be seen. Slight hyperpigmentation of the basal layer of the epidermis is common, but melanocytes are not increased.

Treatment

The treatment of AN must address the underlying cause rather than the appearance of the skin. For example, if insulin resistance is present, it should be managed appropriately. Symptomatic treatments for cutaneous changes include topical antibiotics, topical or systemic retinoids, and keratolytics (20). At times, corticosteroids are utilized. If an underlying endocrinologic abnormality is the cause, the best treatment is weight loss (21) (Table 1).

MELANOCYTIC LESIONS

A variety of melanocytic tumors exist. Benign tumors consist of mainly melanocytic nevi and benign vulvar melanosis (lentigo), while melanoma represents the most common malignant melanocytic tumor type.

Table 1 Acanthosis Nigricans

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Acanthosis nigricans	Asymptomatic generally, but may have pruritus and local irritation	Found in intertriginous areas Areas of darkening and thickening of the skin; may have a velvety or warty appearance	Addison’s disease Intertrigo Hemochromatosis Pellagra Becker nevus Hypertrophic seborrheic keratosis Ichthyosis hystrix Linear epidermal nevus Pemphigus vegetans Hidradenitis suppurativa	Address underlying cause Topical antibiotics Topical or systemic retinoids Keratolytics Corticosteroids



Figure 2 Melanosis (lentigo). Diffuse pigmentation changes are present.

Melanosis

Benign vulvar melanosis (melanotic macule or genital lentigo) consists of a brown discoloration and is generally asymptomatic (Fig. 2). Table 2 outlines the symptoms, clinical appearance, differential diagnosis, and therapy of melanosis. It can be found in a variety of vulvar locations including the periurethral area (22). Often, there will be more than one lesion present. Melanosis may be found incidentally during a pelvic examination. Melanosis of the vulva may mimic melanoma on visual appearance with intensely pigmented irregular macules (Fig. 3) (23–25).

The size of the various forms of melanosis varies, but it tends to be several millimeters (general range of 1–15 mm in diameter) (26). The margins vary from smooth to jagged. There is an even distribution of brown to black pigmentation. This condition is not associated with systemic diseases or induced by sunlight exposure. It may occur in episiotomy sites. At times, lentigines may be an expression of a genetic disorder such as Peutz–Jeghers syndrome or LEOPARD syndrome. Also, they have been reported in association with lichen sclerosus (27). The patient in Figures 4 and 5 has extensive lentigos, and, in addition, a biopsy from her superior right vulvar aspect revealed thick hyperkeratosis with changes in the papillary dermis of lichen sclerosus.

If small, and the area is concerning, an excisional biopsy is recommended to completely remove the area of concern for diagnostic confirmation. If the darkened area is large, an incisional biopsy may be performed.

Table 2 Melanosis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Melanosis	Asymptomatic	Pigmentation; irregular tan to brown/black patches Margins can be jagged or smooth	Melanoma Atypical junctional melanocytic hyperplasia Vulvar intra-epithelial neoplasia Seborrheic keratosis	Generally, no therapy required once diagnosis is established



Figure 3 Diffuse darkening, grossly suspicious for melanoma; however, a biopsy revealed melanosis (lentigo).

Histopathology

On visual inspection of the vulva, it can be difficult to differentiate melanosis from melanoma; however, it is not difficult on histologic grounds. Melanosis lacks a substantial melanocytic proliferation, nesting pattern of melanocytes, or melanocyte atypia. Dendritic melanocytes are normal in number or only slightly increased along the basal layer of the epidermis in association with hyperpigmentation (Fig. 6). On occasion, the melanin pigment is also located in the upper dermis. Acanthosis may be present (28).



Figure 4 Lentigo extensively involving the vulva. Of note, pruritus present on superior right vulva. This patient was found to have lichen sclerosus as well as the itch–scratch cycle.



Figure 5 Higher magnification of extensive lentigo involving both labia minora.

Treatment

Melanosis is a benign process, and thus no treatment is needed once the diagnosis is made (24). However, it is important to visualize the entire vulva when examining these patients and consider biopsy if any areas are concerning. Figure 7 demonstrates VIN 3 with a darkened, gray-brown appearance. At times, VIN may be associated with melanosis (Fig. 8).

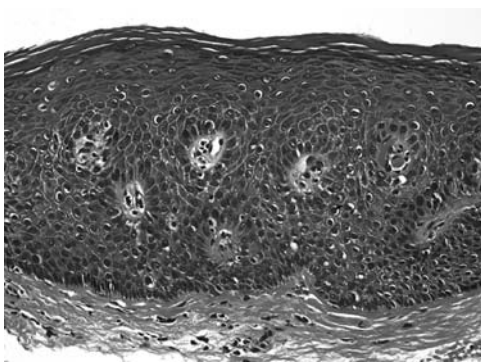


Figure 6 (See color insert) Melanotic macule (lentigo and melanosis). Basal layer hyperpigmentation is seen without an increase in melanocytes or melanocytic atypia.



Figure 7 Gray-brown vulvar intraepithelial neoplasia on the right interlabial sulcus.

Benign Nevus

Melanocytic nevi (moles) on the vulva are relatively common. They present clinically as macules or papules of different shades of brown, sometimes pink or dark blue, occasionally black, generally with a smooth surface. Melanocytes are found in the basal layer of the epidermis, every 4th to 10th cell, as well as in hair follicles throughout the entire skin surface. Melanocytic nevi are benign neoplasms composed of nests of modified melanocytes (nevus cells) located in the epidermis, dermis, or both. The nevus cells are sometimes dendritic in appearance with vacuolated cytoplasm. They may be congenital or acquired lesions. Most nevi appear during childhood and puberty. Figure 9 demonstrates a benign nevus that is brown, located on the right labium minus. However, some lesions are pedunculated and may also contain hair.

Histopathology

Histologically, nevus cells may be confined to the junctional region of the dermis and epidermis (junctional nevus), dermis (intradermal nevus), or both (compound nevus), where they have a propensity to nest formation (Fig. 10). When a dermal component of nevus is present, the nevus cells become smaller and disperse from nests with greater depth in the dermis. Mitotic figures in the dermis are usually absent. Some genital nevi demonstrate atypical histologic features such as variability

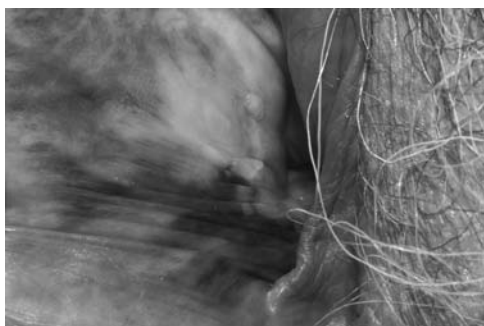


Figure 8 Acetowhitening associated with the melanosis (lentigo) that was found to be vulvar intraepithelial neoplasia.



Figure 9 (See color insert) Benign nevus on right labium minus.

in size and shape of nests and fusion of some nests resulting in confluence along the basal layer of the epidermis and cytologic atypia of nevus cells.

Treatment

Observation without treatment is recommended for a stable, unchanging benign nevus. However, if change in size, shape, color, pruritus or any difference in appearance occurs, removal is recommended (Table 3).

Atypical Junctional Melanocytic Hyperplasia

Atypical junctional melanocytic hyperplasia (AJMH) is a superficial process localized to the junctional region. This condition is distinctive from common acquired nevi. These changes are macular, often clinically ill-defined, may be large and uniformly darkly pigmented, with an asymmetric outline and irregular borders (29) (Table 4). The biologic behavior of AJMH is uncertain and unpredictable. However, AJMH may progress to melanoma and is associated with frequent local recurrence after incomplete removal, over months or decades. Immunosuppressed patients (e.g., transplantation patients) with AJMH may have a higher incidence of progression to melanoma (29). Figures 11–15 show the appearance of AJMH on the vulva (changes vary from mild to severe atypia).

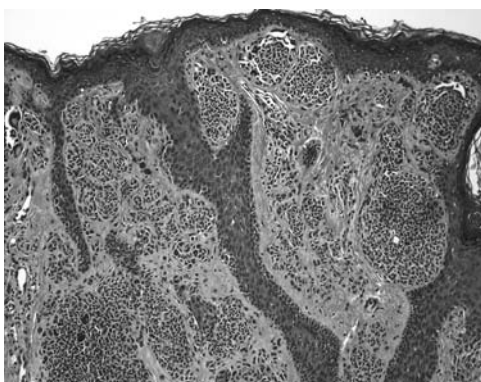


Figure 10 Genital compound nevus. Nests of cells are visible in the epidermis and dermis.

Table 3 Nevus

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Nevus	Usually asymptomatic	Colors range from brown to pink to dark blue	Melanoma Atypical junctional melanocytic hyperplasia Melanosis (lentigo) Endometriosis	No treatment usually required Excision for changes in appearance or pruritus

Grossly, it is not possible to distinguish the degree of atypia. It is interesting to note the combination of AJMH and lichen sclerosus in Figures 13 and 14. Further discussion on the association of lichen sclerosus and melanoma will follow.

Histopathology

As the name implies, AJMH has an increased number of predominantly single-unit, cytologically atypical melanocytes located in the basal layer of the epidermis and upper dermis, at the junction between the epidermis and the dermis (Fig. 16). AJMH may also arise in a nevus, where it often has extension of the atypical intraepidermal melanocytic hyperplasia beyond the shoulder of the nevus component; however, most AJMH lesions do not have a nevus component. In AJMH, the density of the melanocytes does not achieve that seen in melanoma, and pagetoid scatter of cells in the epidermis is minimal to absent.

AJMH may arise *de novo*, in association with another lesion such as melanosis or genital nevi, as a field effect in the setting of vulvar melanoma where it is often multifocal or represents the trailing edge of melanoma *in situ* (MIS). Thus, the significance of AJMH rests on the clinical context in which it is seen (29).

Treatment

Suspicious areas should be removed with an attempt for clear margins. When atypia is found at the peripheral margins, a repeat attempt to obtain clear margins should be considered because these cells may progress to melanoma. Future studies investigating the molecular characteristics of AJMH are necessary to determine its significance. Until these markers are developed, complete removal is the only



Figure 11 Atypical junctional melanocytic hyperplasia, slight atypia on left labium minus.

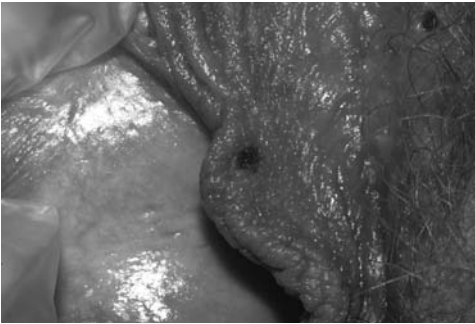


Figure 12 Higher magnification of Figure 11. Atypical junctional melanocytic hyperplasia on left labium minus.

way to ensure local tumor-free margins in clinical situations concerning for progression to melanoma (30). However, there are times when complete removal is not recommended and close observation is preferred, primarily based on morbidity of the procedure required for complete removal. Figure 15 illustrates AJMH with mild atypia on the clitoris of a 21-year-old patient. For the clitoral disease, close following was recommended rather than excision, after tissue biopsy confirmed the diagnosis.



Figure 13 Whitened, crinkled appearance of the vulva with an area of brown-black discoloration, found to be atypical junctional melanocytic hyperplasia, moderate-to-marked atypia in association with lichen sclerosus.

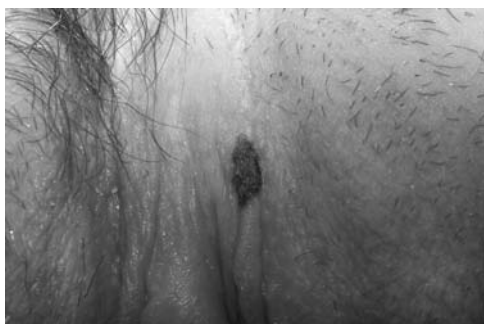


Figure 14 Higher power of atypical junctional melanocytic hyperplasia, moderate-to-marked atypia in association with lichen sclerosus.

Melanoma In Situ

MIS is defined as Stage 0, confined to the epidermis and adnexal epithelium. It was classified as a subset of the International Society for the Study of Vulvovaginal Disease classification of VIN (31) but has subsequently been discarded in the newer classification (31a). The concept of MIS was first described in 1949. In 1992, a panel at the Consensus Development Conference sponsored by the National Institutes of Health officially acknowledged this diagnostic category (32). The terminology was inspired by that of cutaneous squamous cell carcinoma; however, there is one major difference. Squamous cell carcinoma in situ is a premalignant condition, whereas MIS is considered a malignancy with a risk of metastasis, where there is an inability to detect an invasive component with tissue processing with standard histopathological techniques.

MIS often presents as a macular deeply pigmented lesion, initially uniform in appearance, but with time develops asymmetry, irregular borders, and color variegation (Table 5).

Histopathology

MIS is characterized histologically by a proliferation of malignant melanocytes confluent in the epidermis (Fig. 17). In the mucosal lentiginous type, the melanoma cells are arrayed predominantly in single cells in association with elongation of rete ridges. Pagetoid intraepidermal spread of melanoma cells is usually minimal to



Figure 15 Atypical junctional melanocytic hyperplasia, slight atypia on prepuce, frenulum, and clitoris.

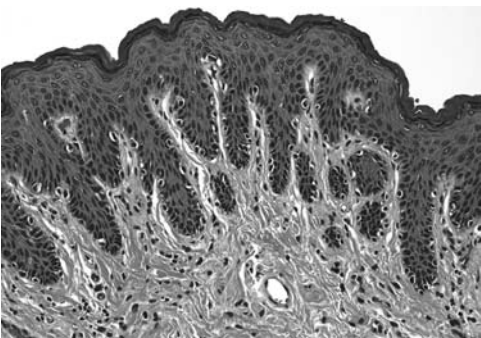


Figure 16 (See color insert) Atypical junctional melanocytic hyperplasia of the vulva. Melanocytes with slight cytologic atypia are arrayed as solitary cells along the basal layer of the epidermis.

absent. In contrast, MIS of the superficial spreading type has prominent pagetoid scatter of melanoma cells in the epidermis.

Treatment

Excision with 0.5 to 1 cm margins is recommended for treatment. Positive margins require additional excision until clear histopathological margins are obtained. Additionally, referral to a melanoma specialist is indicated to examine the entire skin surface, which is at increased risk of additional primary melanomas, and complete melanoma education and prevention (33).

Melanoma

History of Disease

Melanoma is the second most common malignancy to affect the vulva (squamous cell carcinoma is the most common). Vulvar melanoma represents approximately 2% of all melanomas (34). Risk factors for melanoma include a prior personal or family history of melanoma, blue/green eyes–red/blonde hair phenotype, and the presence of many nevi or atypical (dysplastic) nevi. While UV light exposure is a known risk factor, its relevance for vulvar melanoma is doubtful. Many case series of melanoma of the vulva have been reported (35–45). The reported age range is large (7–97 years of age).

The true incidence rate of vulvar melanoma is unknown. This is secondary to the failure to separate vulvar melanoma into a separate category in any large tumor registry (46). Few large studies exist on vulvar melanomas; thus, many questions remain unanswered about the biology, etiology, risk factors, and optimal

Table 4 Atypical Junctional Melanocytic Hyperplasia

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Atypical junctional melanocytic hyperplasia	Generally asymptomatic	Macular Often ill-defined Often large, pigmented lesions	Nevus Melanoma Melanosis Lentigo	Local excision (initial 0.5 cm margins)

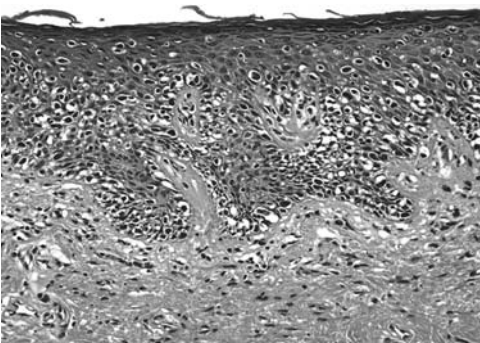


Figure 17 (See color insert) Melanoma in situ of the vulva. Cytologically atypical melanocytes are present in all levels of the epidermis.

management. Both genetic and environmental factors are involved in the pathogenesis of cutaneous melanoma; thus, it is likely that an assortment of risk factors will be identified for vulvar melanoma (30).

Clinical Features—Signs and Symptoms and Gross Appearance

Signs consist of a mass, lump (bump), polyp, swelling, abscess, bleeding, discharge, weight loss, nonhealing sore, or change in a preexisting mole. Symptoms consist of irritation, dysuria, pain or discomfort, and pruritus. However, many patients are asymptomatic. In a study by Raspagliesi et al., the mean interval from the beginning of symptoms until seeking medical advice was four months (range, 2–48 months) (47).

The differential diagnosis of melanoma includes AJMH, Paget’s disease, squamous cell carcinoma, and benign pigmented lesions such as lentigo, melanosis, nevus, AN, seborrheic keratosis, and VIN, to name a few (48).

Diagnosis

Traditionally, patients and health-care providers have utilized the ABCD rule for identifying lesions suspicious for melanoma.

The ABCD rule may be helpful to raise suspicion of the possibility of a melanoma.

- Asymmetry
- Border irregularity

Table 5 Melanoma In Situ

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Melanoma in situ	Generally asymptomatic	Macular pigmented lesion, initially uniform in appearance, but with time may develop asymmetry, irregular borders, and color variegation	Atypical junctional melanocytic hyperplasia Nevus Melanosis (lentigo) Melanoma	Excision with 0.5–1 cm margins



Figure 18 (See color insert) Melanoma of the left labium minus characterized by an irregular dark area. Source: From Refs. 30 and 50.

- Color: The color over the mole is not the same. Differing shades of tan, brown, or black, and sometimes patches of red or white are present.
- Diameter: The mole is generally wider than 6 mm, although in recent years, melanomas as small as 3 mm have been found. The newest classification uses D to describe difference—any difference or change in a lesion, or a new lesion (49).

Figure 18 demonstrates a classic appearance of a melanoma on the left labium minus. It is asymmetric, irregular, and has differing colors. While visual inspection can make the patient or clinician suspicious of the diagnosis of a melanoma, the ultimate diagnosis is via tissue biopsy and evaluation. Other studies to aid in diagnosis for equivocal lesions include immunohistochemical studies, most commonly with S-100, human melanoma black (HMB-45), or Melan-A.

Histopathology

The first step in evaluating any lesion suspicious for melanoma is an excisional biopsy. The ideal margin width for excisional biopsy is 1 to 2 mm. This provides a complete specimen for accurate diagnosis and microstaging. Wide excision for diagnosis is not recommended in the event that sentinel lymph node biopsy (SLNB) is indicated, because SLNB cannot be performed as accurately after a wide local excision has been done in the location. There are a variety of ways to perform the primary lesion biopsy including an elliptical excision, punch, or saucerization (a modified shave technique extending to the adipose tissue). Superficial shave biopsies are not recommended because there is a risk of transecting the lesion, decreasing the accuracy of tumor thickness measurement. However, if the lesion is too large or too close to vital structures to excise completely, an incisional biopsy may be preferred (46). An incisional biopsy for melanoma does not increase the risk of tumor seeding, metastasis, or decrease survival (51,52).

The various common patterns of vulvar melanoma include superficial spreading, mucosal lentiginous, unclassified, and nodular (30,53).

The most common histologic pattern subtype reported for cutaneous melanoma is superficial spreading. The frequencies of histologic subtypes in vulvar melanoma in a recent series were superficial spreading (45%), mucosal lentiginous (30%), unclassified (15%), and nodular (10%) (30). The histologic pattern subtype, in general, does not correlate with prognosis or survival after correction for tumor thickness, ulceration, and other prognostic parameters (46).

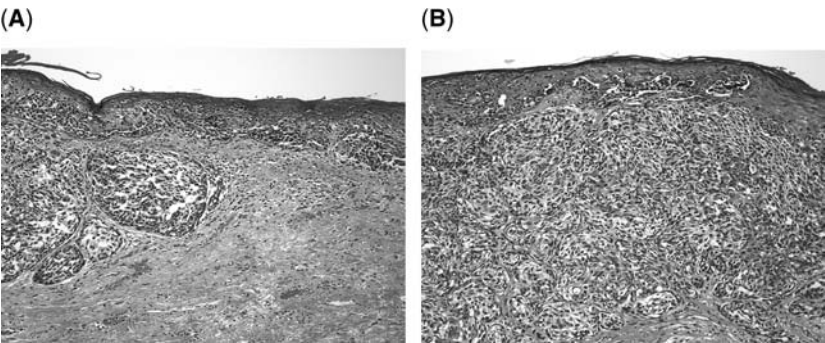


Figure 19 Melanoma of the vulva. (A) Transition from in situ to invasive melanoma. (B) The invasive component displays a sheet-like growth pattern of melanocytes with uniform cytologic atypia.

The pattern of mucosal lentiginous melanoma is characterized by a confluent proliferation of uniformly cytologically atypical melanocytes on elongated rete ridges and without significant pagetoid intraepidermal scatter of melanoma cells. In contrast, superficial spreading melanoma lacks the elongated rete ridges and is dominated by pagetoid array of melanoma cells (Fig. 19). Nodular melanoma lacks significant extension of in situ melanoma beyond the lateral limits of the invasive melanoma in the dermis. Regardless of the type of melanoma, the invasive dermal component is composed of cytologically atypical melanocytes identical to those in the epidermis (Fig. 19). Mitotic figures are often seen in the invasive melanoma.

Staging System

Accurate staging for melanoma is the primary prognostic indicator. The International Federation of Gynecology and Obstetrics (FIGO) staging system for all vulvar cancers has not been found to be as accurate a predictor of prognosis for melanoma of the vulva as the American Joint Commission for Cancer (AJCC) staging system. Historically, there have been three microstaging systems for vulvar melanomas (43,54,55). Table 6 outlines the Clark Level System. Table 7 outlines the Breslow depth parameters. Of these systems, the Breslow is the most frequently used system for vulvar melanoma and correlates best with treatment indications and prognosis. The Chung staging method was initially designed specifically for vulvar melanoma. Chung recognized that vulvar skin differed in structure from skin elsewhere on the body. On the vulva, there is no well-defined papillary dermis or

Table 6 Clark’s Levels

I	In situ melanoma (intraepithelial)
II	Extension of cells into papillary dermis
III	Interface between papillary and reticular dermis (filling papillary dermis)
IV	Extension into the reticular dermis
V	Invasion into the subcutaneous tissue

Note: The Clark system is based on depth of invasion related to the anatomy of the skin and its appendages.

Source: From Ref. 54.

Table 7 The Breslow Index

Stage I	Invasion < 0.76 mm
Stage II	Invasion between 0.76 and 1.50 mm
Stage III	Invasion between 1.51 and 2.25 mm
Stage IV	Invasion between 2.26 and 3.00 mm
Stage V	Invasion > 3.00 mm

Source: From Ref. 57.

squamous mucous membrane in the labia. Chung's early and advanced levels are the same as Clark's, but the intermediate levels differ and are based on the depth (in millimeters) from the granular layer of the skin or the outermost epithelial layer (56). It is rarely used in clinical practice today.

Breslow Thickness

The Breslow system is based on the thickness of invasion, measured in millimeters. It is the most commonly used system for vulvar melanoma. The thickness of the melanoma is measured from the granular layer of the overlying epithelium to the deepest point of invasion (53).

Treatment

Historically, vulvar melanomas were treated with radical resections involving en bloc vulvectomy and inguinofemoral lymphadenectomy through a single incision. This procedure is associated with significant complications and offers no additional overall or disease-free survival benefit over narrower wide local excision with adequate tumor-free margins. Vulvar melanoma is treated with a local excision with margins based on the Breslow depth (Table 7). It is important to obtain adequate and histologic tumor-free margins.

Table 8 describes the recommended margins that should be obtained for various tumor thicknesses. Frozen section analysis is neither sensitive nor specific for histologic evaluation of local margins for melanoma and, therefore, is contraindicated (46). If permanent sections reveal positive margins, subsequent excision is indicated to obtain tumor-free margins.

Lymph Node Evaluation for Clinically Localized Disease

Elective lymph node dissection (ELND) is never indicated for melanoma based on high levels of evidence gained through randomized trials. However, a small

Table 8 Recommended Clinical Margins for Melanoma Excision

Tumor thickness	Recommended clinical margins
In situ	0.5 cm
≤1.0 mm	1.0 cm
1.01–2.0 mm	1–2 cm
2.01–4.0 mm	2.0 cm
> 4 mm	2.0 cm

Source: Adapted from Refs. 58 and 59.

subset with positive occult nodal metastasis may benefit from immediate complete lymphadenectomy. Lymph node assessment by sentinel lymph node biopsy (SLNB) was developed as a minimally invasive procedure to identify those with occult metastasis while sparing those without metastasis the morbidity associated with ELND. SLNB is recommended in relatively healthy patients with lesions equal to 1 mm or more in tumor thickness or in cases more than 1 mm with ulceration. If the SLNB is positive, complete regional lymphadenectomy is indicated.

The sentinel lymph node can be identified from 95% to 99% of the time, with less than 5% false-negative results in highly experienced centers that perform the procedure routinely (57). Sentinel nodes should be fixed and stained with both hematoxylin and eosin (H&E) and immunohistochemical stains if H&E is negative (e.g., S-100, HMB-45, and Melan-A) because H&E alone will miss up to 12% of positive nodes (58). Because patients with melanomas that are 1.0 mm or less in thickness rarely have nodal disease (59), sentinel node evaluation is generally reserved for patients with melanomas that are 1 mm thick or more. Randomized, prospective trials are being performed, evaluating the survival benefit with SLNB. Even if no survival benefit is proven, SLNB still has several benefits, including accurate prognostic staging information for counseling and addressing important emotional distress issues associated with the diagnosis of cancer, identifying patients who may benefit from early therapeutic lymphadenectomy and adjuvant therapy, and grouping patients into more homogeneous cohorts for better clinical trials (60).

A staging system for cutaneous melanoma was published in 2001. The 2002 AJCC tumor node metastasis (TNM) staging system for melanoma can be found at the website of the National Comprehensive Cancer Network (58).

Histologic Evaluation

Numerous histologic factors are routinely reported for melanoma with potential prognostic and treatment effects (63). Histological diagnosis and interpretation by a pathologist with expertise in melanoma is critical. The factors routinely reported in a melanoma profile from the University of Michigan Multidisciplinary Melanoma Program include the following: body site, classification, Clark's level, Breslow depth, host response, regression, mitoses/mm², growth phase, satellitosis, ulceration, angiolymphatic spread, neurotropism, margins, and coexisting nevus.

Numerous tumor markers are available to improve sensitivity and specificity in identifying melanoma (64), but most are easily diagnosed without additional studies by a pathologist with expertise in melanoma. Table 9 lists other tests that are utilized to assist in the diagnosis of a melanoma. These include immunohistochemistry with antibodies to S-100 protein (S-100) (65), melanoma antigen-encoding genes *MAGE 1* and *MAGE 3* (66,67), melanoma antigen recognized by T-cells 1 (MART-1), (68) monoclonal antibody HMB-45, and microphthalmia transcription factor (Mitf); (69–72) and molecular diagnostic tools and reverse transcriptase polymerase chain reaction (RT-PCR) positivity (73–77).

Prognosis

The most important prognostic factor is the Breslow depth of invasion of the primary lesion, followed by ulceration status and mitotic rate. The most powerful predictor of overall survival is the status of the SLN in those with lesions more than 1 mm in tumor thickness. Vulvar melanoma tends to be detected later than cutaneous melanoma because of the location. This results in more advanced lesions with deeper Breslow thickness at presentation, hence a poorer prognosis. Once metastasis occurs,

Table 9 Tests Used to Assist in Melanoma Diagnosis

I: Immunohistochemistry (see antibodies below)	These tests are used in the traditional evaluation of melanoma. However, examination of tissues for nodal metastases by H&E alone can result in overdiagnosis or underdiagnosis.
S-100	This calcium-channel binding protein is a sensitive marker of melanocyte differentiation. It is highly sensitive but not specific for melanoma. It is also seen in benign nevus cells, histiocytes, schwannomas, neurofibromas, and malignant peripheral nerve sheath tumors.
<i>MAGE-1</i> and <i>MAGE-3</i>	These markers are highly specific for melanomas.
MART-1/Melan-A	The MART-1/Melan-A recognizes a protein of 18 kDa. The MART-1 recognizes a subcellular fraction in melanosomes. This test is moderately sensitive but not specific for melanoma. Melan-A is a useful addition to melanoma panels because it is apparently specific for melanocytic lesions. Expression of MART-1 micrometastasis in sentinel lymph nodes has been correlated with poorer survival in some studies. Studies have shown that MART-1 is more sensitive than HMB-45 when labeling metastatic melanomas.
HMB-45	HMB-45 is a highly sensitive but not specific test for melanoma. The antibody HMB-45 reacts with a 10 kDa cytoplasmic glycoprotein (part of the gp100 premelanosome complex). It demonstrates a lack of reactivity with spindle melanomas, thus limiting its usefulness as an immunohistochemical marker for melanoma.
Microphthalmia transcription factor (Mitf) and tyrosinase	Mitf is a transcription regulator of the tyrosinase gene, which exhibits highly sensitive and specific immunoreactivity for melanocytic lesions, with the exception of desmoplastic melanomas. The expression of Mitf has also been linked to prognosis in melanomas of intermediate thickness. Tyrosinase is a key enzyme in melanin biosynthesis, catalyzing the conversion of tyrosine to dihydroxyphenylalanine (DOPA) and DOPA to dopaquinone. The monoclonal antibody developed against tyrosinase is immunoreactive against normal melanocytes, nevus cells, and melanoma cells. Tyrosinase expression diminishes in higher-stage melanomas, with 100% staining in Stage I and II lesions, but only 86% in Stage III and IV tumors.
II: Molecular diagnostic tools	A need for greater sensitivity and specificity for lymph node screening has prompted the use of molecular techniques to detect micrometastasis.
III: Reverse transcriptase polymerase chain reaction (RT-PCR) positivity	RT-PCR assay for molecular detection of melanoma-specific tumor markers such as tyrosinase messenger RNA in lymph node tissue is more sensitive for the detection of occult metastases than routine histology; its sensitivity approaches the overall incidence of metastatic disease.

Abbreviations: MAGE, melanoma antigen–encoding genes; MART-1, melanoma antigen recognized by T-cells 1.

Source: Adapted from Ref. 64.

prognosis is based on the number of nodes involved, ulceration status of the primary lesion, and status of extracapsular spread. Distant metastasis is associated with a grave prognosis with metastasis to the skin and subcutaneous tissue, at best associated with an 18% five-year survival. Brain metastasis is the most ominous and is

associated with a three to six month mean survival. Serum lactate dehydrogenase (LDH) levels are also utilized for Stage IV prognosis.

For all forms of melanoma, cutaneous melanomas have a higher five-year survival (80–90%) compared with mucosal melanomas (25.0%) and female genital melanomas (11.4%) (78). This estimate for female genital melanoma in the large National Cancer Data Base analysis includes vaginal melanoma, which has an even poorer prognosis than vulvar melanoma. Another factor in poorer prognosis for vulvar melanomas may be the extent of disease at the time of diagnosis (79). There is no evidence that vulvar melanomas behave in a different fashion from melanomas located in other skin areas, and poorer prognosis is likely related to delayed detection because of location (40).

Because the majority of new melanoma data, including that on staging, comes from the cutaneous melanoma literature, movement to extend the cutaneous melanoma staging system to vulvar melanoma is logical. Furthermore, results of the Gynecology Oncology Group trial showed that the AJCC staging system for cutaneous melanoma, when applied to vulvar melanoma, was the single most powerful predictor of disease-free survival based on shared prognostic features of tumor thickness (80) and ulceration status of the primary lesion and nodal status as noted previously. This also provides support for adoption of the most recent version of the AJCC cutaneous melanoma staging system implemented in 2002 (81,82).

Melanoma in the Younger Age Group

Approximately 2% of melanomas occur in patients younger than 20 years of age. It is rarely found in prepubescent children (0.3–0.5% of cases) (83). It is rarely diagnosed in childhood (41,45,84–89). Currently, there are 13 cases of vulvar melanoma in children under the age of 16 in the literature. The diagnosis of vulvar melanoma in children remains a challenge, given that screening is infrequent and high-risk features may not be clinically apparent (90). A rare association of lichen sclerosus and melanoma of the vulva has been noted. Lichen sclerosus has been associated with other cancers [Merkel cell carcinoma (91), spindle cell carcinoma (92), and basal cell carcinoma] (93). Recently, a 10-year old was found to have two primary vulvar melanomas (Breslow depth 1.0 and 0.36 mm) in association with lichen sclerosus (94). Figures 20 and 21 demonstrate a melanoma occurring in a 10-year-old child.



Figure 20 (See color insert) Melanoma in 10-year-old child on two areas of the vulva in association with lichen sclerosus. Source: From Ref. 30.

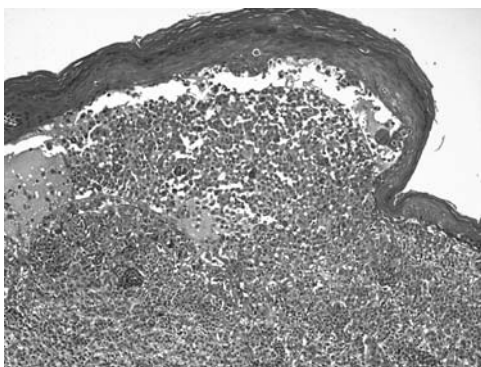


Figure 21 Melanoma (mucosal lentiginous type) Breslow depth 1.48 mm. Atypical junctional melanocytic hyperplasia, moderate-to-marked atypia extends to peripheral margins in multiple areas.

This child was found to have lichen sclerosis. Melanoma in association with lichen sclerosis of the vulva has been reported in other childhood cases (83,84,89). The malignant transformation of squamous-cell carcinoma has been periodically linked with preexisting lichen sclerosis, so it has been further hypothesized that lichen sclerosis may in fact be associated with melanoma in a similar context with malignant transformation of melanocytes (95). The concomitant presence of lichen sclerosis may hinder the accurate diagnosis of vulvar melanoma. Benign vulvar melanocytic lesions occurring with lichen sclerosis are already well known to be a diagnostic challenge, as they may simulate MIS or persistent nevi histologically (95). It also has been proposed that lichen sclerosis may represent a pattern of host immune response to melanoma (89). Therefore, accurate diagnosis of melanoma in the setting of lichen sclerosis, particularly in a child, requires a high index of suspicion (Table 10).

Table 10 Melanoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Melanoma	Asymptomatic at times, but irritation and pruritus may be present	Irregular pigmentation The color over the mole is not the same. Differing shades of tan, brown, or black and sometimes patches of red or white are present	Melanosis (lentigo) Junctional nevi Compound nevi Intradermal nevi Atypical junctional melanocytic hyperplasia Acanthosis nigricans Seborrheic keratosis Pigmented basal-cell carcinoma Vulvar intraepithelial neoplasia Squamous-cell carcinoma Paget's disease	Wide local excision and possible sentinel node sampling with possible additional node removal

CONCLUSION

A variety of vulvar conditions are associated with pigmentation abnormalities. Visual examination can help to identify abnormalities at an early disease stage. Vulvar self-examination is important, allowing patients to benefit from early disease diagnosis. Removal of abnormal and changing vulvar lesions for histologic evaluation is of utmost importance. When vulvar melanomas are identified in patients, they should be referred to centers experienced with this disease process. A multidisciplinary approach to treating and following these patients is required for optimal care and outcomes. Vulvar melanoma behaves biologically similarly to cutaneous melanoma with similar prognostic factors. An important goal is to improve knowledge and facilitate grouping of cases from different institutions to optimize diagnosis and treatment regimens for patients with vulvar melanoma.

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6

Neoplasms and Related Lesions of the Vulva

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CYSTS

Bartholin's Cyst and Abscess

The two Bartholin's gland ducts drain into the posterolateral vestibule (Fig. 1A and B). Bartholin's duct cysts develop secondary to blockage of the duct and may become infected, leading to abscesses. A variety of aerobic and anaerobic organisms have been isolated from these abscesses, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and various bowel flora (1). Bartholin's duct cysts/abscesses are most common during reproductive life. A Bartholin's mass in a woman over the age of 40 always raises the question of a malignancy, and a tissue specimen for pathological examination is indicated. Most therapeutic options for treatment of a Bartholin's cyst or abscess do not lead to a surgical pathology specimen; however, if one is received, the Bartholin's gland and duct may be recognized by their unique mix of epithelial types; mucinous in the glands, transitional in the ducts, and squamous at the orifice, with some admixture of types in the ducts common (Table 1).

Epidermal Inclusion Cyst

Epidermal inclusion cysts are common on the vulva, and may be multiple (Fig. 2A and B). They present as firm smooth nodules, and are filled with keratinaceous debris. They tend to enlarge. Histologically they are lined by stratified squamous epithelium, which may contain the granular cell layer (2). The lesions have also occurred in the clitoral area in women undergoing female circumcision (3). They do not require therapy, but may be excised if symptomatic (Table 2).

Mucinous and Ciliated Cysts

Mucinous cysts and ciliated cysts of the vulva are uncommon lesions (Fig. 3A–C) (4–7). Their origin is uncertain, with theories including paramesonephric or mesonephric

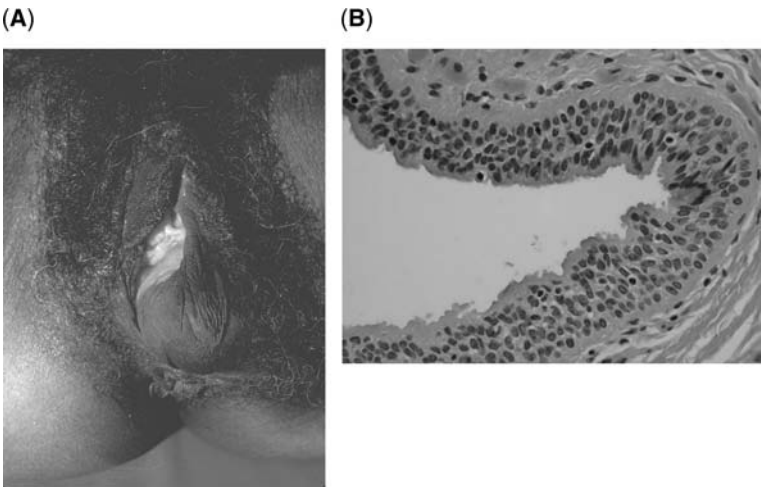


Figure 1 Bartholin’s cyst. (A) A large swelling is noted on the left. (B) The cyst wall is lined by transitional epithelium, consistent with Bartholin’s duct.

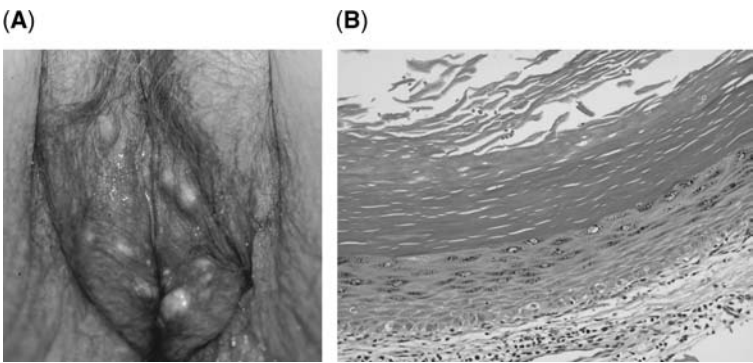


Figure 2 Epidermal inclusion cysts. (A) Multiple firm tan nodules are seen. (B) The cyst is lined by stratified squamous epithelium. The cyst contents are composed of keratinaceous debris.

Table 1 Bartholin’s Cyst and Abscess

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Bartholin’s duct cyst/ abscess	Cystic mass at the 4 or 8 o’clock position of the introitus. Painful if inflamed	Cystic mass. May be up to 8 cm or more	Epidermal inclusion cyst, mucinous cyst of vestibule, hidradenoma, papilliferum, lipoma, cystic lesions of vagina	Surgical, including Word catheter placement for abscesses, marsupialization of cysts, or occasionally gland excision, usually in older women

Table 2 Epidermal Inclusion Cyst

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Epidermal inclusion cyst	Cosmetic issue. May rupture and drain foul smelling contents	Single or multiple dome-shaped nodules with smooth external surface	Usually not a diagnostic challenge	None, excision, or evacuation

origin and origin from the urogenital sinus, metaplasia, or heterotopia. They may be seen in the vestibule, or in the superior aspect of the labia minora in multiparous women. Mucinous cysts are lined by a single layer of mucinous columnar epithelium. Pure ciliated cysts lined by ciliated columnar epithelium are rare; however, ciliated cells are often present in predominantly mucinous cysts. Papillary infoldings of the mucosa is commonly seen in these cysts (Table 3).

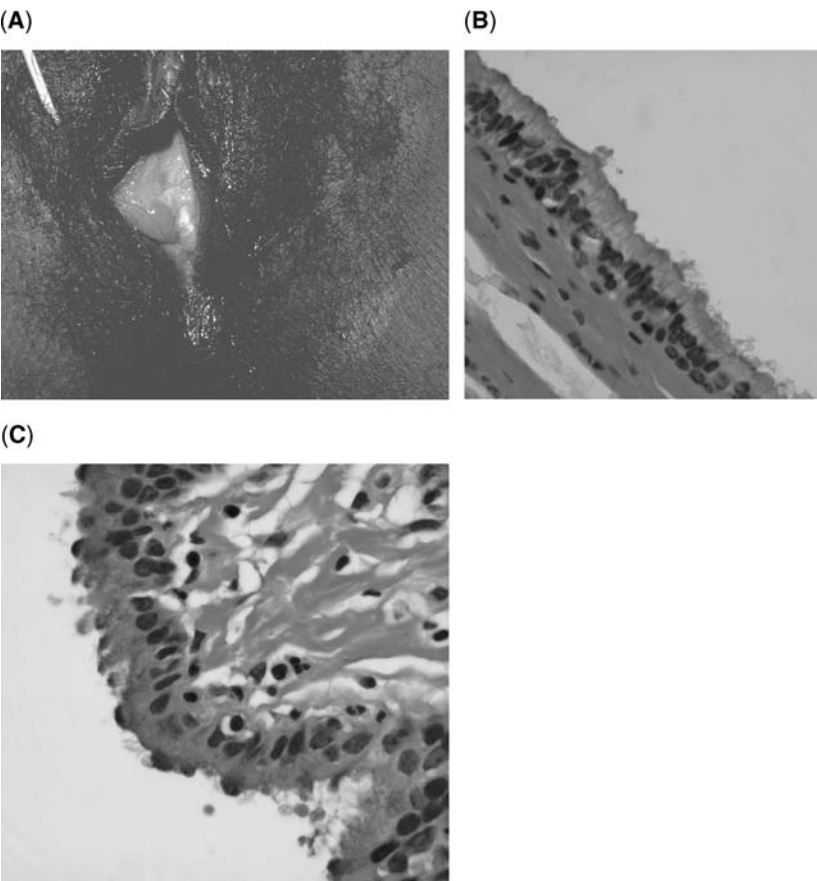


Figure 3 (A) (*See color insert*) Mucinous cyst of the vestibule. (B) Mucinous cyst of the vestibule: the cyst is lined by a single layer of mucinous columnar epithelium. (C) Mucinous and ciliated cyst: the cyst is lined by a combination of mucinous and ciliated columnar epithelium.

Table 3 Mucinous and Ciliated Cysts

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Mucinous or ciliated cyst	Discomfort or pain because of location, or asymptomatic	Cyst, usually of vestibule or labia minora	Epidermal inclusion cyst, Bartholin’s duct cyst, and vaginal cysts	Simple excision

Mesonephric-Like Cyst (Wolffian Duct-Like Cyst)

While cysts of the vulva are more likely to be mucinous than nonmucinous, the nonmucinous ones have been postulated to arise from Wolffian duct remnants (Fig. 4) (8). These are much less common than cysts of Müllerian origin. Grossly, they are usually thin-walled cysts. They can occur along the tract of the Wolffian duct, and, so while more often occurring in the lateral vaginal wall, may be seen in the upper vulva near the hymen (9). They are lined by a cuboidal to columnar epithelium (Table 4).

Cyst of the Canal of Nuck (Mesothelial Cyst)

Cysts of the canal of Nuck arise from the processus vaginalis and are analogous to the male hydrocele (Fig. 5). These mesothelial-lined cysts may fill with peritoneal fluid, giving rise to a cystic mass in the labia majora. These may be associated with an inguinal hernia (Table 5) (10).

BENIGN TUMOR-LIKE LESIONS

Vestibular Adenosis

Adenosis, the presence of cervical, tubal, or endometrial type glands within the wall of the vagina, has been extensively described as resulting from in utero exposure to

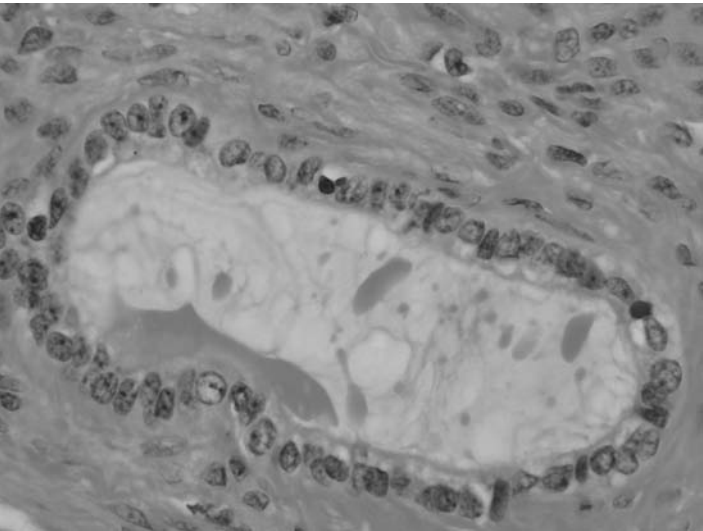


Figure 4 Mesonephric cyst: mesonephric cysts are lined by a cuboidal nonciliated epithelium as shown in this mesonephric remnant. Often abundant eosinophilic material is seen in the lumen.

Table 4 Wolffian Duct Cyst

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Wolffian duct cyst	Discomfort if large	Cystic mass	Other cystic masses of the vulva	Can be excised or marsupialized, biopsy recommended

diethylstilbestrol (Fig. 6). However, it occurs spontaneously as well. It is felt to result from the persistence of Müllenau epithelium in the region after embryogenesis. It may occasionally extend to the vulva and present in the vestibule at the introitus. Gross appearance is extremely variable and may appear as redness, nodularity, or granularity, cysts, ulcers, or protuberances (12). Possible symptoms include soreness, bleeding, and mucoid discharge. Adenosis has also been reported as a sequela of CO₂ laser therapy (13), and after Stevens–Johnson syndrome (Table 6) (14).

Endometriosis

Endometriosis of the vulva is uncommon, and most likely to occur in scars such as episiotomy scars (15) or may occur secondarily to implantation of endometrial tissue after a surgical procedure or trauma (Fig. 7A–C). It has also occurred within the Bartholin’s gland (16). There is cyclical symptomatology, including pain and dyspareunia. Grossly, the lesions appear as firm nodules that may have a blue cast to them. Histologically, the diagnosis is confirmed by the presence of endometrial glandular epithelium and stroma (Table 7).

Fibroepithelial Stromal Polyp (Acrochordon, Skin Tag)

Fibroepithelial polyps (acrochordons) are more common in the vagina, but are seen in the vulva. They may be single, or multiple, particularly during pregnancy

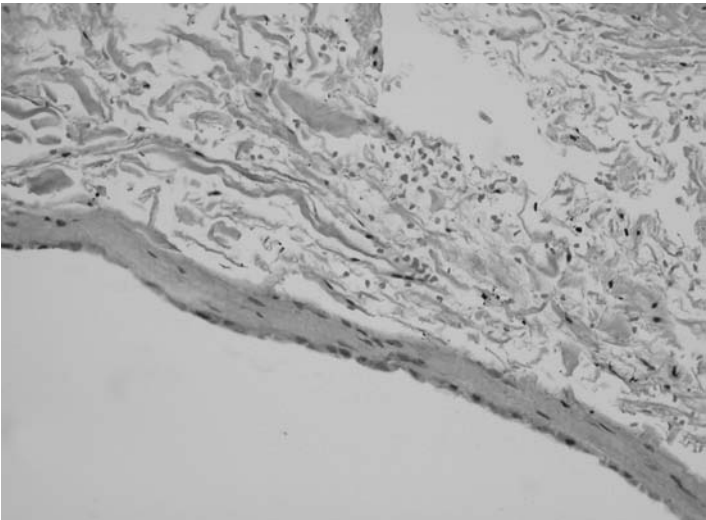


Figure 5 Cyst of the canal of Nuck: cysts of the canal of Nuck are lined by a flattened mesothelial lining.

Table 5 Cyst of the Canal of Nuck

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Cyst of the canal of Nuck	Inguinal or labial mass. Hernia may become incarcerated	Cystic mass of labia majora	Lipoma, leiomyoma, Sarcoma (11), indirect hernia, Bartholin’s cyst, or abscess, inguinal adenopathy	Excision

(Fig. 8A–C) (17). The diagnosis is straightforward in most cases, both clinically and pathologically. The usual fibroepithelial polyp is an epithelium-covered stromal polyp with a stroma that may be loose or more collagenous, and contains bland spindle cells. A fibrovascular core is often present. Histologically worrisome features may be seen, particularly in the pregnant patient, with hypercellularity, nuclear pleomorphism, and increased mitotic activity in the stroma, prompting the use of the term “pseudosarcoma botryoides.” Characteristic stellate and multinucleated cells aid in the distinction from a true sarcoma. These pseudosarcomas may recur, particularly if not totally excised, but have no destructive or metastatic potential (18,19). The stromal cells often exhibit positivity for vimentin, desmin, and estrogen (ER) progesterone (PR) receptors. They may occasionally recur in subsequent pregnancies, but are not infiltrative, and can be re-excised (Table 8) (20).

Micropapillomatosis Labialis

Micropapillomatosis labialis (MPL) is characterized by multiple, small uniform finger-like projections, usually on the inner labia minora and within the vestibule (Fig. 9). The projections are composed of a stromal core covered by unremarkable

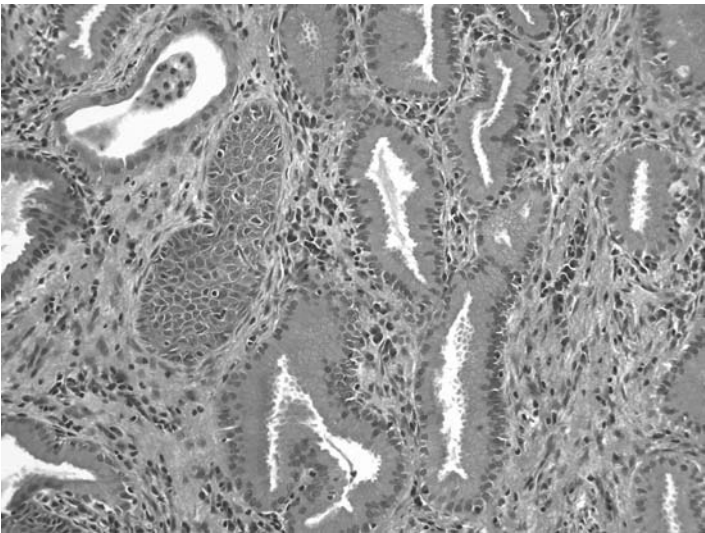


Figure 6 Adenosis: here mucinous glands undergoing squamous metaplasia are seen.

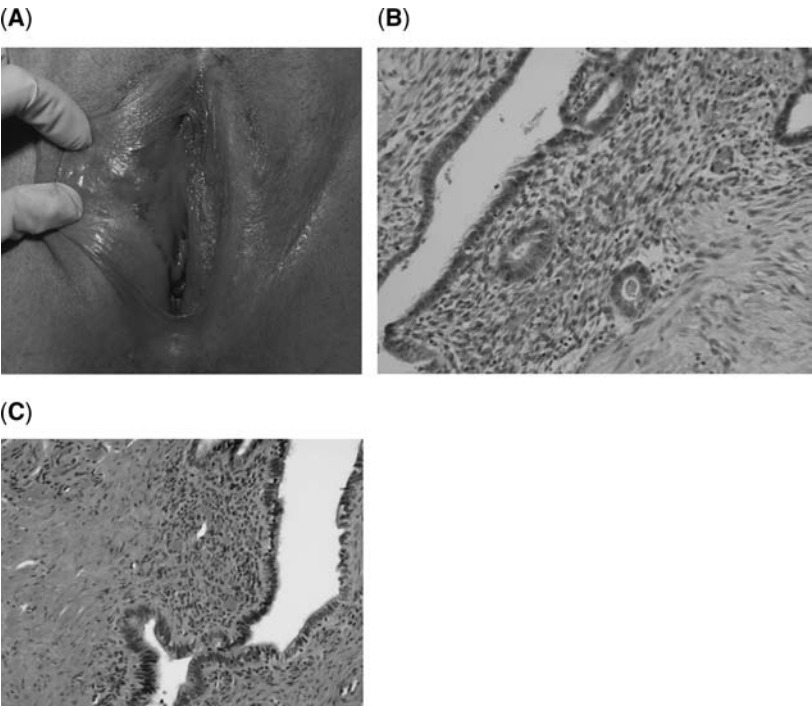


Figure 7 Endometriosis. (A) (*See color insert*) Grossly endometriotic implants on the vulva often have a blue appearance. (B,C) The criterion for definitive diagnosis of endometriosis histologically is the presence of endometrial glandular epithelium and stroma. In (B), actual glands are formed, while endometrial-type epithelium is seen lining a space in (C).

Table 6 Vestibular Adenosis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Vestibular adenosis	Bleeding, particularly postcoital, pain	Variable. May be red and granular, nodular, or form cysts or masses	Endometriosis, vestibulitis	Observation, laser vaporization, excision

Table 7 Endometriosis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Endometriosis	Pain, dyspareunia, often cyclical	Firm nodules, may be bluish in color	Other nodular lesions	Excision

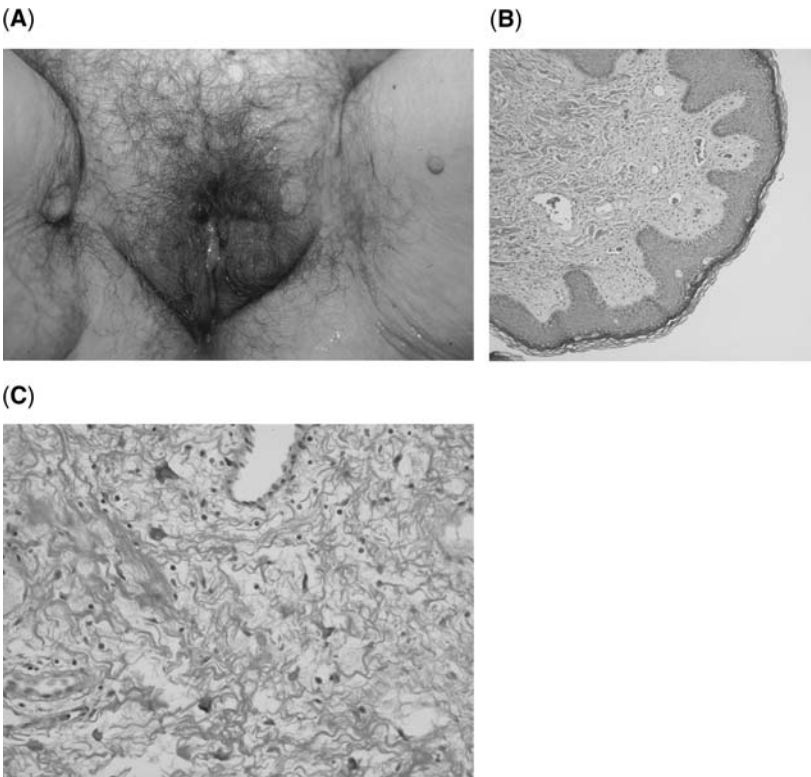


Figure 8 Acrochordons. (A) Multiple acrochordons (skin tags) are present on the inner thighs. (B) Unremarkable squamous epithelium lines a loose fibrovascular tissue. (C) Occasionally large stellate cells are seen in the stroma and should not be mistaken for evidence of malignancy.

squamous epithelium. The lesions are not felt to be related to human papillomavirus (HPV) (21) and can be distinguished from condyloma acuminatum by the more uniform appearance of the projections. Histologically, the epithelium of MPL does not show the characteristic cytopathic effects of HPV (koilocytosis). The colposcopic appearance resembling endocervix may be alarming to neophytes (Table 9).

Table 8 Fibroepithelial Stromal Polyp

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Fibroepithelial polyp	Usually none	Usually small, rarely larger, sessile or polypoid epithelium-covered mass	Aggressive angiomyxoma, angiomyo fibroblastoma, cellular angiofibroma, smooth muscle neoplasms (1,7)	Excision



Figure 9 Micropapillomatosis labialis: small finger-like projections are seen in the vestibule. *Source:* Photograph courtesy of Hope Haefner, MD, Department of Obstetrics and Gynecology, The University of Michigan Hospitals, Ann Arbor, Michigan, U.S.A.

BENIGN NEOPLASMS

Neoplasms of Dermal Appendages

Papillary Hidradenoma (Hidradenoma Papilliferum)

Hidradenomas are benign sweat gland tumors that may raise the issue of malignancy with both clinicians and pathologists (Fig. 10A and B). The clinician may observe a flesh-colored or blue nodular lesion, frequently with central umbilication, usually less than 1 cm. Hidradenomas may become ulcerated, exposing bright red papillary tissue (22), hence raising the concern for malignancy. Histologically, the lesion is composed of tightly packed cystic and glandular spaces lined by a two-cell layer, an inner cuboidal and an outer myoepithelial cell layer. The tightly packed glands may mislead the observer to consider an adenocarcinoma; however, closer observation shows the characteristic apocrine “snouts” of the inner layer, and the presence of the myoepithelial layer, confirming the true nature of the lesion, which may also be found in the axilla (Table 10).

Trichoepithelioma

Trichoepitheliomas and other related adnexal neoplasms of hair follicles (trichoblastoma, trichodiscoma, trichomyxoma, trichofibroma, and trichofolliculoma) are

Table 9 Micropapillomatosis Labialis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Micropapillomatosis labialis	None	Multiple small uniform papillary projections of inner labia minor/introitus	Condyloma acuminatum	None necessary

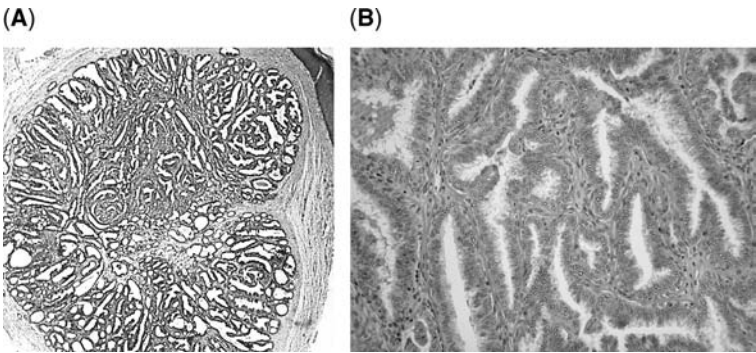


Figure 10 Hidradenoma. (A) Low-power view shows a well-circumscribed lesion. (B) On higher power, the spaces are seen to be lined by a double layer, inner epithelial and outer myoepithelial.

benign tumors (Fig. 11A and B). They may rarely occur on the vulva (23,24). Trichoepitheliomas may be single or multiple and are usually less than 1 cm, flesh-colored papules or nodules (25). They may be seen on histologic section to arise from hair follicles, in which case invasion may be mistakenly diagnosed. The lesions may be confused with basal cell carcinomas because of the similarity of cell type; however, trichoepitheliomas lack ulceration or inflammatory tissue reaction and are often associated with keratinous cysts (25). Trichoepitheliomas may also raise concern of malignancy because of the active mitotic rates that may be present (Table 11) (23).

Syringoma

Syringomas are benign neoplasms of eccrine sweat glands (Fig. 12). The lesions are small and frequently multiple, flesh-colored papular lesions that may occur in a variety of locations (26). When on the labia majora, they are frequently bilateral. Histologically, they are composed of intradermal solid or cystic nests of epithelial cells. Cystic spaces may be lined by one or two layers of flat-to-cuboidal pale cells (22). The lesions often have a characteristic comma shape (Table 12).

Epithelial Lesions

Seborrheic Keratosis

Seborrheic keratoses can occur anywhere on the body, but are occasionally seen on the vulva, usually in middle-aged to older women (Fig. 13A and B). The lesion

Table 10 Papillary Hidradenoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Papillary hidradenoma	None, or mass	Nodule 1 cm or less, often red and ulcerated	Clinically squamous cell carcinoma, microscopically adenocarcinoma	Simple excision

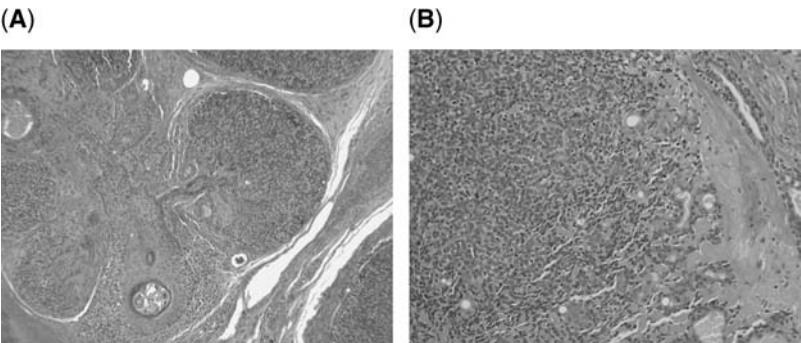


Figure 11 Trichoepithelioma. (A) Epithelial subunits surrounded by a dense fibroconnective tissue stroma. (B) Detail of basaloid cells of an epithelial subunit.

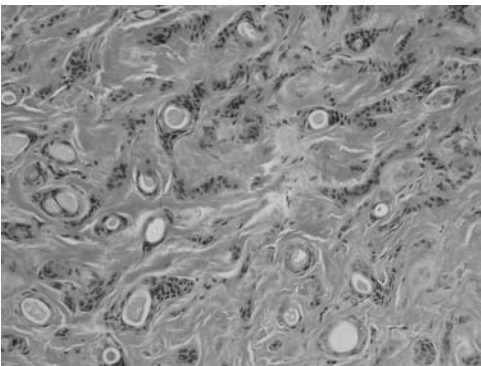


Figure 12 (See color insert) Syringoma: the characteristic comma-shaped epithelial nests in a collagenous background are seen.

Table 11 Trichoepithelioma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Trichoepithelioma	None	Small, flesh-colored plaque or nodule	Basal or squamous cell carcinoma	Excision

Table 12 Syringoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Syringoma	None or pruritus	Multiple small flesh to yellow colored papules or nodules	Candidiasis, lichen simplex chronicus, condyloma acuminatum, hemangioma, lymphangioma circumscriptum, Fox-Fordyce disease (26)	None usually required, but are sometimes excised

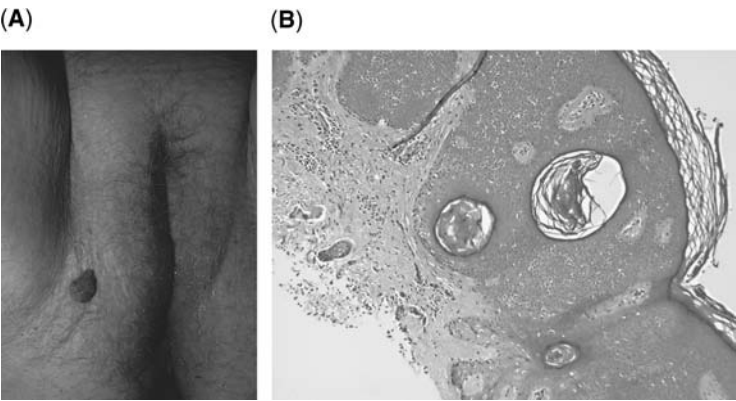


Figure 13 Seborrheic keratosis. (A) Seborrheic keratoses are in the differential diagnosis of pigmented lesions. (B) Benign squamous epithelium containing several horn cysts containing keratin.

presents as an elevated flesh-colored to brown papule or plaque, usually up to several millimeters in diameter, with a “stuck-on” appearance. The lesion may be slightly greasy to the touch. Histologically, there is hyperkeratosis, acanthosis, papillomatosis, and intraepidermal horn cysts (Table 13) (22).

Warty Dyskeratoma

Warty dyskeratomas (WDs) may occur anywhere on the skin, and occasionally occur on the vulva (Fig. 14A and B). The lesions are single, which distinguishes them from Darier’s disease, a histologically identical condition inherited in an autosomal dominant fashion and manifested as multiple lesions (27). Grossly, the lesions present as single flesh-colored to brown papules. The most common and distinctive histologic manifestation of WD is a cup-shaped lesion filled with a parakeratotic plug, although the lesions may also be cystic or nodular (28). The proliferating cells of the lesion show dyskeratosis and suprabasal acantholysis and may resemble koilocytes. Studies have not shown an association with HPV, however (Table 14) (27).

Keratoacanthoma

Keratoacanthomas are benign neoplasms that may raise the concern of malignancy because of their rapid growth. They then tend to regress in three to six months (Fig. 15A and B) (29).

Table 13 Seborrheic Keratosis

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Seborrheic keratosis	None, or may be a cosmetic issue	Papule or plaque, brown to flesh colored, slightly “greasy” to touch	Nevus, condyloma, squamous cell carcinoma, melanoma	None required, but local destruction/excision sometimes utilized

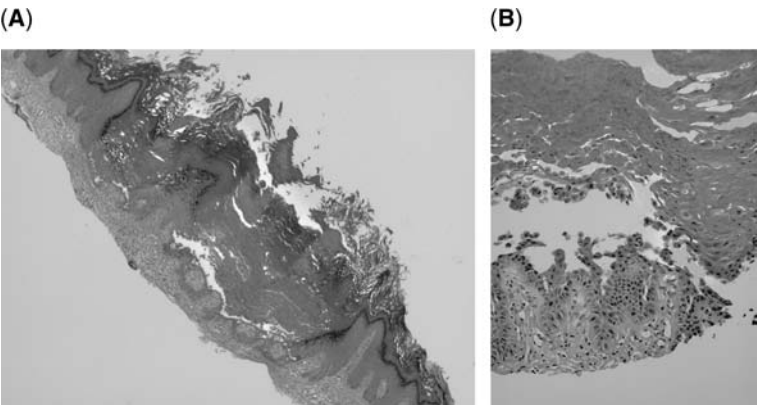


Figure 14 Warty dyskeratoma. (A) Low power shows the typical suprabasal acantholysis. (B) Suprabasal acantholysis with acanthosis, hyperkeratosis, and dyskeratosis.

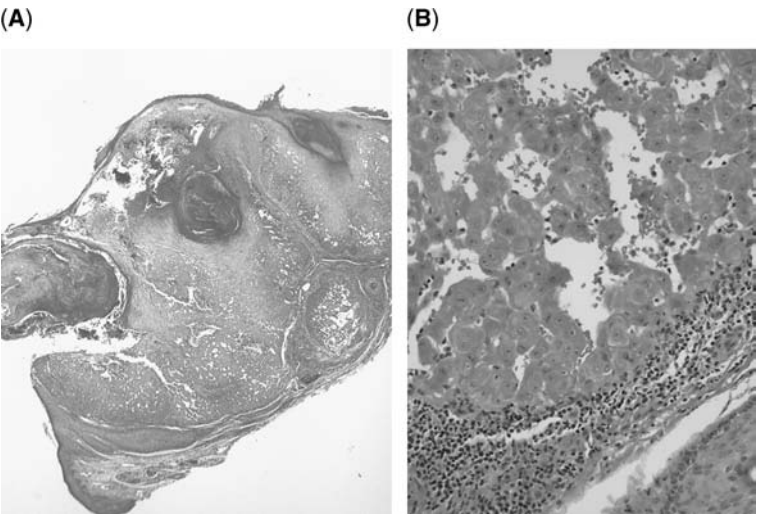


Figure 15 Keratoacanthoma. (A) Low-power view of a papule with a central hyperkeratotic plug. (B) The typical eosinophilic cells of the lesion. The rapid growth as well as the atypia that may be seen histologically may lead to a suspicion of a squamous cell carcinoma.

Table 14 Warty Dyskeratoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Warty dyskeratoma	None	Single flesh to brown papule with hyperkeratotic plug in center	Seborrheic keratosis, vulvar intraepithelial neoplasia, SCC, condyloma, Darier’s disease, keratoacanthoma	Excision

Abbreviation: SCC, squamous cell carcinoma.

Table 15 Keratoacanthoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Keratoacanthoma	Rapidly growing nodule	Raised pink or flesh-colored nodule on vulva, up to several cm, with keratinaceous plug	Squamous cell carcinoma, warty dyskeratoma	Excision or observation as lesion regresses

Keratoacanthomas are raised pink or flesh-colored lesions with a characteristic central invagination filled with keratin (22). If untreated, they will eventually involute and leave a scar. Histologically, the characteristic cup-shaped architecture with the keratin-filled crater is best appreciated on lower power. The cytoplasm of the squamous cells may be very eosinophilic and “glassy” (22), with minimal atypia or mitotic activity (29). The lesion may be difficult to differentiate from squamous cell carcinoma on a small biopsy, and a larger excisional biopsy may be required to make the distinction (29). The cup shape of the lesion may mimic a WD; however keratoacanthomas are likely to lack the acantholysis of WD, as well as have more atypia and mitotic activity than WD (Table 15) (28).

Mesenchymal Lesions

Dermatofibroma

Dermatofibromas are rare on the vulva (Fig. 16). They are usually slow-growing solitary reddish brown lesions that are flat or slightly raised, typically less than 1 cm in diameter. Characteristically, a “dimple sign” may be seen, a central umbilication upon squeezing the lesion. Histologically, the lesion is well circumscribed, with histiocytes and spindle cells interspersed with collagen bundles. Xanthoma cells and multinucleated giant cells may also be present. Overlying epithelium may show acanthosis and increased pigmentation (Table 16) (22).

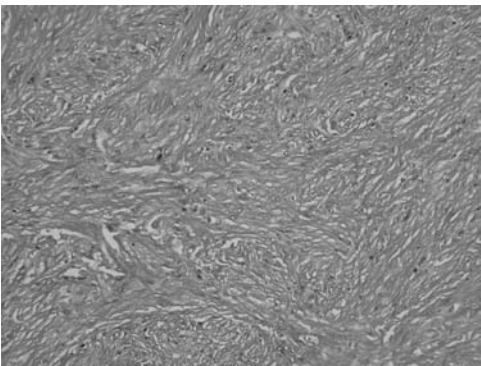


Figure 16 Dermatofibroma: benign-appearing fibroblasts in a collagenous background. The lesions also contain histiocytes, and Touton giant cells may be seen in some cases.

Table 16 Dermatofibroma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Dermatofibroma	Usually none	Small flat or nodular lesion, reddish brown	Pigmented lesions including nevus, melanoma Dermatofibrosarcoma protuberans	Excision

Hemangioma (De Morgan’s Spots) and Senile Telangiectasiae

Small capillary hemangiomas (cherry angiomas, De Morgan’s spots) of the vulva are not unusual in adults, particularly in the fair-skinned elderly (Fig. 17A). They are usually asymptomatic, but may rarely enlarge and bleed with pregnancy (30). Congenital capillary hemangiomas of the vulva may also occur in children and follow the usual history of growth, a static period, and then involution in most cases. Rarely, the potential for significant hemorrhage can occur with a larger congenital hemangioma (31). Histologically, cherry angiomas are characterized by a dermal proliferation of endothelial-lined vessels (Fig. 17B). Senile telangiectasiae occur with increasing frequency with age, and are more common in Caucasian women. They are blue-purple smooth-surfaced lesions, and occasionally rupture with trauma and bleed (Fig. 17C) (Table 17).

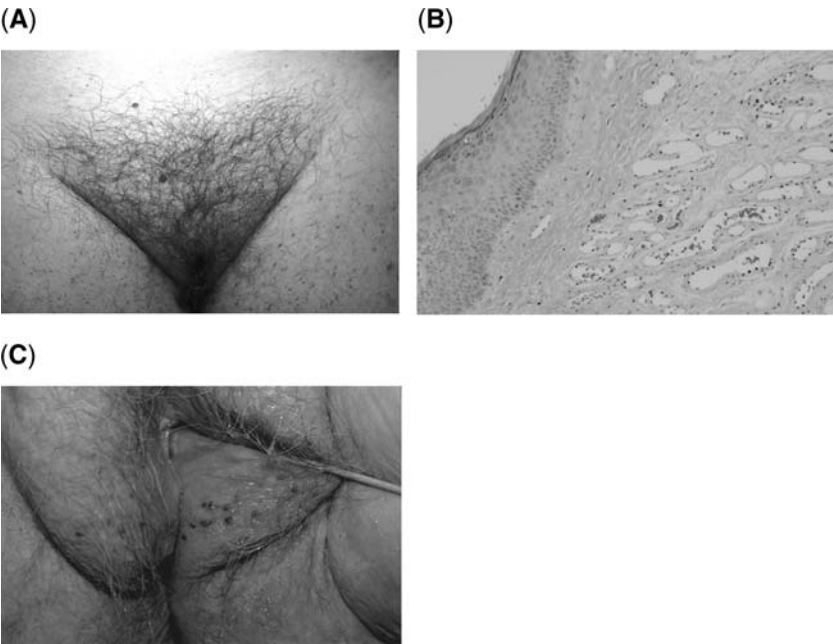


Figure 17 (A) Hemangioma: raised lesions which are red in color are seen. (B) Hemangioma: the lesion is composed of multiple dilated vascular spaces. (C) (*See color insert*) Senile telangiectasiae.

Table 17 Hemangioma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Hemangioma	Usually none. May rarely bleed	Red to purple dome-shaped papules in adults	None	None in most cases. If bleeding, can electrodessicate

Angiokeratoma

Angiokeratomas are uncommon on the vulva (Fig. 18). These benign lesions usually occur under the age of 50 and present as multiple, small purple unilateral papules. Histologically, the lesions comprise dilated vessels in the papillary dermis. The overlying epidermis shows hyperkeratosis, acanthosis, and papillomatosis. Degenerative changes may be seen in the perivascular elastic tissue. The vessels may be thrombosed (Table 18) (32).

Pyogenic Granuloma (Granuloma Pyogenicum)

Pyogenic granulomas occur in various regions of the body, and hence may be seen on the vulva (Fig. 19). They are usually single lesions with a tendency to occur in pregnancy. Grossly they are pink-red papular or nodular lesions, which may be pedunculated. The surface may ulcerate. Histologically, there is often central ulceration with the formation of a peripheral epithelial collarette as the epithelium grows downwards (22). The lesion is characterized by proliferation of capillaries, hence the other name, lobular capillary hemangioma, and histologically resembles granulation tissue. It is thought to occur secondary to trauma or a prior irritant condition rather than representing true neoplasm (Table 19) (33).

Lymphangioma Circumscriptum

Lymphangiomas of the vulva are rare, and may be either superficial or deep (Fig. 20). They may be either congenital or acquired. Superficial lesions (lymphangioma circumscriptum) are translucent or flesh-colored to pale papules, nodules, or vesicles. Lymphangioma circumscriptum may be congenital. For acquired lesions, the mean

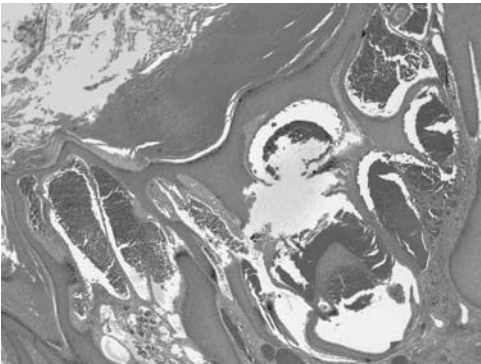


Figure 18 Angiokeratoma: cavernous vascular spaces in the papillary dermis with acanthosis and hyperkeratosis.

Table 18 Angiokeratoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Angiokeratoma	Usually none, but may have bleeding, pruritus, pain	Multiple purple papules < 1 cm	Infectious and inflammatory lesions, other vascular lesions (hemangioma, lymphangioma, pyogenic granuloma), various benign and malignant epithelial tumors (32)	None, or excision, electrodesiccation or laser therapy

age is about 42, but it affects a wide age range (34). The deeper lesions form an ill-defined mass with normal-appearing overlying epithelium. Histologically lymphangiomas are composed of dilated endothelial-lined spaces, and the lumens may contain lymphoid cells, red blood cells, or both. There may be overlying hyperkeratosis and acanthosis of the squamous epithelium (34). Valvular structures may be seen in the dilated channels, distinguishing the lesion from hemangioma (Table 20) (22).

Angiomyofibroblastoma

Angiomyofibroblastomas of the vulva are most often seen in reproductive age or early postmenopause (Fig. 21A–C) (20). They are well circumscribed and may be clinically interpreted as a Bartholin’s duct cyst or lipoma (17,35). Histologically, this benign lesion is characterized by a mass composed of hyper- and hypocellular areas containing spindle-to-round cells and delicate vessels in a collagenous or loose edematous background. Stromal cells typically stain for vimentin, desmin, ER, and PR and are negative for smooth muscle action (SMA), but there may be overlap with the staining pattern of aggressive angiomyxoma. These lesions must be distinguished histologically from aggressive angiomyxoma (see below). Vessels are more frequent and less likely to be hyalinized in angiomyofibroblastomas, and the stroma is more cellular (36). This and the circumscription of angiomyofibroblastoma, absent in aggressive angiomyxoma,

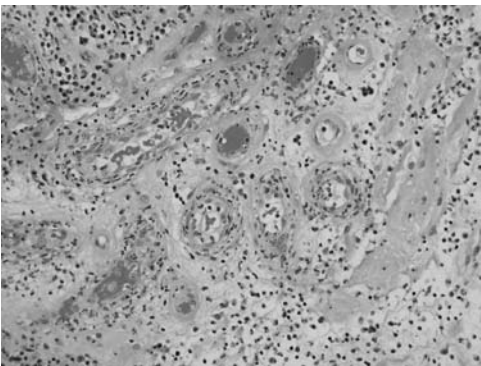


Figure 19 Pyogenic granuloma: granulation tissue, with numerous new vessels and abundant inflammatory cells.

Table 19 Pyogenic Granuloma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Pyogenic granuloma	None	Often pedunculated nodule, red granulation tissue-like appearance	Condyloma acuminatum, verrucous carcinoma, hidradenoma	Excision

aid in the distinction. There are sporadic case reports that suggest that rarely angio-myofibroblastoma may undergo sarcomatous transformation (Table 21) (20).

Aggressive Angiomyxoma

These lesions are locally aggressive and infiltrative, but metastasis is exceptional (Fig. 22) (20). They may be interpreted as a cyst on clinical examination. Grossly, they have a rubbery or gelatinous cut surface. Histologically, the lesion is poorly circumscribed—an important distinction from angio-myofibroblastoma. The cellular-ity is low—a distinction from the more cellular angio-myofibroblastoma. The histology of aggressive angiomyxoma is one of bland spindle cells in a myxoid matrix. Collagen and smooth muscle cells may cuff thick hyalinized vessels. Extra-vasated erythrocytes may be seen in the stroma (36). The lesions may be positive for desmin and actin (17), as well as ER and PR (20). Paravaginal origin with caudal extension may present at the vulva (Table 22).

Granular Cell Tumor

Granular cell tumors are usually benign solid lesions that can occur in a variety of locations on the body, but are seen in the vulva in about 10% of cases (Fig. 23) (37). They may be multiple, and may involve other organs as well (38). They are unencapsulated, which probably contributes to the tendency to recur locally, and rare malignant cases have been described (39,40). The name relates to the micro-scopic “granular” appearance of the sheets of large polygonal, spindle, or round cells with abundant eosinophilic cytoplasm. Although there have been multiple theories as to the cell of origin, granular cell tumor is now believed to most likely be of Schwannian derivation, and stains for s100 protein and CD 68. Treatment is

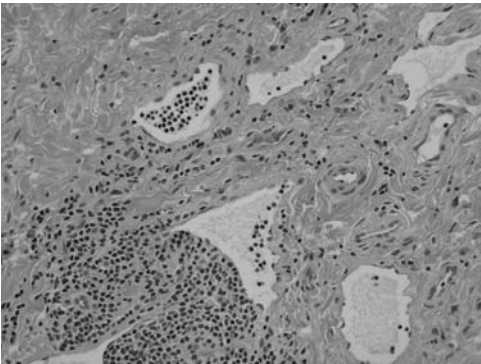


Figure 20 Lymphangioma: dilated lymphatic vascular spaces, some containing lymphocytes, are seen.

Table 20 Lymphangioma Circumscriptum

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Lymphangioma circumscriptum	Often none. May see oozing of fluid, pain, pruritus, swelling, cellulitis	Small pale papules if superficial, mass if deep	Condyloma acuminatum, blistering conditions	None, or electro-desiccation, excision, laser therapy or sclerosing therapy for small lesions, excision for large ones

Table 21 Angiomyofibroblastoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Angiomyofibroblastoma	Mass lesion	Well circumscribed, < 5 cm	Clinical: Bartholin’s cyst, lipoma. Pathological: aggressive angiomyxoma, fibroepithelial polyp, cellular angiofibroma	Excision

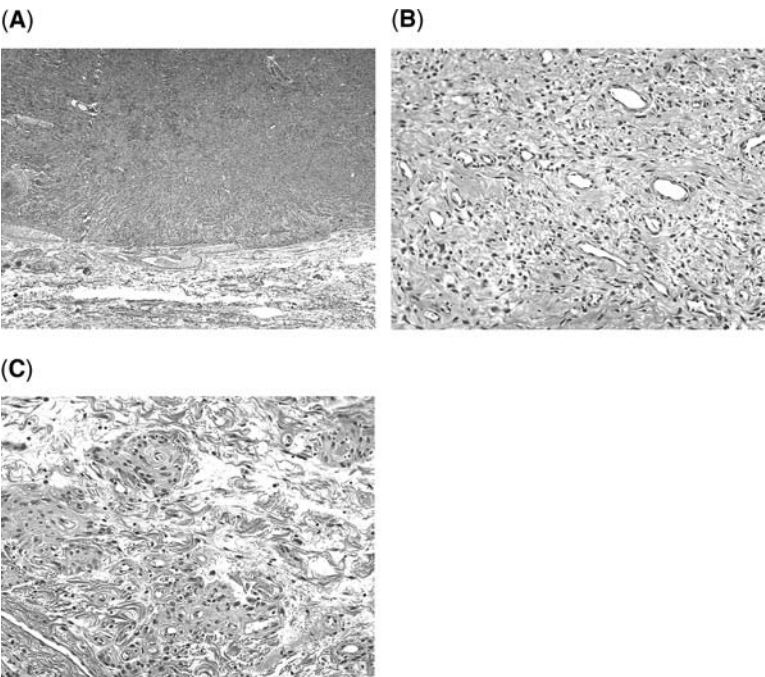


Figure 21 Angiomyofibroblastoma. (A) The lesion is well circumscribed. (B) (*See color insert*) Bland spindle cells in a collagenous background with numerous thin-walled vessels. (C) Mixed hypocellular and more hypercellular areas, with cells tending to cluster around vessels. *Source:* Courtesy of James Scurry, MD, Nextpath, Newcastle, Australia.

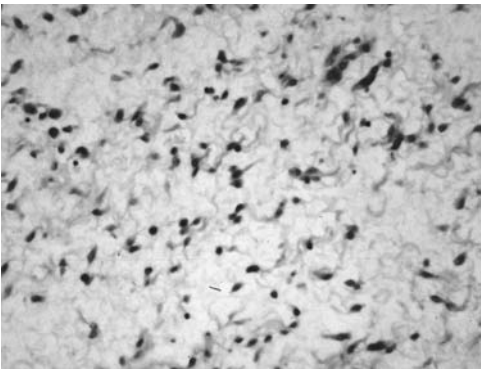


Figure 22 (See color insert) Aggressive angiomyxoma: the lesion tends to be more hypocellular than angiomyofibroblastoma, with a myxoid background. Vessels tend to be thicker walled. The lesions are poorly circumscribed.

excision. In addition to the potential clinical impression of carcinoma because of the present of a mass, the overlying squamous epithelium often shows pseudoepitheliomatous hyperplasia, which may be mistaken histologically for a squamous cell carcinoma, particularly on superficial biopsies (Table 23) (37).

Leiomyoma

Smooth muscle neoplasms of the vulva are relatively uncommon (Fig. 24). They are usually benign, although leiomyosarcomas have been described arising in the vulva. The age range of cases is wide. Theories of origin of smooth muscle neoplasms in this region have included erectile tissue, blood vessel smooth muscle, round ligament, dartos muscle, and erector pili muscle (41). The lesions stain for smooth muscle markers immunohistochemically. The criteria for distinguishing benign from malignant tumors is less well established than in the uterine counterpart. Histology may be variable, with epithelioid cells in a plexiform pattern and myxoid change not infrequent. Features associated with recurrence or metastasis in one series (42) were size of 5.0 cm or greater, infiltrative margin, five or more mitoses per 10 HPF, and grade 2 to 3 nuclear atypia. The authors diagnosed leiomyosarcoma when at least three of these criteria were met, atypical leiomyoma when two were met, and leiomyoma for one or none. Nucci and Fletcher (17) suggest that any mitotic activity, nuclear pleomorphism, or infiltrative margin are risk factors for local recurrence, often many years later, and term a lesion with any of these features, but falling short of the definition of sarcoma, atypical (Table 24).

Table 22 Aggressive Angiomyxoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Aggressive angiomyxoma	Mass	Mass, cyst	Clinical: Bartholin’s cyst, or other cystic lesion. Pathologic: angiomyofibroblastoma, fibroepithelial polyp, myxoma, other myxoid lesions	Complete excision

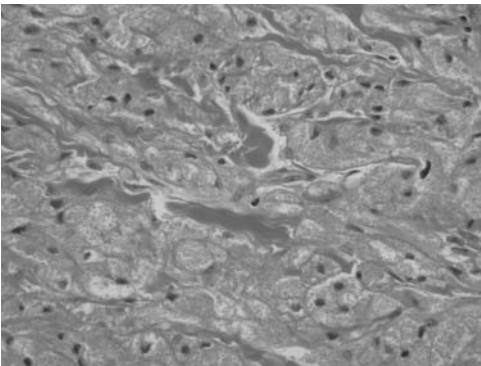


Figure 23 (See color insert) Granular cell tumor: the name comes from the granular appearance of the eosinophilic cytoplasm.

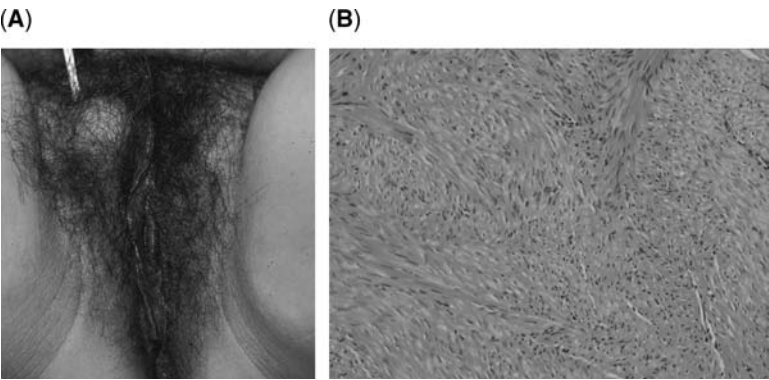


Figure 24 Leiomyoma. (A) A large nodule is seen in the right labium majus. (B) Typical appearance with interlacing fascicles of bland smooth muscle cells.

Table 23 Granular Cell Tumor

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Granular cell tumor	Small painless mass	Firm subcutaneous mass < 5 cm	Bartholin’s duct cyst, lipoma, hidradenoma, fibroma. Squamous cell carcinoma or sexually transmitted disease may be suspected by the clinician if overlying squamous epithelium is ulcerated (39)	Wide excision

Table 24 Leiomyoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Leiomyoma	Painless mass. Erythema, pruritus, pain also occur	Wide range of size. Well circumscribed.	Bartholin duct cyst, fibroma	Excision

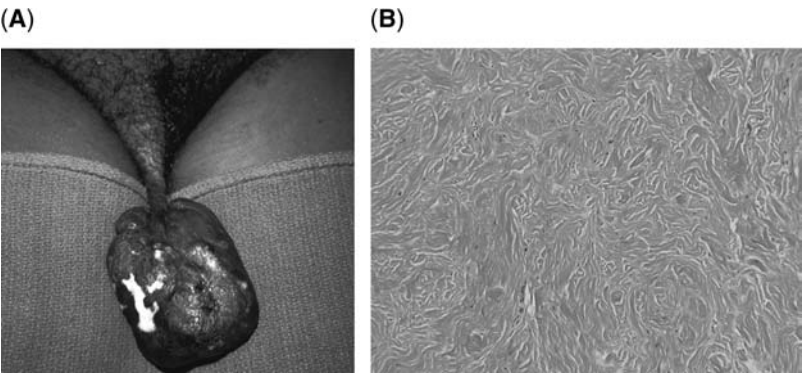


Figure 25 Fibroma. (A) Typical pedunculated lesion. (B) The lesion is composed of fibroblasts and abundant collagen.

Fibroma

Fibromas, while uncommon, are the most common benign neoplasm of the vulva, occurring most often in women aged 20 to 40, but have been reported across a broad age range (Fig. 25A and B). They may be small, but if over 8.0 cm, are usually pedunculated (42). They have an intact overlying squamous epithelium and are hypocellular lesions composed mainly of collagen, with a fibroblast component (Table 25) (22,42).

Lipoma

Lipomas are composed of mature adipose tissue with a thin fibrous capsule (Fig. 26A and B). They are generally asymptomatic, however may be of cosmetic concern. Rarely liposarcomas and atypical lipomas have been described. In Nucci’s series (43), most resolved with excision, although one incompletely resected lesion recurred. These lesions were less circumscribed and showed varying degrees of atypia. One case was described as presenting as a Bartholin abscess (44). Recently, characteristic cytogenetic aberrations have been described as important in predicting the behaviors of lipomatous tumors (45); hence fresh tissue should be provided for cytogenetic analysis in lesions that are large and/or deep seated (Table 26).

Mammary-Like Tissue Within Vulva

Van der Putte (46) has described anogenital “sweat” glands that mimic the histology of breast tissue, most highly concentrated in the interlabial sulcus of the vulva. These are distinct from, but with some similarities to both apocrine and eccrine glands. Further postulated is that a variety of lesions can arise in these glands, ranging from fibrocystic change to fibroadenomas (47), hidradenoma papilliferum, and cases of

Table 25 Fibroma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Fibroma	None for smaller lesions, discomfort/pain for larger	Pedunculated mass	Leiomyoma	Excision

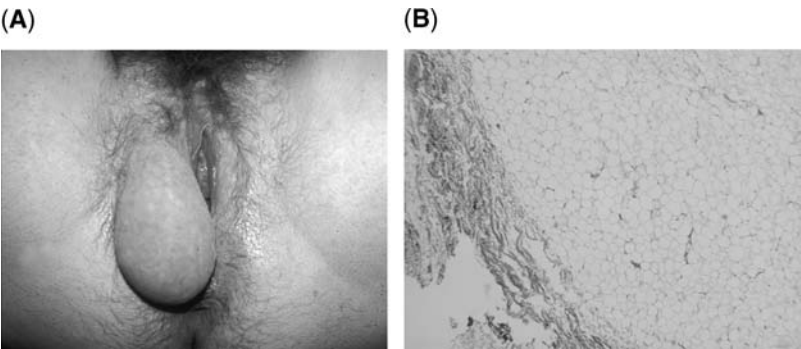


Figure 26 Lipoma. (A) Lesions may be large and pedunculated. (B) Lesion is composed of well-circumscribed adipose tissue.

Paget’s disease and invasive adenocarcinomas that are not of sweat gland origin. Supernumerary nipples (polythelia) or breasts (polymastia) usually occur along the milk line, and hence such a lesion can occur on the vulva. Breast tissue in a vulvar location may not be apparent prior to the hormonal stimulation of puberty or pregnancy. Ectopic breast tissue may develop the same lesions as eutopic breast tissue (48). Polythelia may be associated with other anomalies, particularly renal or cardiac (49). While usually a straightforward clinical diagnosis, excision of an ectopic nipple may be performed for diagnosis or cosmetic reasons (Table 27) (Fig. 27).

Neurofibroma

Neurofibromas of the vulva are rare (Fig. 28A and B). They may occur as isolated lesions, or may be part of the cutaneous manifestations of neurofibromatosis I (Von Recklinghausen’s disease). The labia may be involved, as may the clitoris (50). Labial lesions are usually small, rubbery lesions that may be nodular or polypoid; however giant lesions have been described (51). Clitoral enlargement because of a neurofibroma may mimic an intersex condition. There is a small risk of malignant transformation. Histologically, the lesions contain the elements of peripheral nerve (Schwann cells, neurons, and fibroblasts) in a disorganized pattern. The lesion is often seen in association with a peripheral nerve (Table 28).

PREINVASIVE (IN SITU) NEOPLASMS OF THE VULVA

Squamous Intraepithelial Neoplasia (Vulvar Intraepithelial Neoplasia)

There are two distinct types of vulvar intraepithelial neoplasia (VIN). One is related to HPV, the usual type of VIN, and is discussed here (Fig. 29A–D). VIN

Table 26 Lipoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Lipoma	Usually none	Soft mass lesion	Bartholin’s duct cyst, fibrolipoma, angiolipoma (variants)	None, excision, liposuction



Figure 27 Ectopic nipple: this example of ectopic mammary tissue is seen on the thigh.

unrelated to HPV, differentiated VIN, is discussed below. Usual VIN has a wide variety of clinical appearances and may appear as red, white, dark, flat, raised, or ulcerated lesions. Lesions may be multifocal or confluent. These HPV-related lesions are more common and more often recurrent in patients with immune suppression, or who smoke cigarettes. Terminology is variable, and encountered terminologies may include the three-tiered VIN 1,2,3, or the two-tiered low- and high-grade squamous intraepithelial lesion. Whether VIN 1 exists or is actually the same as a reactive lesion or condyloma is controversial, and recently the International Society for the Study of Vulvovaginal Disease (ISSVD) has adopted a terminology that only includes VIN as a high-grade lesion (see below). Histologically, VIN may have a warty or basaloid configuration (52). Warty lesions have a prominent HPV cytopathic effect with koilocytosis, but are distinguished from condyloma acuminatum by the degree of maturation abnormality. Basaloid lesions resemble the smaller cells of the basal epithelial layer with hyperchromatic nuclei, which as part of the maturation abnormality, extend up above the basal layer (above the lower third). Patterns may be mixed as well. In cases of low-grade lesions where diagnosis is uncertain, positive Ki-67 (MIB-1) immunostaining above the basal layer is helpful in confirming the diagnosis (53). Immunostaining above the basal layer is also seen in high-grade lesions, which occasionally may be confused with atrophy (54) (Table 29).

ISSVD terminology for squamous VIN 2–3, high-grade VIN (2003)

1. VIN, usual type
 - a. VIN, warty type
 - b. VIN, basaloid type
 - c. VIN, mixed (warty/basaloid) type
2. VIN_r differentiated type^a

^a The occasional example of VIN that cannot be classified into either of the above VIN categories (usual type and differentiated type) may be classified as VIN, unclassified type. The rare VIN of pagetoid type may be classified as such, or placed in this category.

Table 27 Ectopic Nipple

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Ectopic nipple	Usually none	Usually recognizable	Other pigmented lesions. If ectopic breast tissue, other mass lesions	Excision if warranted

Differentiated Vulvar Intraepithelial Neoplasia

Differentiated VIN, a lesion unrelated to HPV, is much less common than the usual HPV-related VIN (Fig. 30A and B). It occurs in postmenopausal women, significantly older than women in whom usual VIN is seen, and is thought to pose a more significant risk of progressing to invasive squamous cell carcinoma (55). It is associated with, and may be seen adjacent to, the non-HPV-related squamous cell carcinomas of the vulva that arise in older women. Clinically, the lesions of differentiated VIN are more subtle than usual VIN lesions. They may be unifocal or multifocal and tend to be pale white or gray plaque-like or nodular areas. They may appear simply as thickened areas. Differentiated VIN is often seen in a background of lichen sclerosus or squamous hyperplasia (56,57) The lesion may also be quite subtle histologically, and may be misdiagnosed as squamous cell hyperplasia because of the parakeratosis and acanthosis. Atypia is minimal, and confined to the basal layers, with large eosinophilic keratinocytes containing nuclei with coarse chromatin and prominent nucleoli. Whorls of differentiated cells with or without keratin pearls may be seen (56). The lesion usually stains for p53, as opposed to usual VIN, which does not (Table 30) (57).

Paget's Disease of the Vulva (Extramammary Paget's Disease)

Paget's disease of the vulva presents as a velvety red lesion with overlying white plaques and may present with severe pruritis, burning, or bleeding (Fig. 31A and B).

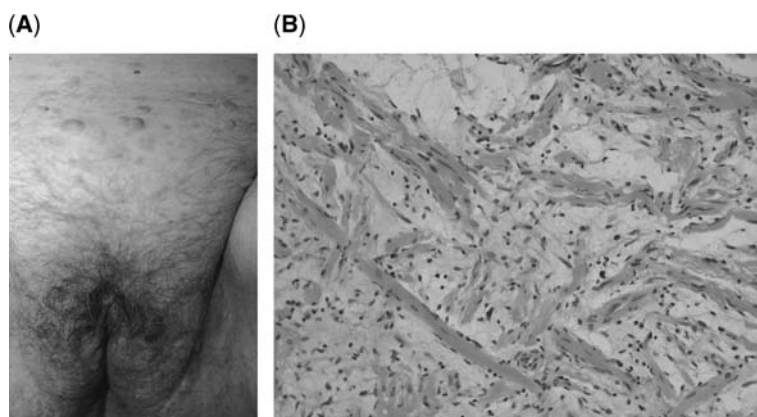


Figure 28 (A) Neurofibromatosis: numerous lesions are seen on the mons pubis. (B) Neurofibroma: typical “shredded carrot” bundles of collagen in a myxoid background containing cells of neural origin.

Table 28 Neurofibroma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Neurofibroma	None if small. Mass lesion if large. May cause clitoral enlargement	Small brown nodules or plaques. May be pedunculated. May have a violaceous color	Other pigmented lesions	Excision if warranted

The lesion tends to recur, probably related to the fact that histologically the lesion extends beyond the grossly detectable borders. It is associated with both underlying skin adnexal and Bartholin’s adenocarcinomas, as well as noncontiguous adenocarcinomas of other organs such as the rectum or breast (58,59). The incidence of these

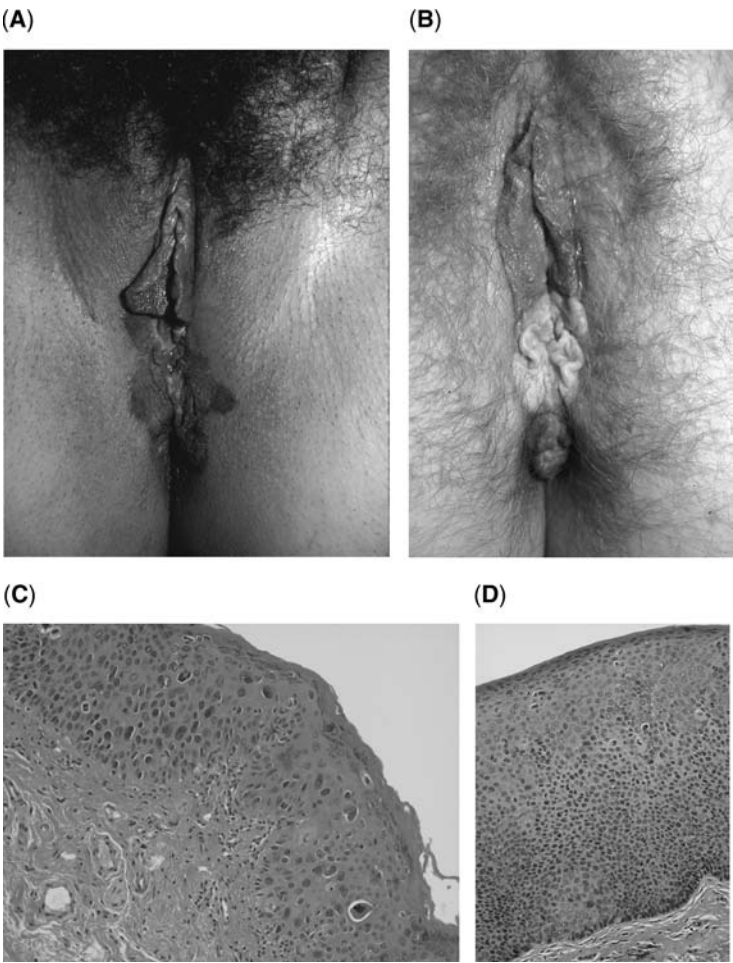


Figure 29 Vulvar intraepithelial neoplasia (VIN), usual type. (A) (*See color insert*) This VIN lesion is pigmented. (B) (*See color insert*) This is an example of a depigmented VIN lesion. (C) (*See color insert*) In the warty pattern, cytopathic features of human papilloma virus are prominent. (D) In the basaloid pattern, the entire epithelium is placed by small basaloid cells.

Table 29 Vulvar Intraepithelial Neoplasia, Usual Type

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Vulvar intraepithelial neoplasia	None, pruritus	Widely variable	Wide, depends on lesion color	Excision, imiquimod

carcinomas varies widely in different series, but these cancers have occurred in less than one-third of cases in most reports (60). Histologically, the large eosinophilic Paget cells may be seen in the basal layer of the epithelium, around skin appendages, and percolating up the epithelium (“Pagetoid spread”). Most cases of Paget’s represent an in situ carcinoma; however, invasive Paget’s disease may occur, with Paget cells invading the dermis. Extramammary Paget’s disease may also represent a manifestation of an underlying adenocarcinoma of skin appendages such as sweat gland adenocarcinoma. Paget’s disease must also be differentiated from pagetoid spread of urothelial or an anorectal carcinoma. All these variants of Paget’s disease will appear similar, both clinically and histologically. Primary vulvar Paget’s disease stains for CK7 and GCDFP-15, but rarely for CK20. Anorectal lesions stain for CK20 and are negative for GCDFP-15, and usually for CK7. Urothelial lesions stain for CK7 and CK20 and are negative for GCDFP-15 (61). Melanomas may also exhibit Pagetoid spread, but will stain for HMB-45, Melan-A, and S100 and be negative for cytokeratins (Table 31).

INVASIVE NEOPLASMS OF THE VULVA

Squamous Cell Carcinoma

It is now recognized that there are two types of squamous cell carcinoma (SCC) of the vulva: the human papilloma virus (HPV)-related lesions seen in younger women and those unrelated to HPV seen in older women (Fig. 32A–D). The HPV-related lesions

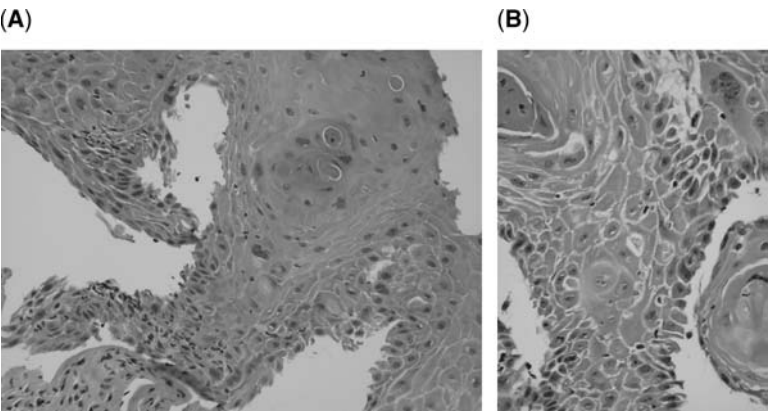


Figure 30 Differentiated vulvar intraepithelial neoplasia (VIN). (A) The atypia of differentiated VIN is often subtle, with a few basal atypical cells, and dyskeratosis. (B) (*See color insert*) The cells show glassy eosinophilic cytoplasm, pronounced cell borders, and prominent nucleoli. There is a keratin pearl in the left upper portion of the field.

Table 30 Differentiated Vulvar Intraepithelial Neoplasia

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Differentiated vulvar intraepithelial neoplasia	Usually none	Pale plaque(s) or nodules	Squamous cell hyperplasia	Excision

often have a basaloid, warty, or mixed histology (see description in VIN, usual type), while the HPV-unrelated lesions are well-differentiated carcinomas with abundant keratinization and pearl formation (57). HPV-negative carcinomas may be associated with lichen sclerosus and squamous cell hyperplasia, and whether or not these lesions pose a risk of developing carcinoma is still controversial although Fox and Wells (57) have stated that women with lichen sclerosus, while they do not usually develop carcinoma, are clearly at increased risk (57). Because this is the most common malignant vulvar neoplasm, it is often suspected in a wide variety of lesions, and clinicians are trained to be liberal in their biopsy practices. Squamous cell carcinomas may be endophytic or exophytic lesions and may be pale or red most often. Histologically, the invasiveness of the lesion can be confirmed by the stromal response, desmoplastic or inflammatory, to the invasive nests of squamous epithelium. Lesions associated with HPV are often warty, basaloid, or mixed, as in the HPV-related VIN lesions. Similarly, the non-HPV-related invasive carcinomas have some of the features of differentiated VIN and are usually well differentiated with abundant keratinization and keratin pearls (Table 32).

Verrucous Carcinoma

Verrucous carcinomas are large exophytic lesions that resemble large condylomas (Fig. 33A–D). This gave rise to the older term “giant condyloma of Buschke-Loewenstein.” It is better to avoid that terminology, as it may give a false sense of

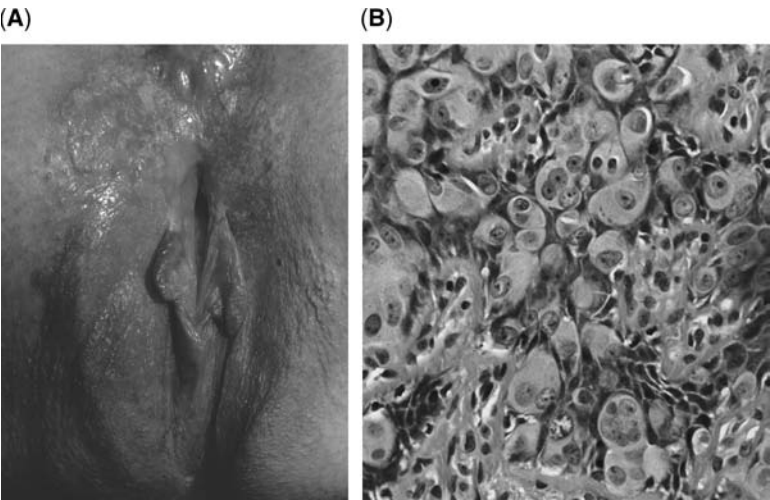


Figure 31 (See color insert) (A) Paget’s disease: the lesions are red and velvety, with white patches. (B) The typical large Paget cells contain abundant pale cytoplasm and are seen at the dermal–epidermal junction, as well as percolating up the epidermum.

Table 31 Extramammary Paget’s Disease

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Extramammary Paget’s disease	Pruritus, burning, bleeding	Red velvety lesions with white plaques	Melanoma (histologically), Paget’s disease of urothelial or anorectal origin	Wide excision for non-invasive disease

benignity to the clinician. These lesions are associated with HPV type 6 and 11 (62). There is often reactive induration of tissue adjacent to a verrucous carcinoma, as well as reactive lymphadenopathy, which may raise the clinical suspicion of metastatic disease (63). Pathological diagnosis may be difficult, as superficial biopsies may not

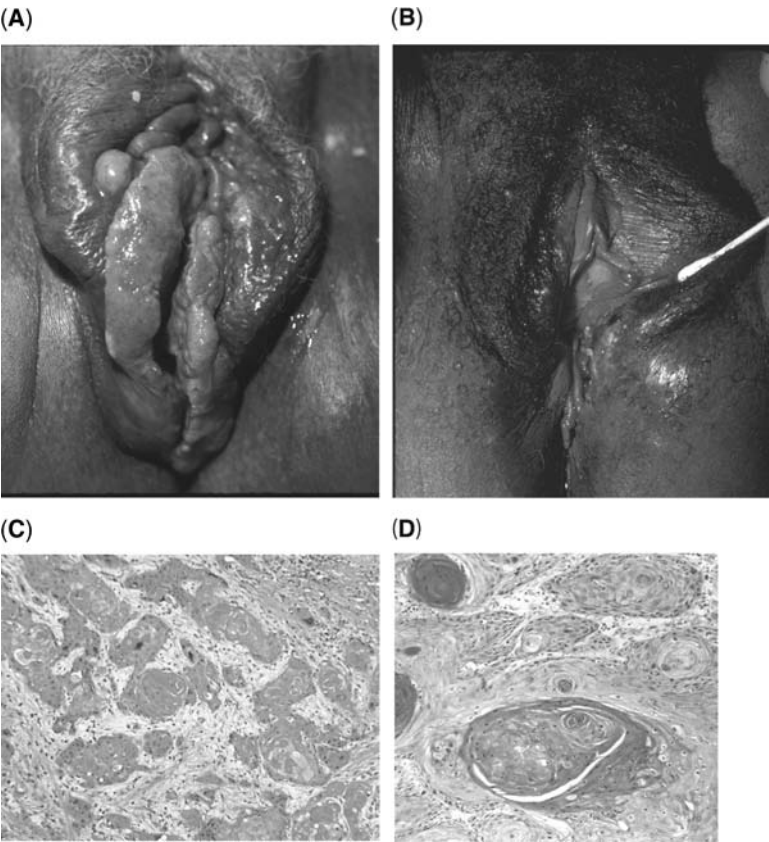


Figure 32 Squamous cell carcinoma of the vulva. (A) This is an example of an exophytic lesion. (B) (See color insert) This is an example of an endophytic lesion. (C) Typical appearance of squamous cell carcinoma, non-HPV-related type. Irregular tumor nests are invading the stroma, which is exhibiting a desmoplastic reaction. (D) In the non-HPV-related tumors, the lesions are often well differentiated and exhibit keratin pearls as demonstrated here. Abbreviation: HPV, human papilloma virus.

Table 32 Squamous Cell Carcinoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Invasive squamous cell carcinoma	None when small. Pruritus and bleeding when large	Ulcerating or exophytic lesion	Basal cell carcinoma, keratoacanthoma, sexually transmitted diseases if ulcerative	Usually radical surgery, with possible adjuvant radiation therapy. Cryosurgery to the primary lesion has been reported in advanced disease

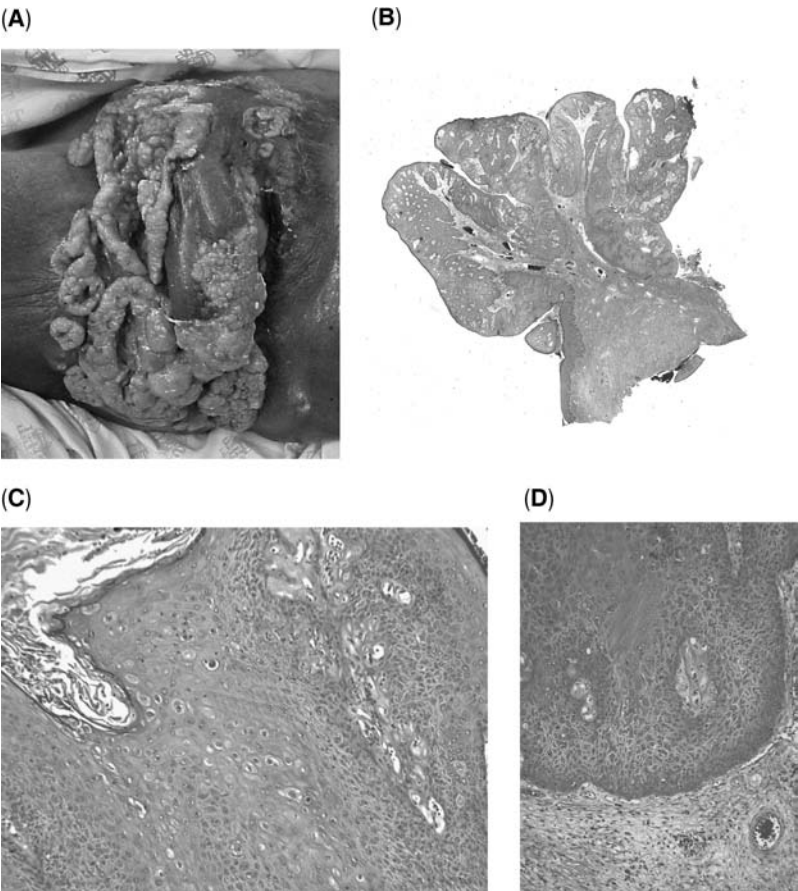


Figure 33 Verrucous carcinoma. (A) Lesions grossly appear large and warty. (B) Low-power view demonstrating the warty architecture. (C) Lesions show minimal atypia, and there may be human papilloma virus cytopathic changes. (D) These lesions exhibit a “pushing” border, in contrast to the invasive border seen in usual squamous cell carcinoma.

Table 33 Verrucous Carcinoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Verrucous carcinoma	Mass, pruritus	Large exophytic warty mass	Condyloma acuminatum, squamous cell carcinoma	Wide local excision

include the deeper portions needed to histologically document invasion. The overall histology is similar to that of condyloma acuminatum, with minimal atypia, and possible koilocytosis, but verrucous carcinomas have a pushing invasive front. These lesions rarely metastasize. Radiation therapy has been reported to induce anaplastic change (Table 33) (59).

Melanoma

Although not commonly encountered in routine practice, melanoma is the second most common vulvar invasive malignancy after squamous cell carcinoma (Fig. 34A and B) (See chapter on pigmented lesions of the vulva) (59). Pigmented lesions of the vulva must be viewed with this in mind, as prognosis for melanoma relates to depth of invasion (thickness), and hence early diagnosis is critical. The cells of melanoma may percolate up through the epithelium in a manner similar to Paget's cells, but can be distinguished by their staining for HMB-45, S100, or Melan-A. Therapy is surgical. Depth of invasion is measured differently than in squamous cell carcinoma (where it is measured from the most adjacent dermal papilla), utilizing a Breslow thickness, which is the entire thickness of the lesion from the top of the granular layer, excluding the acellular keratin to the deepest area of invasion. Chung's levels, a variant on the Clark's levels used for cutaneous melanoma, have also been applied, recognizing the difference in vulvar skin (lack of a distinct papillary and reticular dermis) (Table 34).

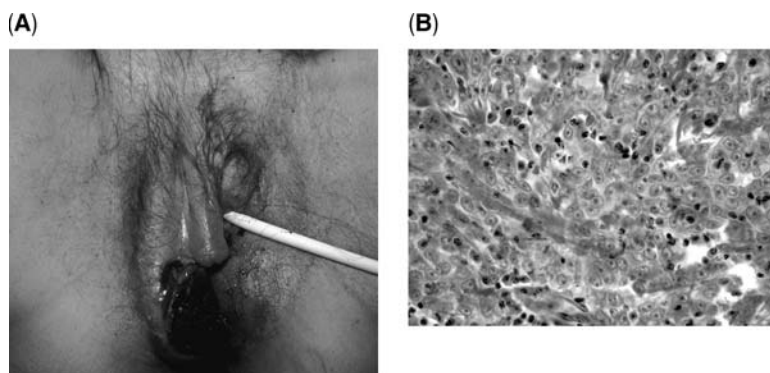


Figure 34 Melanoma. (A) Darkly pigmented lesion. (B) (See color insert) The lesion is often composed of epithelioid cells with prominent nucleoli. Melanin pigment may be present or not. Melanomas may mimic a variety of neoplasms, and a variety of stains are available to confirm the nature of the lesion.

Table 34 Melanoma

Diagnosis	Symptoms	Appearance	Differential diagnosis	Therapy
Melanoma	None, mass, itch	Usually raised, pigmented, often on labia minora or clitoris (59)	Other pigmented lesions	Surgical

Basal Cell Carcinoma

Although common on the skin, basal cell carcinoma of the vulva represents only about 2% to 3% of vulvar carcinomas (Fig. 35) (64). These tend to be locally invasive lesions, but can rarely metastasize, particularly if associated with more aggressive histologic subtypes, including basosquamous, morpheaform, metatypical, or micronodular (65,66). Vulvar basal cell carcinomas usually occur on the labia majora, and are most often found in Caucasian women 70 years of age and older (66). Diagnosis is often late because of lack of symptoms. The tumor suppressor protein P16, overexpressed by HPV, has been detected immunohistochemically in some cases (Table 35) (67).

Lymphoepithelioma-Like Carcinoma

Although a common Epstein–Barr virus (EBV)-associated nasopharyngeal tumor, lymphoepithelioma-like carcinoma is rare in the vulva, and may not be associated with EBV (Fig. 36) (68). Although reported to behave less aggressively in extranasal sites, the case of Niu et al. (68) was associated with inguinal lymph node metastasis. The tumor is composed of sheets of epithelioid cell with a dense lymphoplasmacytic infiltrate (Table 36).

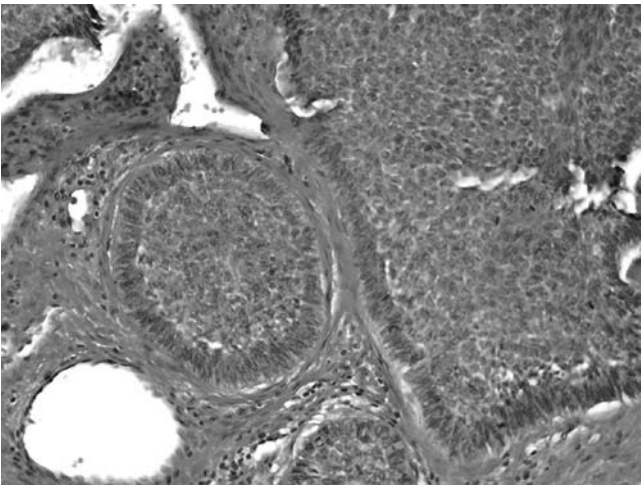


Figure 35 Basal cell carcinoma is characterized by peripheral palisading of the basaloid cells in the tumor nests.

Table 35 Basal Cell Carcinoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Basal cell carcinoma	None, or mass or ulceration, itching, bleeding	Mass with ragged ulcer	Clinical psoriasis, eczema, pathologic-squamous cell carcinoma	Wide local excision

Bartholin’s Gland Carcinoma

A mass in the region of the Bartholin’s gland in a woman over the age of 40 should raise suspicion of a Bartholin’s gland carcinoma, although a cyst or abscess is significantly more common (Fig. 37A and B). Carcinoma becomes a significant concern if the patient is postmenopausal. Most carcinomas of the Bartholin’s gland present as painless masses. Itching and bleeding may also occur (69). As carcinomas may arise from the gland or rarely from the duct, it is possible to have adenocarcinomas, squamous cell carcinomas, and transitional cell carcinomas. A rare variant is adenoid cystic carcinoma, with its characteristic cribriform appearance, with hyalinized material in the cystic spaces. Residual normal glandular elements may be recognized in Bartholin’s carcinomas. Overlying skin is usually intact (Table 37).

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a low-grade malignancy normally seen in subcutaneous tissues (Fig. 38A and B). It rarely involves the vulva. It tends to recur after excision but rarely metastasizes (70), although the rare development of fibrosarcoma has been described (71). Histologically, DFSP is composed of bland spindle cells that stain for CD34. It often extends beyond the obvious gross borders in small projections, which is probably contributory to the recurrences (Table 38).

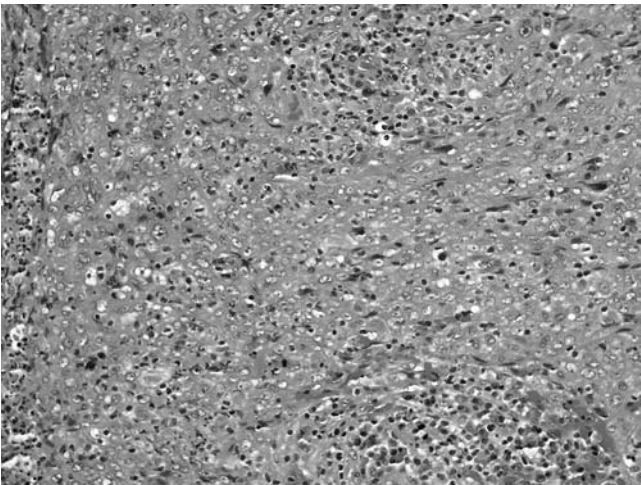


Figure 36 Lymphoepithelial carcinoma: a mix of neoplastic glassy epithelioid cells and lymphocytes is seen.

Table 36 Lymphoepithelioma-Like Carcinoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Lymphoepithelioma-like carcinoma	Mass	Mass	Lymphoma	Surgical

Metastatic Tumors to Vulva

A variety of neoplasms have been reported to metastasize to the vulva, including other neoplasms of the genital tract (endometrium, ovary, and cervix) (Fig. 39). Gastrointestinal and urinary tract neoplasms may also metastasize to vulva on occasion, and rare cases of metastatic breast cancer to vulva have also occurred (72). Clinically, the lesions may appear similar to a primary vulvar carcinoma. Treatment is directed to the primary neoplasm, although excision for palliation may be utilized (Table 39).

BENIGN LESIONS OF THE URETHRA

Urethral Prolapse

Urethral prolapse is seen primarily in African-American girls under the age of five, or in postmenopausal Caucasian women (Fig. 40) (73). The condition may present with bleeding. Examination reveals a donut-shaped mass of red tissue surrounding the urethral meatus, with a centrally placed opening. Medical measures are usually attempted prior to surgery. In the postmenopausal patient, the concern for a urethral carcinoma may arise (Table 40) (74).

Urethral Caruncle

Urethral caruncles are not uncommon in postmenopausal women, but their bright red fleshy appearance may occasionally raise the concern for a carcinoma (Fig. 41).

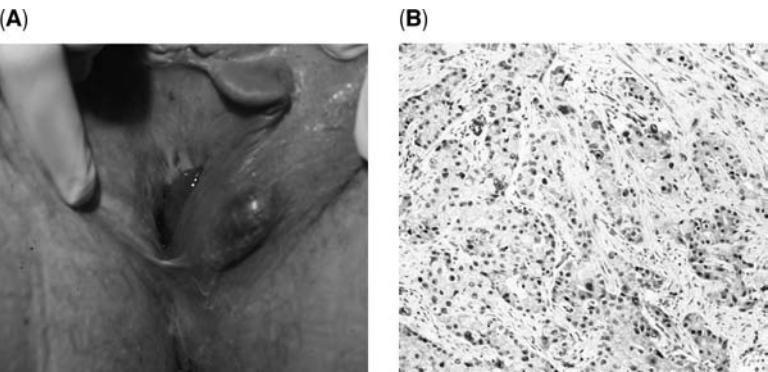


Figure 37 Bartholin’s carcinoma. (A) Note swelling in the region of the left Bartholin’s gland. (B) These lesions may be squamous, transitional, or adenocarcinoma as shown here.

Table 37 Bartholin's Gland Carcinoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Bartholin's gland carcinoma	Painless mass, itching, bleeding	Mass in region of Bartholin's gland	Bartholin's cyst or abscess	Surgery, usually modified radical vulvectomy, and lymphadenectomy. Adjuvant radiation may be utilized, and rarely chemotherapy

Caruncles, which probably represent ectropion of the distal posterior urethra (76), may be related to the hypoestrogenic milieu of menopause. They appear as red polypoid protrusions from the urethra. Histologically, the diagnosis is usually clear cut. The lesion has a polypoid or papillary configuration and is lined by sometimes hyperplastic squamous or transitional cells. There are abundant vessels and inflammatory cells in the stroma, with an appearance of granulation tissue; however, Young et al. (77) have described an unusual variant containing atypical stromal cells mimicking a lymphoma or sarcoma (Table 41).

Malacoplakia of the Urethra

Malacoplakia is a rare form of granulomatous inflammation usually affecting the genitourinary tract (78). Its occurrence in the female urethra is exceedingly rare. Histologically, the lesions are composed of a mixed inflammatory infiltrate with abundant histiocytes with granular cytoplasm, many containing characteristic intra- and extracellular Michaelis–Guttman bodies (Fig. 42). These bodies are felt to arise

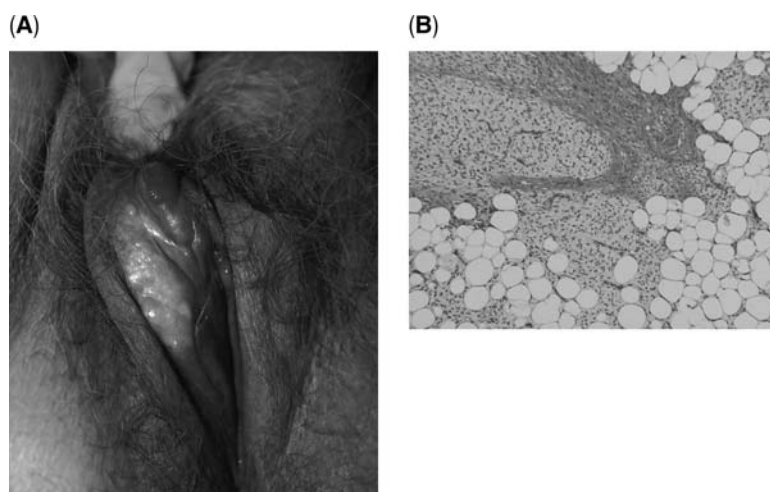


Figure 38 Dermatofibrosarcoma protuberans. (A) The lesion is arising from the inner left labia minora. (B) An important clue to the nature of this bland-appearing spindle cell lesion is its infiltrative nature, as seen in this subcutaneous adipose tissue.

Table 38 Dermatofibrosarcoma Protuberans

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Dermatofibrosarcoma protuberans	Mass, ulceration, pain, bleeding	Red, brown, or flesh-colored nodules (70)	Benign fibrous histiocytoma, dermatofibroma	Wide local excision

from mineralization of phagocytosed material (78). A relationship to *Escherichia coli* infection is frequent. Immune dysfunction has been postulated as an etiology (Table 42) (79).

Paraurethral (Skene’s Duct) Cyst

Skene’s duct cysts are uncommon benign cysts that occasionally occur in the para-urethral region in infants as well as adults (Fig. 43). Cysts may arise from Skene’s ducts or some of the smaller periurethral glands. Skene’s glands are analogous to the male prostate, and the glands may contribute to lubrication during sexual arousal. Skene’s duct cysts are lined by transitional epithelium (80). A variety of cysts in this region may be lined by squamous, transitional, or a mixture of epithelia (81). Acquired squamous inclusion cysts, after trauma such as childbirth, as well as Müllerian and Wolffian (mesonephric, or Gartner’s) cysts may also arise in a paraurethral location (82). It is important for periurethral cystic lesions to be appropriately worked up, to avoid inadvertently encountering an ectopic ureterocele. Rare solid benign and malignant neoplasms may also be encountered in the periurethral



Figure 39 Metastatic renal cell carcinoma to vulva: there is nothing distinctive in the gross appearance to distinguish whether this is a primary or metastatic lesion, and histology and clinical history are important.

Table 39 Metastatic Malignancy to the Vulva

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Metastatic malignancy to vulva	Mass, nodule, plaque, ulcer	Similar to a primary neoplasm mass or ulcer	Primary vulvar carcinoma. Metastatic breast carcinoma must be distinguished from a primary carcinoma arising in breast-like tissue of vulva	Directed at primary tumor. Excision may be utilized

Table 40 Urethral Prolapse

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Urethral prolapse	Bleeding	Periurethral mass	Urethral caruncle or carcinoma in older patients. Prolapsed ureterocele, condyloma (acumination) rhabdomyosarcoma in children (75)	Medical measures including reduction, topical estrogen, particularly in children. Surgery for refractory cases. Surgery more usual in older patients

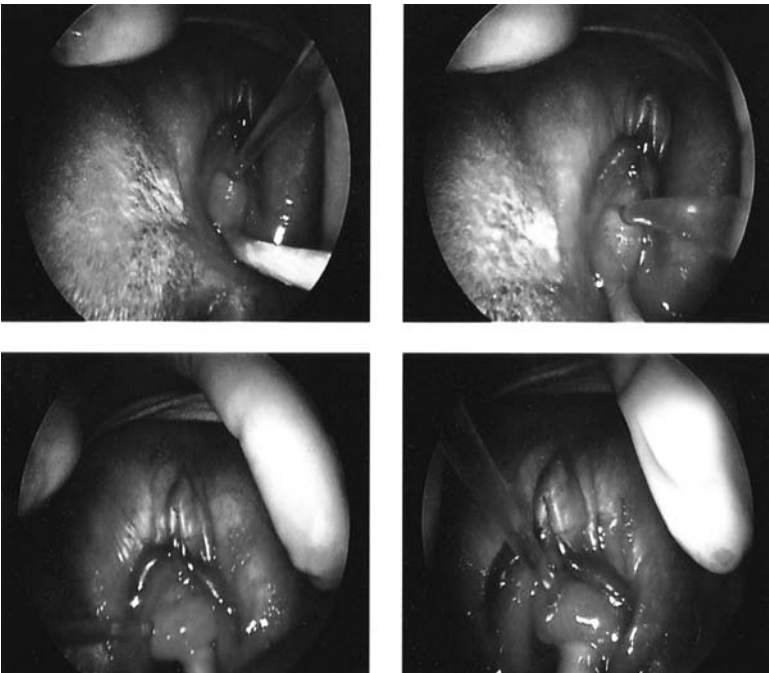


Figure 40 Urethral prolapse: images from reduction of a urethral prolapse in a child. *Source:* Courtesy of Natalie Roche, MD, UMDNJ–New Jersey Medical School, Newark, New Jersey, U.S.A.



Figure 41 Urethral caruncle: a fleshy red caruncle is seen protruding through the urethral orifice. In addition, clitoromegaly and a pessary are also seen.

region, including leiomyomas and vaginal neoplasms (73). Skene’s gland adenocarcinoma resembling a prostatic carcinoma has been described (Table 43) (83).

Suburethral Diverticulum

The etiology of urethral diverticulum is unknown (Fig. 44). Although postulated to occur as a result of childbirth trauma, they occur in nulliparous women as well. One theory is that they result from infection of Skene’s glands, and frequent catheterizations have also been proposed as an etiology (84). Urethral diverticuli are most common in the third to fifth decade (84). They may be difficult to diagnose (84), but may cause significant symptomatology. Occasionally calculi may form because of urinary stasis (85). Histologically, they are usually composed of fibroconnective tissue. Often, an epithelial lining is not present, but may be squamous or transitional (Table 44) (76).

Table 41 Urethral Caruncle

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Urethral caruncle	None, or pain, bleeding, discharge, hematuria	Small polypoid fleshy lesion at the urethral meatus	Urethral prolapse, urethral carcinoma, urethral condyloma	None may be required. Topical estrogen. Surgery or electrocautery rarely needed

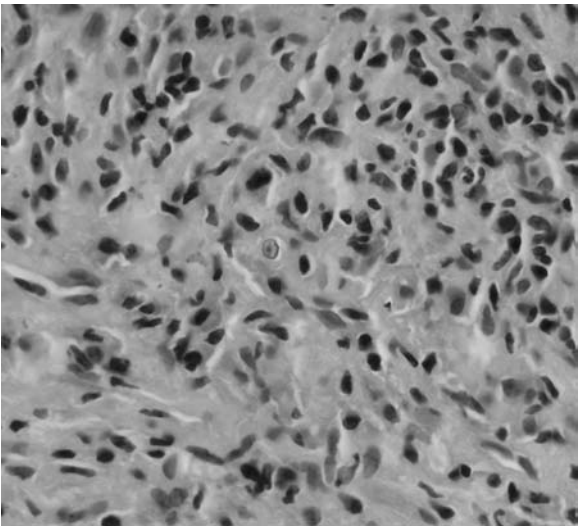


Figure 42 Malacoplakia: a characteristic Michaelis–Guttman body is seen in the center of the picture.

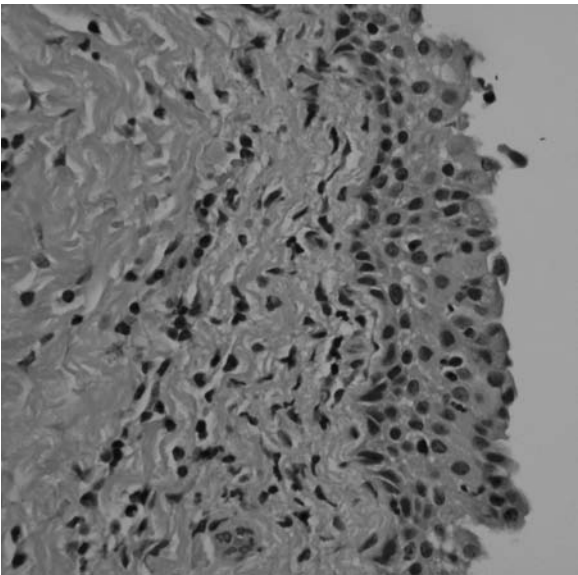


Figure 43 Skene’s (paraurethral) cyst: the cyst wall is lined by transitional epithelium.

Table 42 Malacoplakia of the Urethra

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Urethral malacoplakia	None, may have hematuria	May have a mass	Other urethral lesions including polypoid lesions, prolapse	Excision

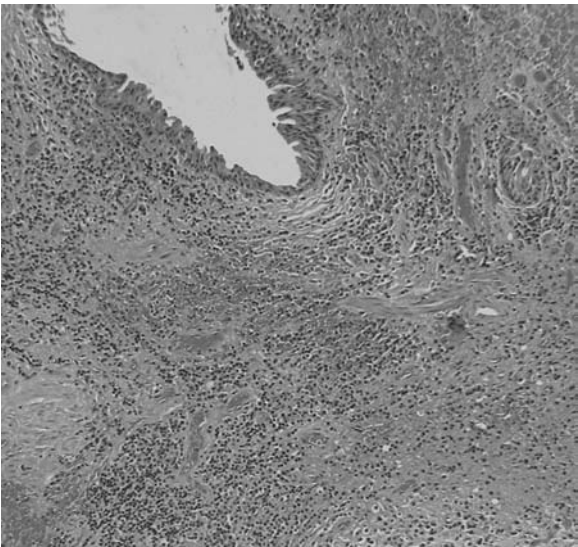


Figure 44 Suburethral diverticulum: the wall of the diverticulum shows marked inflammation.

Leiomyoma of the Urethra

Urethral leiomyomas are rare (Fig. 45). They present as masses in the vaginal wall, or protruding through the urethral meatus (86). Pathogenesis is uncertain; however they are felt to be ER dependent (87,88). Malignant transformation has not been reported. Histologically, they are composed of interlacing bundles of benign smooth muscle cells (Table 45).

Table 43 Skene’s Duct Cyst

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Skene’s duct cyst	Mass, dysuria, urinary spraying, pain, discharge, dyspareunia	Cystic mass	Urethral diverticulum, prolapsed ectopic ureterocele, cystocele, urethrocele, Gartner’s (Wolffian) or Müllerian duct cyst	Excision, marsupialization, needle aspiration

Table 44 Suburethral Diverticulum

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Urethral diverticulum	Recurrent urinary tract infection, incontinence, postvoid dribbling	Anterior vaginal wall suburethral mass, which may drain purulent or bloody fluid, or urine (81)	Ectopic ureterocele, paraurethral cyst, Gartner’s duct cyst, inclusion cyst, urethral carcinoma	Surgical

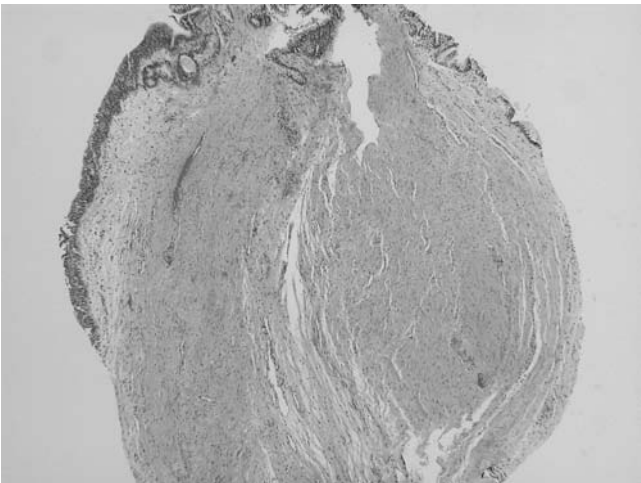


Figure 45 Urethral leiomyoma: small leiomyoma lined by urethral epithelium.

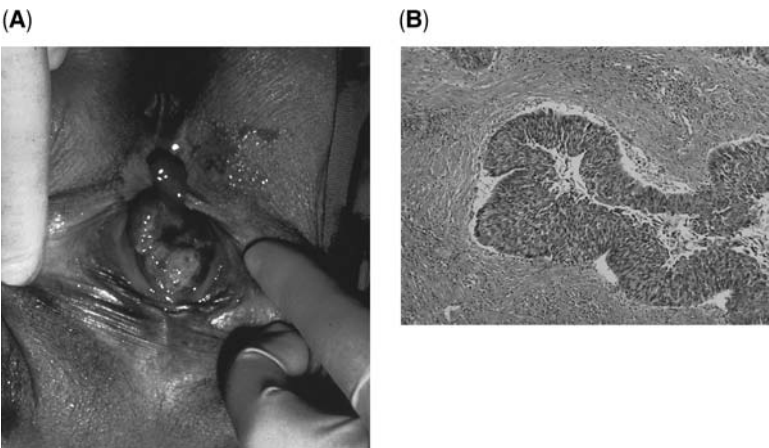


Figure 46 Urethral carcinoma. (A) Tumor mass protruding through urethra. (B) Infiltrating transitional cell carcinoma.

Table 45 Leiomyoma of the Urethra

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Urethral leiomyoma	Dysuria, difficulty voiding, urinary tract infection, hematuria	Urethral mass	Urethral caruncle	Surgical

Table 46 Urethral Carcinoma

Diagnosis	Symptoms	Clinical appearance	Differential diagnosis	Therapy
Urethral carcinoma	Obstruction, hematuria, vaginal/urethral bleeding, urinary tract infection, dysuria, frequency, incontinence	Mass	Caruncle, condyloma, urethral polyp, urethral prolapse	Surgery, possible radiation

MALIGNANT LESIONS OF THE URETHRA

Urethral Carcinoma

Primary urethral carcinomas are rare in women, but are more common than in men in most series (Fig. 46A and B) (89,90). They tend to occur in postmenopausal women (90). While potentially curable if of low stage, the vagueness of early symptomatology may lead to late diagnosis and poor outcome (91). Distal urethral neoplasms are more likely to be diagnosed at an earlier stage than proximal ones. Histology is variable, and carcinomas may be squamous cell, adenocarcinoma, adenosquamous carcinoma, transitional cell, or undifferentiated carcinoma, reflecting the variability of the lining cells in the female urethra. Carcinoma can arise in a urethral diverticulum (92), and these may be clear cell adenocarcinomas (90). Distal carcinomas tend to be squamous cell carcinomas, while proximal lesions are more likely either transitional or adenocarcinoma (90). Rare adenocarcinomas with enteric differentiation have also been described (Table 46) (93).

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7

Commentary

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INTRODUCTION

The combination of increasing longevity in the industrialized nations and disease processes more commonly found in the elderly may contribute to a heightened awareness of vulvar disease, much of which is related to advanced age.

LICHEN SCLEROSUS ET ATROPHICUS

Lichen sclerosus et atrophicus (LSA) may be found in males and females of all ages (1,2), but is typically a problem in older women appearing in the vulvar “keyhole” distribution (3,4). While it is generally assumed that LSA is an acquired disease, there are no longitudinal studies demonstrating its origin in normal skin, so that the possibility of congenital predisposition cannot be ruled out. Because the disease is occasionally found in premenarchal girls, an argument for congenital origin or genetic control may have some weight.

Attention has been paid to a potential defect in the immunological process leading to the development of LSA although laboratory evidence is not generally supportive (5–7). The mechanism leading to the histologic appearance of the dermis in LSA has not been elucidated but could be related to some deranged local tissue response, leading to the loss of defined architecture referred to as “homogenization” and the chronic inflammatory dermal response with round-cell infiltrate. A therapeutic inference from this consideration led to trials of topical tacrolimus and pimecrolimus that as macrolide immunosuppressants may be effective by inhibiting T-cell activation and cytokine production (6,8).

A familial tendency to LSA has been noted on occasion (9) but with only an occasional phenotypic demonstration, there is no significant impact on understanding this disease. I have personally seen a postmenopausal patient with LSA, whose sister also had the disease and I treated another patient with coexistent LSA and squamous cell carcinoma (SCC) whose daughter had severe LSA but no SCC. The issue of genetic predisposition would be of greater importance if a preventive therapy were available.

LSA AND SCC

Vulvar LSA has been incriminated as a precursor to some vulvar SCC, but the progression is suggested to occur in only 3% to 4% of patients with LSA (10–12). There are no studies to show LSA attack rates in the normal vulva with subsequent “progression” to SCC. The finding of LSA in patients with SCC does not necessarily confirm a causal relation as this may be pure coincidence, but a somewhat higher risk for SCC probably exists for vulvar dysplasia/hyperplasia (13). Because vulvar LSA is a pathologic condition, its ultimate cause may also predispose to SCC, or the LSA may provide a more fertile milieu for carcinogenesis, possibly abetted by loss of local tissue response or diminished immune surveillance. Because the patient with LSA may be at increased risk for SCC, close follow-up is needed especially in those cases where there has been associated squamous cell hyperplasia. A report from a well-known contributor (14) citing increased metabolic activity in LSA with the implication that this was related to progression to SCC was widely accepted when it appeared. Subsequent review suggested a major error in data analysis indicating that there was, in fact, decreased activity consistent with an atrophic lesion.

In the preceding paragraphs, reference has been made to lichen sclerosus et atrophicus (LSA) as opposed to the more common current use of the simpler term, LS. The use of the older, longer name is continued in some current literature (15) but is clearly fading in popularity. This author had the opportunity to work and study with the gynecologist Henry C. Falk, who, along with his colleague in dermatology, Arthur B. Hyman, was largely responsible for establishing the diagnostic criteria for this entity and clarifying the previous confusion regarding vulvar disease. “Kraurosis,” an imprecise and overly inclusive term, has been appropriately jettisoned. The longer name, LSA is used here, partly out of loyalty (16,17). As in other parts of language, usage dictates meaning and the shorter version is in vogue. But, the histologic appearance of the epithelium certainly merits recognition of atrophy (atrophicus), while the dermal appearance may not be appropriately called sclerotic (sclerosus) and future studies of the mechanism for the homogenization of the dermis with the round cell infiltrate may lead to a more specific name.

LSA TREATMENT

Embryologic homologies and empiric use led to the advocacy of topical androgens for LS. Long clinical experience and anecdotal reports attest to the popularity and apparent success of topical testosterone in the treatment of LS (9,18–21) and there are a few patients whose successful treatment has included low-dose oral testosterone. But, with the advent of the very potent topical corticosteroid, clobetasol, and with reports of its effectiveness (20), topical testosterone has little or no support in recent publications (21–23), but should not be dismissed. An appropriate clinical study to evaluate the efficacy of topical testosterone would be difficult to mount: withholding clobetasol would not be appropriate, but the criteria for determining the benefit of both agents together as opposed to the corticosteroid alone would be hard to construct (23).

Vitamin A, formerly, and the oral retinoid, acitretin, recently, have also been advocated in the treatment of LS and the latter may interact with nuclear receptors to alter gene expression (24).

VULVAR NEOPLASIA

The relation of human papilloma virus (HPV) infection to the development of cervical carcinoma suggests that a similar process may contribute to vulvar neoplasia (25) but additional epigenetic events (26) may be active in the progression to vulvar neoplasia. HPV-mediated transformation of human epithelial cells has been recognized as a multistep process resulting from the deregulated transcription of the viral oncogenes, E6 and E7, in proliferating cells. Interference with cell cycle regulators induces genetic instability and oncogenic alterations may lead to a malignant phenotype with tumor cell immortalization and inactivation of tumor suppressor genes. But, it has been suggested that there are two pathways leading to the development of SCC of the vulva (27). As with cervical carcinoma, one route is HPV dependent with premalignant changes of vulvar intraepithelial neoplasia analogous to cervical disease. But, an HPV-independent genesis without high-risk HPV seems to occur, although loss of or occult HPV may confuse the issue.

The diagnosis of vulvar dysplasia or carcinoma in situ is usually the result of a biopsy provoked by abnormal appearance to vulvar skin with or without symptoms. The risk of progression to invasive carcinoma is not established but local ablation is generally recommended. Options for treatment include surgical excision (wide local excision) or other tissue destruction techniques such as cryosurgery, laser vaporization, or topical chemotherapy, all of which include the side effects of treatment and the possibility of incomplete removal (28–33).

Invasive squamous cell cancer (SCC) of the vulva is usually identified on direct inspection but requires biopsy confirmation (34). Sentinel node sampling is gaining acceptance in the evaluation and management of the extent of disease (35–38). Surgical excision has been the standard treatment with the goal of removing the primary tumor and extending the surgery to include the primary drainage in the groin nodes. For disease extending to Cloquet's node or to the deep pelvic nodes, radiation therapy is generally added. Combined therapy including conventional surgery or cryosurgery or other local destructive therapy for the primary tumor has been used with radiation therapy added for control of nodal disease (34,39–42) and the role of chemotherapy in conjunction with other modalities has been studied (43,44).

PIGMENTED LESIONS

Pigmented lesions of the vulva will usually require biopsy for diagnosis, and 3% of melanomas occur on the vulva that has about 1.5% of the body skin area. Actinic radiation, sunlight, may play a role in the development of melanoma in exposed areas of skin, but the relatively high risk for melanoma of the vulva does not seem to reflect that origin (45,46).

A host of common or rare dermatologic and other diseases may present on the vulva, and a liberal policy of biopsy for visible or symptomatic lesions is mandatory. Access to the world literature through PubMed or other library source is especially important for diagnosis of unusual lesions whose gross clinical appearance may not be diagnostic (47) or for diseases not frequently treated by those who manage vulvar complaints (e.g.: aggressive angiomyxoma) (48,49).

VULVAR SYMPTOMS

In the absence of a histologic abnormality, vulvar pruritus, discomfort, and pain (vulvodynia) may or may not respond to a variety of treatments including improved hygiene, oral or topical medications, injections, or surgery (50). Most clinicians finding local inflammatory conditions of the vulva without a target lesion for biopsy will try to improve the local environment with attention to clothing and cleanliness (51), but if simple measures do not lead to rapid improvement, biopsies are necessary. Although irritant contact dermatitis is more common than allergic contact dermatitis, both the original irritant and the secondary sensitization to topical medications should be considered both in established vulvitis and in the initial treatment of a new complaint (52,53). As in similar complaints on other parts of the body, vulvodynia may persist after the original offending agent is long gone, with continued ineffective and irritating treatment used by the patient in an effort to control local symptoms while exacerbating them. It has been suggested that previous *Candida albicans* infection may predispose patients to a subsequent hypersensitivity response, which may be related to the complaint of discomfort or pain (54).

Vulvar vestibulitis syndrome (VVS) has been cited as the pathologic cause for occasionally intractable pain. Treatment options may include surgery (55) but without a guarantee of good result. With the potential for new or more severe symptoms, extreme caution is necessary before embarking on a surgical attack. The psychological aspects of VVS rank as high as the physical findings in deciding on a management plan (56), although the psychological characteristics as well as the local pathology are inconsistent. It has been suggested that some clinicians encounter, recognize, and treat more cases of VVS than are seen in general gynecologic experience. It is unclear whether referral patterns or diminished threshold for making the diagnosis lead to clustering of patients with this diagnosis.

GENITAL MUTILATION

Victims of female genital mutilation are rarely seen in the United States but are distressingly common in Africa (57,58). Surgical reconstruction will occasionally be useful and there are special considerations for the management of infertility and childbirth (59,60). The management of discomfort and pain will require thoughtful attention. The serious and occasionally lethal damage done to women subjected to female circumcision and infibulation has provoked transient attention in Europe and North America, and the damage has been studied and documented. An excellent review of the history of female circumcision is marred by deference to social custom with tacit partial approbation of this act (61). Equating female circumcision performed by untrained practitioners using primitive instruments without anesthesia to male circumcision performed by trained professionals with an established record of safety is a reckless implication in that review. Male circumcision as practiced in industrial societies does not leave a trail of blood and damage as is found too often with female circumcision, which is occasionally fostered by amateur midwives and others with a social or financial incentive. The generation of political and social pressure to control or eliminate the practice of female genital mutilation merits the support of all.

GENITAL ANATOMY

The clitoris has been the subject of recent studies ranging from description of the anatomy to the alleged functional benefits of clitoral hood piercing (62–64). A chapter in this text adds accuracy and completeness to the subject of genital anatomy, a subject that has been underemphasized in the past despite the valuable contribution of an encyclopedic illustrated text (65). The appropriate restrictions on exposure of the sexual anatomy in the clinical realm lead to a distressing lack of knowledge in medical students whose teaching of this subject is largely from texts that are inadequate in this area. Computerized and virtual anatomy teaching may improve knowledge of this body region.

Although representing only a small fraction of the external topography, the vulva is the location of many vital normal functions including coitus leading to conception, the terminal passage for birth and egress of urine with contributions to the control of defecation. Pathologic processes of the vulva can lead to troubling symptoms as well as life-threatening disease. Sexually transmitted diseases and ectoparasites as well as the full range of other dermatologic conditions and degenerative processes and trauma may involve the vulva. The vulva and its pathology are certainly subjects that merit attention and study and it is hoped that this text reflects those goals, provides useful information and reference sources, and will provoke further like efforts.

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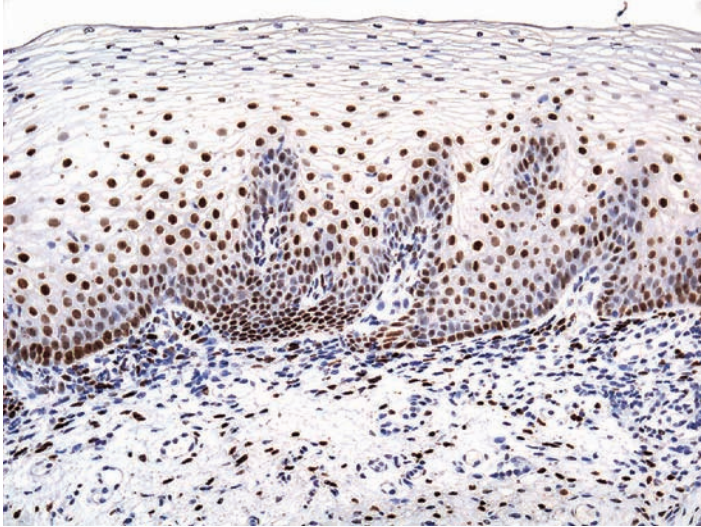


Figure 2.18 Estrogen receptors are positive. (brown-stained nuclei) in the deeper layers of the vestibular epithelium. An identical appearance is seen in the squamous epithelium of the vagina and urethra. (*See p. 29*)



Figure 2.20 Septate vagina, inferior view. *Source:* Courtesy of Dr. John Cassey, Newcastle, New South Wales, Australia. (*See p. 32*)



Figure 2.21 Imperforate hymen in a teenager, inferior view. *Source:* Courtesy of Dr. John Cassey, Newcastle, New South Wales, Australia. (See p. 33)



Figure 3.1 Irritant eczema. Glazed erythema of the most exposed areas in a patient with urinary incontinence. (See p. 38)

(A)



(B)

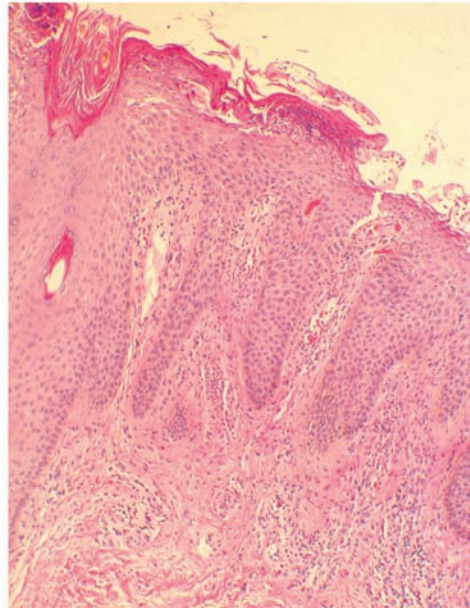


Figure 3.3 (A) Flexural psoriasis. Well-margined erythema of anogenital skin with some crusting. (B) Psoriasis. Characteristic elongated rete ridges and papillae, dilated vessels within papillae, and intraepithelial. (Munro's) microabscess. (See p. 39)



Figure 3.6 Vulvovaginal lichen planus. Glazed erythema on the inner aspects of the labia minora bordered on the left-hand side with a white edge. (See p. 42)



Figure 3.7 Lichen planus. Glazed erythema of the gingiva with striae in the sulcus. (See p. 42)

(A)



(C)

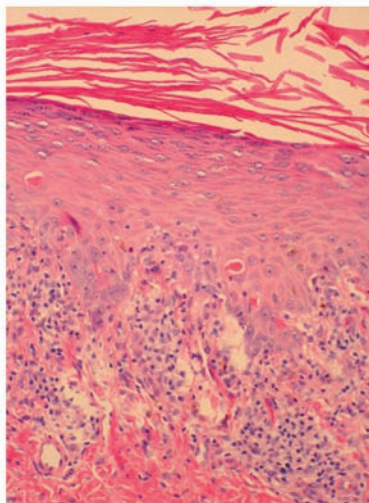


Figure 3.8 (A) Hypertrophic lichen planus. (LP) There is loss of the labia minora and the clitoris is buried. The vulval skin is white and hyperkeratotic with erythema in the inner aspect. (C) LP—saw-toothing deformity of rete ridges, uneven hypergranulosis, and orthokeratotic hyperkeratosis. (See p. 43)

(B)

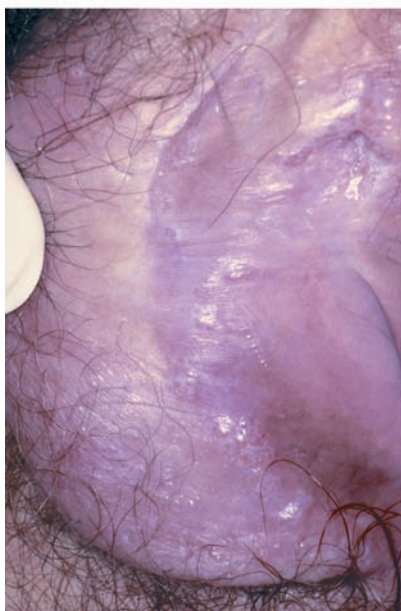


Figure 3.11 Crohn's disease. (B) Inner aspect of vulva in Figure 9. (p. 45) showing lymphangiectasia. (See p. 47)

(B)



(C)

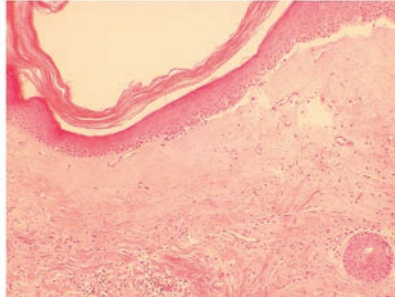


Figure 3.13 (B) Lichen sclerosus involving the vulva and perianal skin with extension into the genitocrural folds, resulting in loss of the labia minora and sealing over of the clitoral hood. (C) Lichen sclerosus—there is thinning of the epidermis with loss of rete pegs and dermal homogenization. Dermal inflammation beneath the area of dermal homogenization is variable and is minimal here. (See p. 50)



Figure 3.14 Benign aphthae with erythematous halo and slough-covered central ulceration. (See p. 52)



Figure 3.15 Lipschutz' ulcer. There are two large and deep ulcers apposed on either side. (See p. 52)



Figure 3.17 Hailey–Hailey disease. There is erythema with maceration in the genitocrural fold and tiny erosions. (*See p. 54*)



Figure 3.19 Erythema multiforme—characteristic targetoid lesions. *Source:* Image courtesy of W. Clark Lambert, MD, PhD., UMDNJ–New Jersey Medical School, Newark, New Jersey, U.S.A. (*See p. 56*)

(A)



Figure 3.22 (A) Bullous pemphigoid. Erythematous lesions with erosions and flaccid blisters. (*See p. 57*)

(A)



Figure 3.23 Pemphigus. (A) Erosions on right side of vulva. (*See p. 58*)

(C)

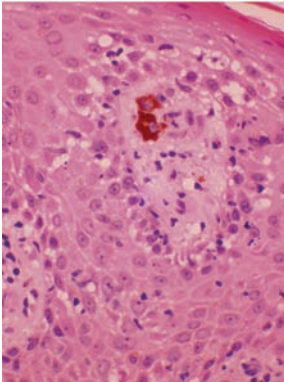


Figure 3.25 (C) Fixed drug eruption—vacuolization of the basal layer and pigmentary incontinence are seen. (*See p. 60*)

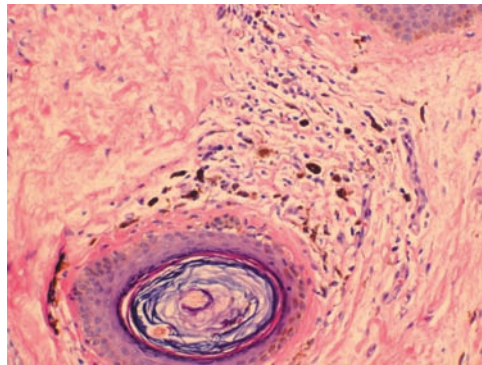


Figure 3.26 Postinflammatory hyperpigmentation—pigment incontinence is seen. (*See p. 60*)



Figure 4.8 Despite the careful descriptions of differing morphologies of ulcers in the various ulcerative sexually transmitted diseases, the ulcers often appear discouragingly similar. This lesion of chancroid cannot be diagnosed on morphology alone, but rather on clinical suspicion and laboratory investigation. (*See p. 82*)



Figure 4.13 Necrotizing fasciitis is characterized by hemorrhagic bullae because of ischemia from underlying infection that has destroyed the cutaneous vascular supply; resulting ulceration and hemorrhage can be seen in this patient who is in the healing phase. (*See p. 89*)



Figure 4.14 Erythrasma resembles tinea cruris, but the color is often more tan than red, and there is no peripheral accentuation of scale. (*See p. 91*)

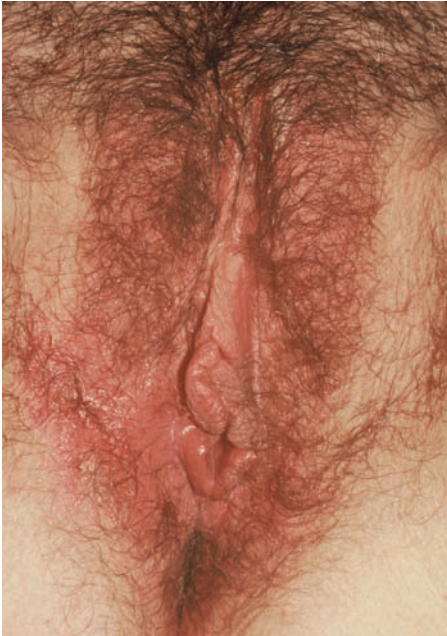


Figure 4.15 In uncommon cases, bacterial vaginitis can occur, extending to infect the skin and producing red, scaling, or exudative skin. (*See p. 92*)



Figure 4.17 Vulvovaginal candidiasis can produce redness, edema, and fissuring. (*See p. 94*)



Figure 4.19 Classic tinea cruris shows a red plaque on the proximal, medial thighs with accentuation and scale at the periphery of the plaque. (*See p. 97*)



Figure 4.21 Pityriasis versicolor is characterized by hypopigmented, pink, or tan. (as seen here) well-demarcated flat papules with very subtle scale. (*See p. 99*)

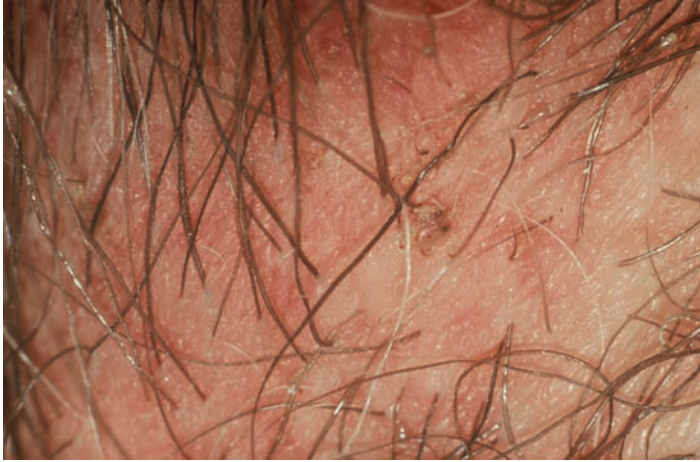


Figure 4.24 Pubic lice are small parasites that cling to pubic hair, with nits appearing as tear-drop-shaped eggs attached to hair shafts. (*See p. 103*)

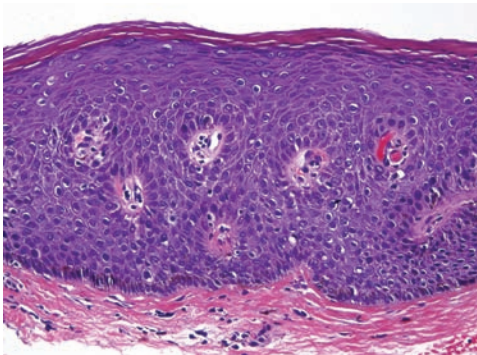


Figure 5.6 Melanotic macule. (lentigo and melanosis) Basal layer hyperpigmentation is seen without an increase in melanocytes or melanocytic atypia. (*See p. 114*)



Figure 5.9 Benign nevus on right labium minus. (*See p. 116*)

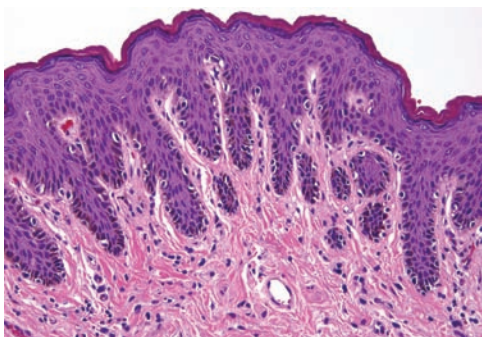


Figure 5.16 Atypical junctional melanocytic hyperplasia of the vulva. Melanocytes with slight cytologic atypia are arrayed as solitary cells along the basal layer of the epidermis. (See p. 120)

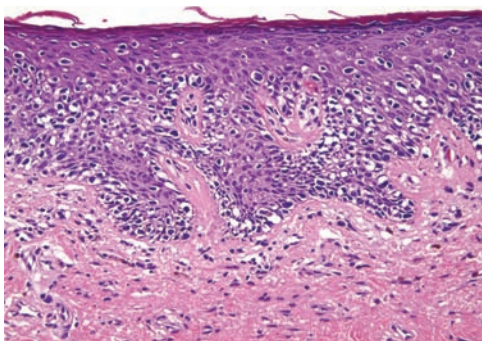


Figure 5.17 Melanoma in situ of the vulva. Cytologically atypical melanocytes are present in all levels of the epidermis. (See p. 121)

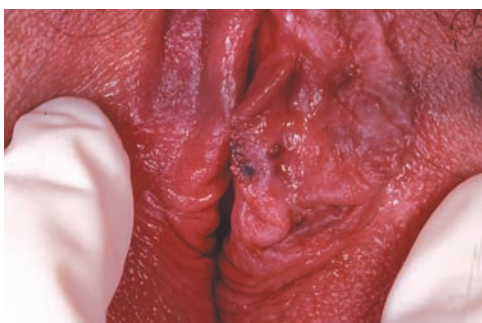


Figure 5.18 Melanoma of the left labium minus characterized by an irregular dark area. Source: From Refs. 30 and 50. (See p. 122)



Figure 5.20 Melanoma in 10-year-old child on two areas of the vulva in association with lichen sclerosus. Source: From Ref. 30. (See p. 127)

(A)



Figure 6.3 (A) Mucinous cyst of the vestibule. (See p. 137)

(A)



Figure 6.7 Endometriosis. (A) Grossly endometriotic implants on the vulva often have a blue appearance. (See p. 141)

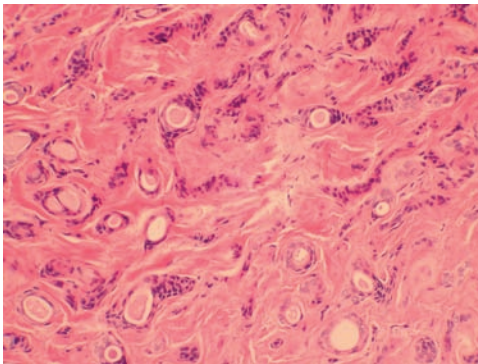


Figure 6.12 Syringoma: the characteristic comma-shaped epithelial nests in a collagenous background are seen. (See p. 145)

(C)



Figure 6.17 (C) Senile telangiectasiae. (See p. 149)

(B)

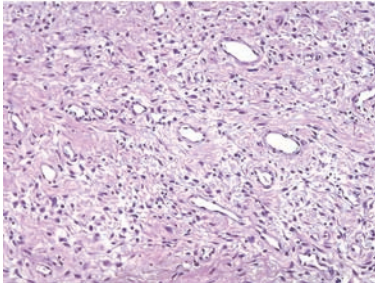


Figure 6.21 Angiomyofibroblastoma. **(B)** Bland spindle cells in a collagenous background with numerous thin-walled vessels. (*See p. 153*)

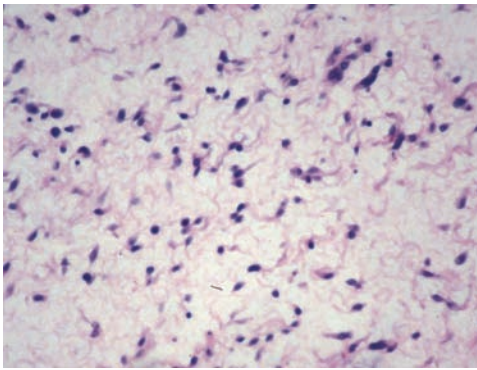


Figure 6.22 Aggressive angiomyxoma: the lesion tends to be more hypocellular than angiomyofibroblastoma, with a myxoid background. Vessels tend to be thicker walled. The lesions are poorly circumscribed. (*See p. 154*)

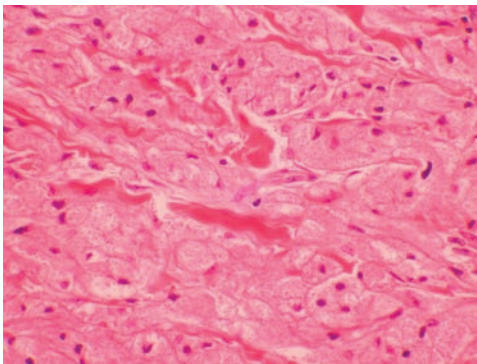


Figure 6.23 Granular cell tumor: the name comes from the granular appearance of the eosinophilic cytoplasm. (*See p. 155*)

(A)



(B)



(C)

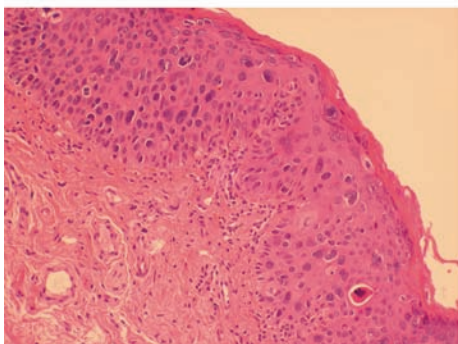


Figure 6.29 Vulvar intraepithelial neoplasia. (VIN), usual type. (A) This VIN lesion is pigmented. (B) This is an example of a depigmented VIN lesion. (C) In the warty pattern, cytopathic features of human papilloma virus are prominent. (See p. 160)

(B)

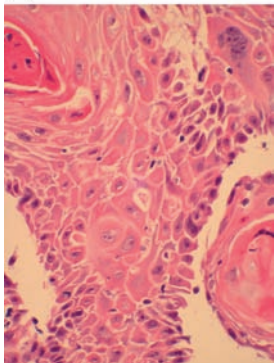


Figure 6.30 Differentiated vulvar intraepithelial neoplasia. (VIN). (B) The cells show glassy eosinophilic cytoplasm, pronounced cell borders, and prominent nucleoli. There is a keratin pearl in the left upper portion of the field. (See p. 161)

(A)



(B)

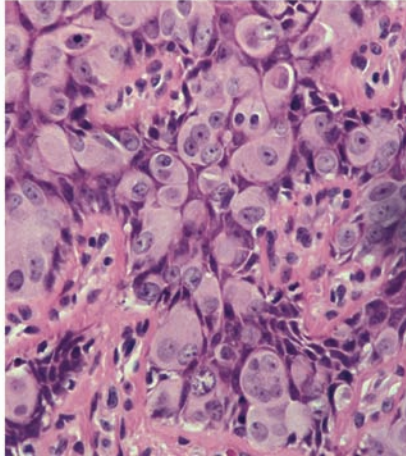


Figure 6.31 (A) Paget's disease: the lesions are red and velvety, with white patches. (B) The typical large Paget cells contain abundant pale cytoplasm and are seen at the dermal–epidermal junction, as well as percolating up the epithelium. (*See p. 162*)

(B)



Figure 6.32 Squamous cell carcinoma of the vulva. (B) This is an example of an endophytic lesion. (*See p. 163*)

(B)

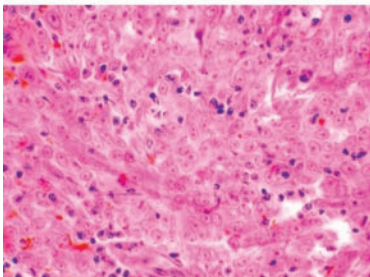


Figure 6.34 Melanoma. (B) The lesion is often composed of epithelioid cells with prominent nucleoli. Melanin pigment may be present or not. Melanomas may mimic a variety of neoplasms, and a variety of stains are available to confirm the nature of the lesion. (*See p. 165*)

about the book . . .

Filling a gap in the literature, this source covers all aspects of vulvar disease with an emphasis on symptoms, identification, and treatment. An excellent resource for this challenging diagnostic area, this guide provides summary tables at the end of each disease entity that expertly depict and analyze the clinical appearance, differential diagnosis, and management of lesions, inflammation and systemic diseases, infections, and benign and malignant neoplasms affecting the vulva.

Written in a convenient atlas format that clearly displays the diagnostic and therapeutic features of a variety of conditions, this source contains an abundance of illustrations and photomicrographs of clinical lesions...supplies diagnostic tables that summarize the symptoms, clinical and pathologic appearance, differential diagnosis, and treatment of specific disease entities...is paired with a CD-ROM that contains all the images in the text...studies the evolution and current approach to the management of vulvar conditions...and represents the collaborative efforts of international authorities in a variety of disciplines, including the Secretary-General of the International Society for the Study of Vulvovaginal Disease.

about the editors . . .

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