Female Genital Pain and Penetration Disorders

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4.1 Introduction

Female genital pain can result from various causes, including inflammation, dermatoses, and infections. In addition, up to 16 % of the female population is diagnosed with vulvar pain syndromes, also known as vulvodynia, defined as genital pain in the absence of an identifiable cause [1].

Often, there is a significant delay in making the actual diagnosis, with a reported mean time of 2 years and evaluation by up to 15 physicians prior to correct diagnosis [2]. This delay adversely affects patients, with subsequent emotional, sexual, social, and interpersonal impact. Causes for this unfortunate situation are multifactorial as it seems that many gynecologists are not familiar with the variety of disorders that cause female genital pain; secondly, in most cases the gynecological exam is not specifically directed at identifying vulvovaginal disorders; and lastly, specialists treating these disorders are scarce. The result is misdiagnoses (usually, "yeast infections") and delay of appropriate treatment.

The objectives of this chapter are to provide practical tools for caregivers who treat patients with genital pain conditions, to provide guidance for the assessment of patients, to discuss the differential diagnosis of female genital pain, and to present current guidelines regarding the management of two vulvar pain disorders, provoked vestibulodynia and generalized vulvodynia.

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4.2 Assessment of Patients with Genital Pain

Vulvovaginitis and vulvar dermatoses may cause itching, irritation, discharge, pain, and dyspareunia. On exam, erythema, edema, discharge, and tenderness may be noted. These symptoms and signs are nonspecific and may represent an inflammatory response to various causes. Most vulvovaginal disorders can be diagnosed by combining medical history, physical examination, and microscopic evaluation of vaginal discharge. In addition, cultures and PCR (polymerase chain reaction) assays are required for the diagnosis of specific pathogens and biopsies may be needed in cases of vulvar skin involvement or suspected neoplastic lesions.

4.2.1 History Taking

History taking may provide many clues required for an accurate diagnosis. A detailed symptom history is important, including the nature of symptoms, their location, severity, duration, whether they are continuous, intermittent or cyclical, whether provoked by touch or spontaneous,

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and what factors worsen or alleviate the complaints. It is important to clarify if the patient experiences discomfort of the external genitalia, the vestibule, or deep in the vagina, as these symptoms may represent different disorders. The patient may use adjectives such as burning, stinging, swelling, or discomfort rather than pain. It is also important to assess the effects on daily life and functioning. Inquire about treatments she might have tried, how these were used, and what was their effect. If a woman reports difficulties with intercourse, it is important to determine whether the pain is superficial, at the point of penetration (likely related to a vulvar or vestibular problem), or deep inside (deep dyspareunia). Inquire about tightening of the pelvic floor (PF) muscles: this may be apparent as painful penetration (vaginismus), urinary frequency, urgency and hesitancy, constipation, hemorrhoids, and anal fissures. It is also important to take a brief gynecological history including menstruation, fertility, parity, and contraception methods. Ask about the presence or history of skin conditions, allergies, and exposure to potential irritants and/or allergens.

While obtaining the history, be familiar with potential diagnoses and open to various possibilities. Don't be distracted as many patients will mention diagnoses they priorly received or have self-diagnosed using the internet. Finally, look for coexisting conditions and avoid the tendency to lump all symptoms into one disorder. It can be helpful to use questionnaires designed for comprehensive evaluation of vulvovaginal complaints (see references below).

4.2.2 Examination

It is important to remember that vulvodynia is a diagnosis of exclusion. Many inflammatory, infectious, and dermatologic disorders present with provoked vestibular pain and dyspareunia, or with unprovoked pain, and they should be ruled out by a comprehensive examination.

The examination should always include observation, evaluation of vestibular tenderness, vaginal examination with assessment of discharge using microscopy, pH measurement and vaginal cultures, pelvic organ and muscle palpation.

The use of a bright light to examine the vulva, vagina, and cervix is recommended. For the evaluation of the vulva, separate the labia with your fingers to look for any lesions, fissures, redness, or swellings. Gently retract the clitoral hood, exposing the clitoris. Examine the vestibule for epithelial thinning associated with estrogen deficiency or skin disorder.

Vestibular tenderness should be evaluated using the Q-tip test in which gentle pressure is applied to several spots in the vestibule using a Q-tip, while asking the patient to quantify the level of discomfort or pain (Fig. 4.1).

Examination of the vagina with a speculum may disclose a normal appearance of the vaginal

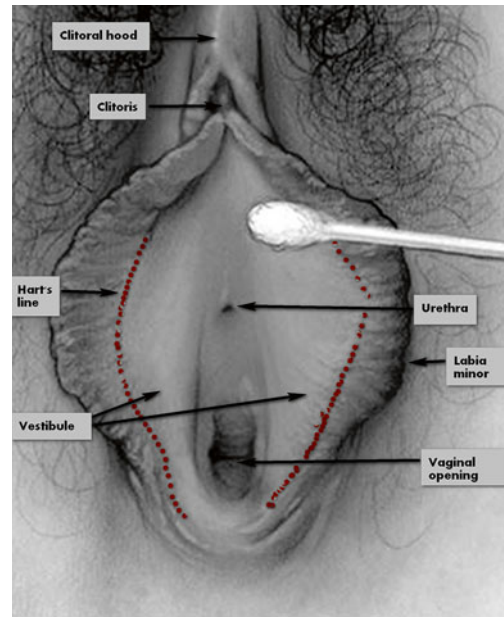

Fig. 4.1 The Q-tip test. The goal of the Q-tip test is to determine if there are areas that exhibit an abnormal pain response in the genital area. Use a cotton-tipped applicator to determine whether pain is provoked by pressure at one or more points. Apply gentle pressure to the following areas: inner thighs, labia major and labia minor, interlabial sulci, clitoris, clitoral hood, and perineum. Sites to be tested within the vestibule can be visualized using a clock face (1–12 o'clock). The anterior vestibular sites [2, 10, 12] are typically assessed first, followed by the posterior sites [5–7]. Apply gentle pressure to each of these sites and ask the patient to rate the pain severity and describe the pain character (burning, raw, etc.)

walls or diffuse redness, erosions, and petechiae, suggesting vaginitis. Notice the presence of discharge, its characteristics (consistency and color), and its origin (vaginal walls or cervix). As the signs on examination are nonspecific, a microscopic examination (wet mount) of vaginal discharge should be performed. Vaginal secretions are placed on microscope slides, and a drop of saline (0.9 % NaCl) and 10 % potassium hydrochloride (KOH) are added to each sample at separate locations. Microscopy can allow for the identification of fungal infection, trichomoniasis, parabasal cells (characterizing vaginal atrophy and estrogen deficiency) and allow for the diagnosis of desquamative inflammatory vaginitis (DIV) (Fig. 4.2).

When appropriate, obtain samples for laboratory studies. These include both cultures for the identification of specific fungal organisms and bacteria, as well as samples for PCR studies, to identify sexually transmitted organisms, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*.

Next, perform a digital palpation of the levator ani muscles for hypertonicity, tenderness and trigger points, palpation of the urethra, bladder trigone, pudendal nerves, uterus and adnexa. Additional studies, including biopsy, patch tests, or imaging should be performed as needed.

After completion of the history and examination, the provider should be able to diagnose the causative factor such as infectious or noninfectious vaginitis, skin disorders, and estrogen deficiency. After all known causes of genital pain are ruled out, vulvodynia can be diagnosed.

4.3 Causes of Female Genital Pain

Vulvovaginal pain may be caused by a variety of disorders. Pain may be constant or intermittent, provoked by touch or spontaneous, and may be classified in various ways. The most common classification system was developed by the International Society for the Study of Vulvovaginal Disease (ISSVD) [3]. It divides possible causes of vulvar pain into four categories: infectious, inflammatory, neoplastic, and neurologic [3]. In addition, it defines the term vulvodynia as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant and visible findings, or specific, clinically identifiable, neurologic disorder." This classification distinguishes between generalized and localized pain, and each of these subgroups is further subdivided into provoked, unprovoked, or mixed (continuous pain, exacerbated by touch). The term vulvodynia is reserved for these cases of vulvar pain occurring in the absence of physical findings [4] and therefore can be used only after specific, recognized disorders are ruled out (Table 4.1).

In the presence of inflammatory conditions, pain and dyspareunia may result from friction and damage of irritated tissues, tears, fissures, and irritation of sensitized and inflamed nerve fibers. It is beyond the scope of this chapter to review in detail the various vulvovaginal disorders. Therefore the discussion will be limited only to common conditions that may cause pain and must be ruled out prior to establishing a diagnosis of vulvodynia.

Yeast Infection is a common cause for vulvovaginitis and 80–90 % of cases are caused by *Candida albicans* [5]. Symptoms vary from slight vaginal discharge and discomfort to a severe form of vulvovaginitis including itching, pain, burning, and dyspareunia. In such cases, vulvar swelling, fissures, and erythema are commonly present (Fig. 4.2a). Most vulvovaginal yeast infections do not present with specific findings on vaginal examination, including the classic curdy cheese-like discharge often associated with Candida infections. As symptoms and signs of vulvovaginal candidiasis are often nonspecific, a laboratory diagnosis is often essential. Microscopic examination may aid with the diagnosis (Fig. 4.2b), but the precise species cannot be recognized; therefore, a culture is needed to identify the specific organism and confirm the diagnosis.

A single episode of yeast vulvovaginitis can cause a short duration of pain. However, 5–8 % of adult women suffer from intractable or recurrent candidal vulvovaginitis (RVVC),

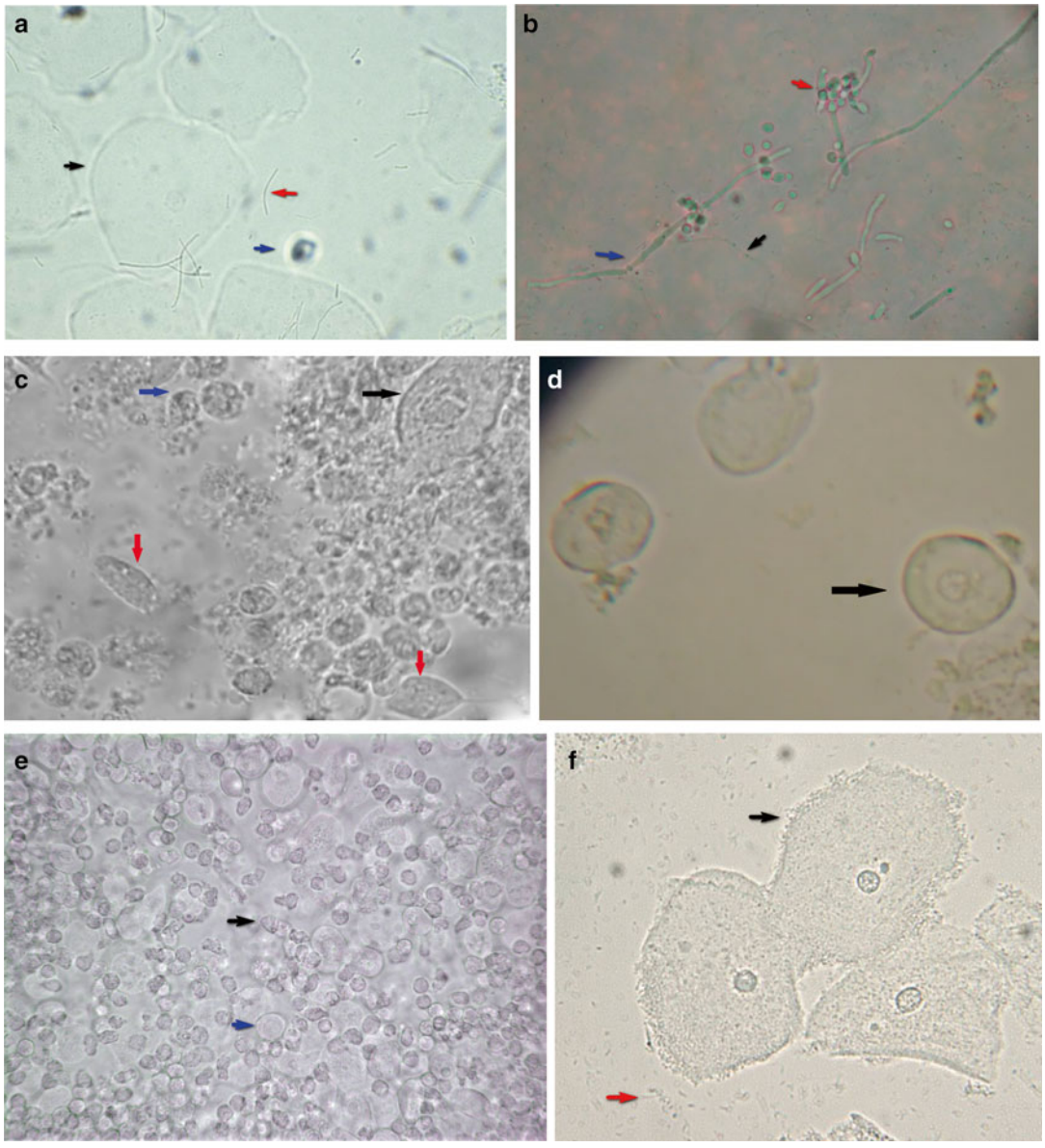

Fig. 4.2 Microscopic findings of vaginal conditions. (**a**) Normal wet mount: Mature squamous epithelial cells (*black arrow*), appear as large, polygonal cells. There is one or no white blood cell (*blue arrow*) per epithelial cell, and gram-positive rods (lactobacillus morphotypes) (*red arrow*) are present. This wet mount represents normal discharge, and is accompanied with normal pH (≤4.5). (**b**) Yeast Infection: mature squamous epithelial cells (*black arrow*), hyphae (*blue arrow*) and budding yeast (*red arrow*). The specific species cannot be recognized from the smear, and a culture is required for identification. (**c**) Trichomoniasis: wet mount reveals an increase of inflammatory cells (*blue arrow*) and parabasal cells (*black arrow*). The parasites *Trichomonas vaginalis* are ovoid shaped and slightly larger than inflammatory cells (*red arrow*), and they are best recognized by their motility. (**d**) Vaginal atrophy: characteristic findings are the presence of parabasal cells (*black arrow*), which are smaller, rounder, and have a large nucleus compared to mature squamous epithelial cells, with scanty vaginal flora as well as an elevated pH (>4.5). (**e**) Desquamative inflammatory vaginitis (DIV): microscopic findings show high number of white blood cells (*black arrow*), an increase of immature, parabasal epithelial cells (*blue arrow*), an absence of lactobacilli and a coccoid flora. The pH is >4.5. (**f**) Bacterial vaginosis (BV): clue cells (*black arrow*) are mature squamous epithelial cells, with adherence of abnormal bacteria to the cell. The flora is comprised of abnormal coccid bacteria (*red arrow*), without elevation of inflammatory cells. BV causes little or no inflammation and therefore it rarely causes pain

Table 4.1 Differential diagnosis of vulvovaginal pain

Vulvar pain related to a specific disorder
Infectious
• Candidiasis
• Trichomoniasis
• Herpes simplex virus
• Group A streptococcus
• (Bacterial vaginosis causes discharge and malodor, but only little or no inflammation and therefore it rarely causes pain)
Inflammatory conditions and dermatoses
• Vulvar contact dermatitis
• Lichen sclerosus
• Lichen planus
• Desquamative inflammatory vaginitis
• Immunobullous disorders
Hormonal
• Vulvovaginal atrophy (estrogen deficiency)
Neoplastic
• Vulvar intraepithelial neoplasia—VIN
• Paget disease
• Squamous cell carcinoma
Neurologic
• Post-herpetic neuralgia
• Multiple sclerosis
• Spinal nerve compression
Systemic disorders
• Behcet's syndrome
• Crohn's disease
Vulvar pain not related to a specific disorder—vulvodynia
1. Generalized
(a) Provoked (sexual, nonsexual, or both)
(b) Unprovoked
(c) Mixed (provoked and unprovoked)
2. Localized (vestibulodynia—previously known as vulvar vestibulitis, clitorodynia, hemivulvodynia, etc.)
(a) Provoked (sexual, nonsexual, or both)
(b) Unprovoked
(c) Mixed (provoked and unprovoked)

which is defined as four or more symptomatic episodes of infection in 12 months. Evaluation of patients for RVVC usually fails to reveal the precipitating cause such as uncontrolled diabetes, immunosuppression, excess of estrogen, or antibiotic usage [6]. The recurrence is believed to result from reinfection or relapse, implying incomplete clearance of candida from the vagina. In such a situation, treatment is directed at control rather than cure, and requires long-term maintenance therapy with a suppressive prophylactic agent [7]. Because of the chronic nature of therapy for RVVC, oral treatments are most useful. The recommended regimen is a weekly oral dose of fluconazole 150 mg. Alternatively, topical prophylactic treatment consists of weekly 500 mg clotrimazole suppositories [8].

Trichomoniasis, a sexually transmitted disease, is caused by the protozoan *Trichomonas vaginalis*. Severity ranges from an asymptomatic carrier state to severe inflammatory vaginitis. Patients may complain of malodorous, yellow-green discharge with vulvar irritation, itch, and dyspareunia. However, many women are asymptomatic [9]. Findings may be absent but are typically characterized by diffuse vaginal erythema and profuse purulent vaginal discharge.

None of the clinical features of trichomonas vaginitis is sufficiently specific to allow for a diagnosis based on signs and symptoms alone; therefore, the definitive diagnosis requires isolation of the organism (Fig. 4.2c). The sensitivity for diagnosing vaginal trichomoniasis by microscopy is low (60–70 %) but for optimal results it is recommended to immediately evaluate a fresh sample of vaginal discharge using a microscope. Other available laboratory methods used for diagnosis include culture, PCR assays, immunochromatographic capillary flow dipstick technology (the OSOM Trichomonas Rapid Test), and more. The recommended treatment is oral metronidazole or tinidazole.

Vulvoaginal atrophy results from inadequate estrogen levels in the vagina. While dyspareunia may affect 10–15 % of fertile women, it affects up to 39 % of postmenopausal women [10]. In this age group, dyspareunia is attributed mainly to vaginal atrophy. Vulvovaginal atrophy occurs most commonly with menopause but can occur due to lactation, medicines, and occasionally, due to usage of extra-low dose contraceptive pills [11]. Estrogen plays a major role in maintaining the normal vaginal environment. Estrogen withdrawal induces significant changes in the vagina causing it to become pale, thin, and less flexible [12]. As a

result, blood flow diminishes, secretions decrease, vaginal flora changes, and pH increases. These changes predispose menopausal women to potential dyspareunia through several mechanisms. Vaginal dryness causes increased friction during intercourse. The thin vaginal walls are friable and prone to mechanical damage and formation of petechiae, ulcerations, and tears occurring with sexual activity. With long-standing estrogen deficiency, the vagina may become shorter, narrower, and less elastic. All of these changes increase the likelihood of trauma, infection, and pain. Furthermore, changes occurring with aging, such as subcutaneous fat loss and decreased skin lipid production, can result in slower healing after injury. Age dependent hypotonia and hypertonia of the pelvic floor muscles can also contribute to dyspareunia [13]. Patients with atrophy may complain of dryness, itching, discharge, pain, dyspareunia, and irritative urinary symptoms [12]. Symptoms are usually progressive and do not resolve spontaneously. Diagnosis is made by identifying characteristics changes on physical examination, noting an elevated vaginal pH and the presence of parabasal cells on microscopy (Fig. 4.2d) [14].

The primary goal of treating symptomatic vaginal atrophy is to alleviate symptoms. First-line therapies include nonhormonal, long-acting vaginal moisturizers and low-dose vaginal estrogen. For women with symptomatic vulvovaginal atrophy who prefer a nonvaginal therapy, transdermal and oral hormone therapy as well as the selective estrogen-receptor modulator, ospemifene, are options [15]. Because the overall dose of estrogen is low and is associated with less absorption, topical estrogen is generally considered safer and is less worrisome to patients. Atrophic changes, including those observed with microscopy, are rapidly and markedly reversed with topical estrogen therapies. Intravaginal estrogen preparations may be insufficient if vestibular symptoms are predominant. This results from preferential distribution of the absorbed hormones to the uterus. The hormonal preparation should be placed in the outer third of the vagina for best clinical results [16].

Desquamative inflammatory vaginitis [14] (DIV) is a rare cause of noninfectious, purulent vaginitis. Its diagnosis is based on symptoms, signs, and laboratory findings that are nonspecific. DIV is a chronic condition, as most patients will have complaints for more than a year before being diagnosed. The most common manifestation of DIV is copious, purulent vaginal discharge. However, 90 % of sexually active patients complain of dyspareunia [17]. As DIV is primarily a vaginal condition, the pain is mainly with thrusting. However, when DIV causes vestibular inflammation or erosions, patients may have pain with intromission as well. Some patients may not know they have dyspareunia because they have ceased having intercourse due to the abnormal discharge. Other symptoms include vulvovaginal burning and irritation [17].

On physical examination, patients may exhibit findings of vulvar erythema and introital ecchymotic spots. A vaginal examination typically reveals diffuse erythema and a purulent yellow or green vaginal discharge (Fig. 4.3b), occasional ecchymotic spots (usually located in the inner third of the vagina), and colpitis macularis. Similar to vaginal atrophy, the pH is elevated and microscopy shows parabasal cells, but there is a marked increase in inflammatory cells (a ratio of inflammatory cells to epithelial cells >1:1), as well as vaginal flora abnormality with the loss of dominant lactobacillus morphotype (Fig. 4.2e) [18].

The differential diagnosis for DIV includes other disorders causing purulent vaginitis. These include infectious vaginitis such as trichomoniasis and Group A Streptococcal vaginitis, dermatologic disorders such as erosive lichen planus and mucosal blistering disorders and usage of chemical irritants. It is therefore essential to exclude other etiologies before confirming diagnosis.

Because of the similarities between vaginal atrophy and DIV, it may be difficult to distinguish them from each another. With atrophy, the epithelial surface remains intact, and response to local estrogen therapy is usually rapid. Thus, failure to reverse the abnormal appearance of the vulvar vestibule or vagina and consequent symptoms with topical estrogen therapy constitutes a diagnostic test.

Little is known regarding etiology, treatment options and long-term follow-up. Both topical vaginal clindamycin and vaginal corticosteroids

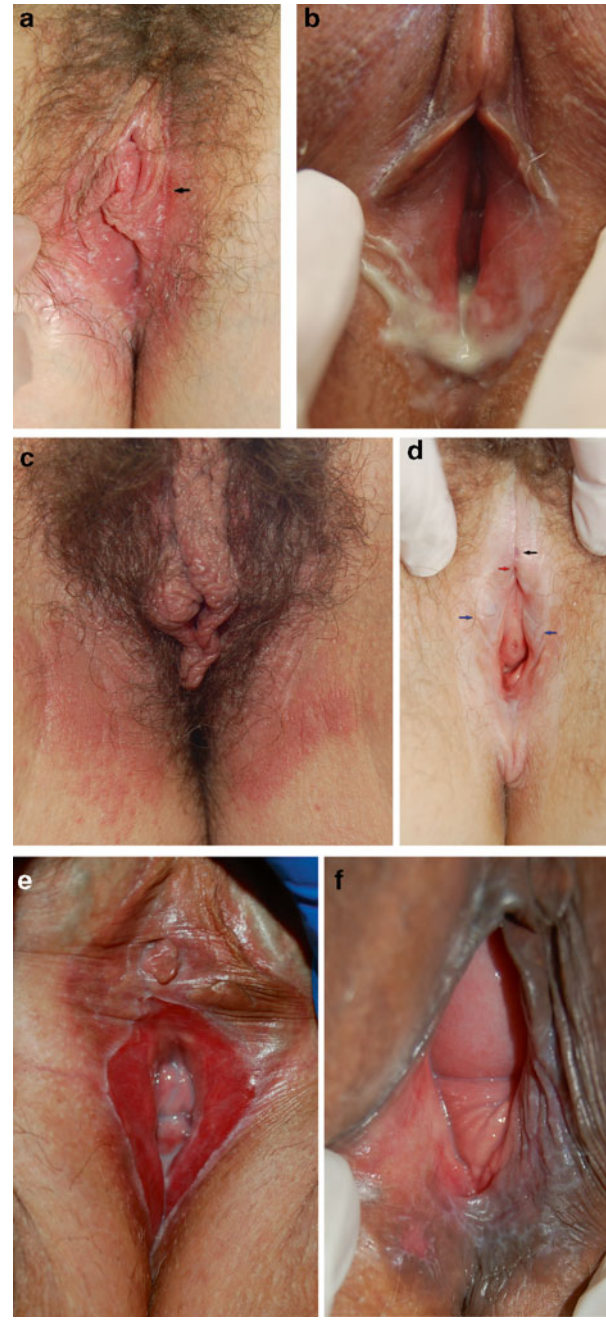

Fig. 4.3 Macroscopic findings in vulvovaginal disorders. (**a**) Vulvovaginal candidiasis—the vulva is inflamed, with erythema and fissures in the interlabial sulci (*arrows*). (**b**) Desquamative inflammatory vaginitis: diffuse erythema and copious purulent discharge. (**c**) Vulvar contact dermatitis—erythema secondary to usage of panty liners. (**d**) Vulvar lichen sclerosus—findings in LS include hypopigmentation, epithelial thinning, hemorrhages (*black arrow*), loss of normal architecture including disappearance of labia minora (*blue arrow*), buried clitoris (*red arrow*) and narrowing of the introital opening. The disease involves the perineal and perianal areas. (**e**) Erosive lichen planus—causes painful vestibular erosion that appears as deep glazed erythema. Note loss of normal architecture with the absence of labia minor, (**f**) Lichen planus—presents with white, reticulate, lacy striae. The lacy pattern is considered pathognomonic

have anti-inflammatory affect and are useful for treating DIV; the choice of treatment should consider the availability and cost of these medications [18]. The treatment, either topical clindamycin or corticosteroids, is administered daily for 2–4 weeks. Initial therapeutic response is extremely encouraging, with 86 % of patients experiencing dramatic improvement; however, relapse and chronic manifestations frequently require long-term topical therapy [18].

Contact dermatitis is an inflammation of the skin due to exposure to an exogenous agent acting as primary irritant or an allergen. As vulvar tissue is more susceptible to irritants than other

tissues, contact dermatitis is common and can complicate all other vulvovaginal conditions. Common vulvar irritants include soaps, panty liners, wet wipes, menstrual hygiene products (pads and tampons), toilet paper, laundry detergents, fabric softeners, cosmetics, spermicides, condoms, lubricants, urine, sweat, and topical medications.

Symptoms are of nonspecific inflammation, and include burning, itching, pain, and fissuring of vulvar tissue. Diagnosis is based on detailed history, exclusion of infectious causes, and high level of suspicion. Physical findings may range from mild erythema (Fig. 4.3c) to severe inflammation (erythema, edema, and fissures), sometimes with a secondary infection. Finalizing the diagnosis may require a biopsy to rule out coexisting conditions. Patch testing may be helpful in cases of allergic contact dermatitis.

Lichen sclerosus (*LS*) is a chronic, inflammatory skin disorder affecting 0.1–1.7 % of women [19] with a distinct predilection for the anogenital region. The mean age at onset of symptoms is 45.5 years, but LS may appear at any age, with 9 % of women experiencing onset of LS in prepuberty, 41 % in the reproductive years, and 50 % postmenopausal [20]. The etiology of LS has not yet been adequately explained, but there is increasing evidence that autoimmune mechanisms play a pathogenic role, with a possible genetic susceptibility.

LS is usually a scarring, chronic progressive or relapsing and remitting, lifelong condition. The characteristic sites involved are the interlabial sulci, labia minora, labia majora, clitoris, clitoral hood, perineum, and perianal area, giving rise to the characteristic "figure-of-eight" appearance. Alternatively, it may involve only small areas of skin. Typically, there is no vaginal involvement.

The typical lesions are porcelain-white papules and plaques with hyperkeratosis. The area evolves into a dry, hypopigmented, sclerotic, and later atrophic lesion. LS causes scarring of vulvar tissue, with loss of normal architecture including disappearance and fusion of labia minora, clitoral adhesions, sealing of the clitoral hood, burying of the clitoris, and narrowing of the introital opening (Fig. 4.3d). Otherwise, it can appear as nonspecific erythema, edema, erosions, fissuring, purpura, and ecchymoses. Tearing during sexual intercourse or physical examination is common.

Clinically, while 10–20 % of patients are asymptomatic, most patients present with itch, chronic scratching, pain, soreness, and dysuria. A high proportion of women report significant sexual difficulties including dyspareunia and apareunia due to continuing inflammatory disease as well as due to anatomic changes and scarring from long-standing active disease.

The diagnosis of LS is usually clinical, and when features are typical, histologic examination is not always essential. However, in the early stages of the disease the diagnosis can be difficult and a biopsy is required.

The gold-standard treatment for LS is topical corticosteroid ointment (such as clobetasol propionate 0.05 %), applied daily or twice a day until active disease has resolved, after which frequency and potency of treatment is gradually tapered to twice weekly. Patients should be counseled that LS is a chronic disease, requiring maintenance treatment and long-term follow-up. Women with LS have higher risk of developing vulvar squamous cell carcinoma.

Lichen planus (*LP*) [21] is a systemic, autoimmune, inflammatory mucocutaneous disorder. It can involve the vagina, vulva and vestibule as well as oral mucosa and skin elsewhere. Vulvovaginal involvement can cause itch, pain, burning, dyspareunia, and dysuria. The most common vulvar variant is erosive LP, causing painful vestibular erosion that appears as deep glazed erythema (Fig. 4.3e). Similar to LS, introital stenosis and destruction of normal vulvar architecture can happen. In the vagina, LP can cause vaginitis or localized erosive lesions. The inflammatory process can subsequently cause adhesions, fibrosis, and even complete vaginal obliteration.

Classic LP presents with white, reticulate, lacy striae (Wickham's striae) (Fig. 4.3f). Diagnosis is based on either typical findings or biopsy. Even though LP is more difficult to treat than LS, the recommended initial treatment is similar, and consists of topical ultrapotent steroids. In unresponsive cases or extensive disease, systemic

immunosuppressive therapy may be necessary. For vaginal involvement, routine usage of vaginal dilators is mandatory. Long-term treatment and follow-up are required.

4.4 Genital Pain Syndromes: Provoked Vestibulodynia and Generalized Unprovoked Vulvodynia

Patients with vulvar pain, in whom there is not a recognized disorder, are diagnosed with vulvodynia. The ISSVD terminology for classification of vulvodynia distinguishes between generalized and localized pain. Each of these two subgroups is further subdivided into provoked, unprovoked or mixed [3]. The majority of clinical presentations is either provoked vestibulodynia (PVD), formerly known as vulvar vestibulitis syndrome, or generalized unprovoked vulvodynia (GVD).

PVD is the term describing a syndrome of provoked, localized allodynia of the vestibule of the vulva, not explained by another condition, and lasting more than 3 months. PVD was first described as a syndrome in 1987 by Dr. Edward Friedrich [22] and was named vulvar vestibulitis syndrome. Friedrich's criteria were [1] severe pain in the vulvar vestibule upon touch or attempted vaginal entry; [2] tenderness to pressure localized within the vulvar vestibule; and [3] vulvar erythema of various degrees.

As inflammation is often not found, in 2003, the term vestibulitis was replaced by the ISSVD to PVD [3], but the diagnostic criteria are similar to those suggested by Friedrich. These include a typical history of pain upon vestibular touch, such as attempted intercourse, gynecological examination, insertion of tampon or other direct contact and a positive Q-tip test, which elicits severe pain or discomfort. Most patients with PVD present with dyspareunia or complete inability to have intercourse.

In *GVD* the patient reports a continuous, unpleasantsensation of pain [3], usually described as burning, stinging, irritating, itching, or a feeling of rawness. Most often the pain is diffuse, without clear borders. Any stimulus which results in pressure on the vulva can exacerbate the pain, including intercourse, tight fitting clothing, sitting, walking, or exercising.

4.5 Causes of PVD

PVD is not a defined disease but rather a symptom. There is a belief that PVD represents a group of distinct disorders that have been classified together simply because they produce pain in the same anatomic location [23]. Causes of these disorders include hormonal imbalance, mainly caused by hormonal contraception [24–27], nerve fiber proliferation in the vestibular mucosa [28–31] and hypertonic pelvic floor dysfunction [32, 33]. PVD may appear with sexual debut or first attempts to insert a tampon (primary PVD) or can be a new onset of pain with activities that did not previously illicit pain (secondary PVD) [34].

Studies found that different factors such as genetic, inflammatory mediators, recurrent vaginitis, allergy, and trauma may be involved in the development of PVD. A high percentage of patients with vulvar pain report an antecedent history of vulvovaginal candidiasis, although it is unknown if this represents a true increase in incidence or a misdiagnosis. It has been suggested that repeated vuvlovaginal infections are a triggering event for some women leading to chronic vulvar pain. This observation has led to hypothesis that in patients with neurogenic vulnerability, an initiating event or series of events may lead to chronic vulvar pain [35–37].

Several studies point to a possible genetic involvement with polymorphisms in genes responsible for regulation of inflammatory response: allele 2 of the IL-1b gene [38], mannose-binding lectin (MBL) [39], melanocortin-1 receptor (MC1R) gene [40], and the gene coding for the inflammasome component NALP3 [41]. The theory suggests that some women with PVD have defective regulation of proinflammatory immune responses due to genetic variations that predispose them to exaggerated inflammatory responses [36, 38, 41, 42]. Chronic inflammation may induce changes in peripheral

nociceptors or may represent an increased exaggerated neurogenic inflammation facilitating central sensitization.

Because the diagnosis of vulvodynia is nonspecific, treatment is not evidence based, and proceeds on a trial-and-error basis. At least 30 different therapeutic interventions have been used for the management of vulvodynia, yet evidence from clinical trials remains largely inconclusive [43]. Recommendations are in favor of a multidisciplinary approach focusing on pain management and re-establishing pelvic floor function [44].

A different approach is suggested by Goldstein [45]. He classifies PVD into groups, based on history and examination findings:

1. Hormonally mediated PVD—the pain began while taking hormonal contraceptive or other medications that affect hormones, after removal of ovaries, breastfeeding or menopause. Typically, patients have a low calculated free testosterone and complain of dryness, decreased libido, and decreased arousal. The entire vestibule is tender and vestibular mucosa is often dry and thin. Treatment includes stopping hormonal contraception and application of topical estradiol (with or without testosterone) to the vestibule [46].
2. Hypertonic pelvic muscle dysfunction—in this subgroup, PF muscles become tight and tender. Patients often have other symptoms suggesting hypertonicity (urinary frequency, urgency and hesitancy, constipation, hemorrhoids, and anal fissures), and predisposing factors, such as musculoskeletal disorders or anxiety, may coexist. Typically, the pain is much worse at 4–8 o'clock position of the vestibule with minimal or no pain in the upper vestibule. Treatment includes PF physiotherapy, with an optional addition of muscle relaxants (valium suppositories), Botulinum toxin injections and cognitive behavioral therapy.
3. Neuroproliferative PVD—in this condition, women have an increased number of nociceptors in the vestibular mucosa. This group is further subdivided into congenital and acquired forms. In the congenital subgroup, vestibular pain has always been present, and there may be sensitivity to palpation of the belly button, due to common embryologic origin (the primitive urogenital sinus) [47]. With acquired neuroproliferative PVD, the pain may begin after a severe allergic reaction or vaginitis. There is tenderness of the entire vestibule. Treatments include topical anesthetics, antidepressants, antiseizure drugs, capsaicin cream, and a surgical procedure, termed "vulvar vestibulectomy." Various surgical approaches were described, in which excision and resection of the painful vestibular tissue is performed [48]. In general, a horseshoe-shaped area of the vestibule and inner labial fold is excised, followed by advancement of the posterior vaginal wall [49].

As with PVD, the term "unprovoked vulvodynia" describes a symptom, and the question is whether we can diagnose a specific cause instead of calling it simply "vulvar pain." It is possible that some cases of GVD may represent pudendal nerve disorders, PF hypertonic disorder, or can be classified as an entity within the spectrum of neuropathic pain syndromes, while in other patients it represents a functional pain syndrome.

4.6 Treatment of PVD and GVD

The state-of-the-art of vulvodynia management is described in "The Vulvodynia Guideline" published in 2005 [50], developed by an expert panel, organized by the ISSVD. The Guideline is largely based on expert opinion and has several disadvantages, including the absence of differentiation between treatments for GVD and PVD, has not been updated with current research and does not clearly state the quality of the supportive evidence utilized. Because the pathogenesis is not defined, treatment of vulvodynia is generally predicated on a trial-and-error basis. The result is that many forms of therapeutic interventions have been used, yet the evidence remains largely inconclusive. Modalities of treatment mentioned in the vulvodynia guidelines include vulvar care measures, topical, oral and injectable medications,

physical therapy, surgery (vestibulectomy) and complementary medicine.

In a review published by Andrews [43], all published studies regarding vulvodynia and PVD were evaluated. The author sought to include only placebo-controlled randomized trials but, not surprisingly, found only a few, so he included studies without a comparator. In most of these studies, the data analyzed was a pretreatment evaluation versus a posttreatment evaluation and the primary outcome was the reported decrease in pain.

Andrews found 447 articles on treatment of PVD and GVD, of which 71 were eligible for review. Fifty-five studies reported 28 different treatments for PVD. The majority of published studies were case series, with success rates varying from no effect to 100 % improvement. There were eleven randomized trials, of which five were placebo controlled. Most of the studies had several methodological weaknesses, including lack of control or placebo group, non-double-blind assessment, no pretreatment pain and functional status assessment, non-validated outcome measures of pain and sexual functioning, and no long-term outcomes.

Of the 71 eligible articles, 16 reported an evaluation of a therapy for vulvodynia, predominantly GVD. Twelve different interventions for GVD were studied. All of the vulvodynia studies had the methodological weaknesses cited above. There were no analytic studies, no randomized controlled trials and all the studies reported a beneficial effect. Andrew's review found insufficient evidence to support that any of the nonsurgical therapies confers a net benefit for patients with PVD, and insufficient evidence for efficacy of any of the treatments studied for GVD.

Furthermore, single placebo-controlled randomized trials have demonstrated evidence for a lack of benefit of topical 5 % lidocaine, oral desipramine, and botulinum-toxin injections. The body of scientific evidence for other interventions was poor, and there was insufficient evidence regarding the efficacy of numerous other interventions, including steroid and anesthetics injections, multilevel nerve blocks, interferon, capsaicin, topical gabapentin, cognitive behavioral therapy, and PF physiotherapy.

Surgical therapy was also evaluated: case series of 1138 patients reported an effect varying between 31 % and 100 %, for patients who reported at least some improvement. Twelve studies reported complete relief as an outcome and the median effect size was 67 %. Therefore, there is fair evidence that vestibulectomy provides a benefit for patients with PVD, but the size of this effect cannot be determined with confidence.

In addition to the above findings, outcomes show a wide range of response to different therapies for vulvar pain syndromes, with 35–79 % of women reporting improvement in pain scores at 6 months [35, 50, 51]. Nevertheless, long-term outcomes are discouraging with up to 66 % of women reporting some improvement, but only 57 % reporting greater than 50 % improvement in pain since diagnosis [52, 53], and more than half still describe severe pain and some level of functional impairment in daily activities [51, 53].

It is suggested that several parameters may be responsible for these discouraging results. First, the expression, clinical presentation, and response to therapy result in a unique pain experience for each patient. There are also other psychological factors that adversely affect the outcome among women with vulvar pain, such as depression, stress, somatization, anxiety, phobic symptoms, and catastrophizing. Failure to identify and address these factors in both the clinical and research settings may affect outcome [23]. Some women have greater evidence of CNS dysregulation, such as enhanced systemic pain responses and more than one pain syndrome. The failure to address this central component may also account for treatment failure [23].

Finally, vulvar pain syndromes may represent a diverse group of disorders with several possible pain mechanisms; therefore, the appropriate treatment varies and is individualized. Unfavorable outcomes to therapy can be explained by grouping patients with different conditions under one diagnosis, and then studying an intervention that might only help one subset of the conditions. This can lead to an apparent lack of effect, due to dilution of the patient subpopulation [43].

Vulvar pain syndromes are complex conditions with a variety of factors contributing to

etiology, symptoms, and response to therapy. The majority of studies involved monotherapy, and demonstrated inadequate results. However, an integrated response addressing a variety of contributing factors offers the best therapeutic result [54]. In fact, several studies found that multidisciplinary approach leads to considerable improvements in vulvar pain and the resumption of intercourse [55–57].

4.7 Summary

Genital pain and dyspareunia are highly prevalent conditions, with a variety of etiologies. The chronic nature of the majority of these conditions as well as the frequent delay in correct diagnosis adversely affect patients emotionally, socially, sexually, and interpersonally.

Accurate diagnosis accompanied by rapid and suitable treatment is of major importance. It may provide immediate cure or control of chronic disorders, and therefore prevent sequelae such as PF dysfunction and emotional stress that may develop if vulvar pain is left untreated. In addition, due to the possibility that intractable vaginitis is a triggering event leading to chronic vulvar pain in vulnerable patients, a quick and accurate diagnosis is important.

Management of vulvodynia can be improved if the etiology of the pain is identified or at least classified better. More research on epidemiology, natural history, and etiology of PVD and GVD is required, as well as standardization of research tools, definitions and outcome measures.

Meanwhile, in the absence of high quality evidence, clinical decisions remain a challenging task. Clinicians should keep in mind that treatment starts with a correct diagnosis. Vulvodynia is a diagnosis of exclusion after other, treatable causes are ruled out through a thorough history, physical examination, microscopy, cultures, and biopsies. Caregivers should believe that a successful outcome is possible and make sure they clarify patients' expectations and goals. A multidisciplinary approach leads to substantial improvements in pain and well-being. Currently, there is no "silver bullet." The patient should realize that adjustments in treatment interventions are typically needed, and that this requires persistence and patience of both the patient and the provider.

4.8 Questionnaires

1. International Pelvic Pain Society
   http://www.pelvicpain.org/pdf/History_and_Physical_Form/IPPS-H&PformR-MSW.pdf
2. ISSVD
   https://netforum.avectra.com/temp/ClientImages/ISSVD/3ef9c6ea-aac7-4d2b-a37f-058ef9f11a67.pdf

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