Clinical manifestations and diagnosis of localized, provoked vulvodynia (vestibulodynia)

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INTRODUCTION — Vestibulodynia (VBY) is a localized, provoked form of vulvodynia. Vestibulodynia refers to a specific type of vulvar pain syndrome with the following characteristics [1]:

- Severe pain upon vestibular touch (ie, light physical contact) or attempted vaginal entry
- Tenderness to pressure (ie, forceful touching) localized within the vulvar vestibule
- Physical findings limited to vestibular erythema.

VBY is a chronic disease. Typically, women present with symptoms that have been present for several months to many years. The diagnosis of VBY should not be made in women complaining of vestibular pain of only a few weeks' duration.

VBY can be primary or secondary:

- Primary VBY refers to introital dyspareunia dating from initiation of sexual activity or (among women who have never been sexually active) intolerable pain consistently present upon insertion of a tampon or vaginal speculum. It accounts for 20 percent of cases [2].
- Secondary VBY describes women who have introital dyspareunia that develops after a period of comfortable sexual relations, tampon use, or speculum examinations.

There are no unique histological findings in primary versus secondary disease. However, the difference in clinical history suggests the possibility of separate etiologies.

The pathogenesis, clinical manifestations, and diagnosis of vestibulodynia will be reviewed here. The treatment of vestibulodynia is discussed separately. (See "Treatment of vulvar pain syndrome".)

PREVALENCE — The prevalence of VBY in the general population is unknown; no studies have used both history and physical examination to evaluate a large number of unselected women. The prevalence of VBY reported in various clinical settings ranged from 1 to 20 percent [3-7]. Prevalence decreases with age; VBY is largely a disorder of premenopausal women.

HISTOLOGY — The histology of VBY has not been characterized. The disorder was initially termed vestibulitis because inflammation of the minor vestibular glands was originally considered the pathologic feature of VBY [8]. Although classic inflammation probably triggers pain in women with VBY [9], most experts believe that it is not an important histological feature. This conclusion is supported by the following lines of evidence:

- The same nonspecific inflammatory infiltrate has been demonstrated in healthy vestibular tissue [10].
- Immunohistochemical analysis of the neuroendocrine cells of the minor vestibular glands of affected patients is similar to that in unaffected controls [11].
- The inflammatory mediators cyclooxygenase-2 and inducible nitric oxide synthase show low expression in both patients and unaffected women [12].
- Expression of interleukin-1B and tumor necrosis factor-A is not consistently different for affected and unaffected women [13,14]. In one study, expression of tumor necrosis factor was actually decreased in the areas of highest hyperalgesia [13].

PATHOGENESIS — No single factor can be held responsible for the majority of cases of VBY [15]. Instead, there is mounting evidence that an insult to the mucous membrane of the vestibule triggers a chronic inflammatory condition that ultimately results in central nervous system sensitization so that the sensation of touch is transformed into that of pain (allodynia) (figure 1) [16-21]. The pain can be accentuated by reflex contraction of the pelvic floor musculature. A variety of insults can trigger the process and the insult varies from woman to woman.

This hypothesis is supported by the observation that women with VBY have a significant increase in the number of intraepithelial nerve endings in the vestibule and increased superficial blood flow and erythema, probably caused by neurogenic inflammation [22-25].

ETIOLOGY AND RISK FACTORS — Over time, a variety of conditions have been considered in the etiology of VBY. Some may be triggers to neuroinflammatory pain, while others may involve other mechanisms.

- Vulvovaginal infection — A history of vulvovaginal candidiasis is the single most consistent feature reported by women with VBY, thus Candida may be a trigger to the neuroinflammatory process [2,8,26-28]. Antifungal treatment usually fails to relieve VBY (and may aggravate symptoms) [29]; however, this is not surprising because antifungal regimens, while eliminating the trigger, do not address the nociceptive pain that results.

An association with bacterial vaginosis has also been reported [30-32]. It is unclear whether there is a relationships between VBY and other vulvovaginal infections [33-36]. There is no relationship with HPV [37,38].

- Hyperoxaluria — Excessive urinary oxalate excretion has been proposed as an etiology of vulvar pain, based upon a case report of one patient in whom complete remission of symptoms occurred with a low oxalate diet and use of calcium citrate [39]. (See "Treatment of vulvar pain syndrome", section on 'Diet'.) However, a controlled study of urinary oxalate excretion did not show differences between women with and without pain [40]. It is possible that oxalate acts as an irritant to aggravate ongoing pain of VBY, but is not a primary cause of the disorder [26].

- Allergy — The vaginal fluid of some women with VBY contained levels of IgE consistent with vaginal allergy [29,41]. Mast cells have also been noted in biopsy specimens from women with VBY. A subset of women with vestibulodynia is sensitized to seminal fluid; an allergic reaction to seminal fluid may be the source of their symptoms [41].
- Genetic factors — It is possible that some women with VBY have a genetic deficiency that impairs their immune system's ability to stop the inflammatory response triggered by exposure to agents such as infection or chemicals [42]. Homozygosity of the 2 alleles of the gene encoding the interleukin 1 receptor antagonist (IL-1RA) occurs in 25 to 50 percent of women with VBY compared with fewer than 10 percent of unaffected controls [43]. This suggests polymorphism in this gene may be a factor influencing susceptibility to VBY, severity of symptoms, or both [42]. IL-1RA homozygosity has also been associated with chronic inflammation at other body sites.
- Hormonal factors — Case controlled studies have reported an association between the use of oral contraceptives and VBY [44-47]. A strong association between VBY and the postpartum period has also been reported [48].
- Somatization — The relationship between psychosexual dysfunction and VBY is debated, with no high quality studies providing evidence to support either side. While psychological factors are clearly operant in some women with vulvar pain [49], they cannot explain the striking sensory abnormalities uncovered in VBY cases compared with controls: lowered pain thresholds, increased sensitivity to heat, cold, vibration and distention [25]. Overall, the background rate of psychological disorders is probably not increased in women with VBY, but the chronic, often severe, pain can lead to secondary psychological effects [3].
- Pelvic floor dysfunction — Some women with VBY have instability of pelvic floor muscles at rest, elevated resting baseline tension, reduced muscle activity, poor muscle recovery, and reduced contraction strength [50]. This destabilization perpetuates vulvar tissue inflammation by its effects on local autonomic (sympathetic) mediated activity, leading to vascular changes and histamine release. Muscles of the pelvic floor may become destabilized from cutaneous vulvar disease or from joint abnormalities of the spine or pelvis [51].
- Interstitial cystitis/painful bladder syndrome — Some women have symptoms of both interstitial cystitis/painful bladder syndrome (IC/PBS) and VBY [52,53]. This association may be related to the common embryological origin of the epidermis of the vestibule, bladder mucosa, and urethra, which are derived from the urogenital sinus. Neural hyperplasia has been observed in biopsies of women with VBY and those with IC/PBS [54]; however, defects in the urogenital epithelium noted in the bladder of patients with IC/PBS have not been identified in patients with VBY [43,55]. (See "Clinical features and diagnosis of painful bladder syndrome/interstitial cystitis".)

CLINICAL MANIFESTATIONS — All women with VBY have introital pain with attempted intercourse; both thermal and incisive pressure type pain have been described and constitute the major feature of this syndrome [56]. Other complaints include discomfort with insertion of a tampon or speculum, tight clothing (eg, pants with a prominent inseam), washing or wiping the vestibule, prolonged sitting, biking, or horseback riding. Discomfort can last hours after the initial provocation. On the other hand, VBY can be asymptomatic when the vestibule isn't being touched. In addition, it is not unusual for

patients to report symptom-free periods lasting days or weeks or transient symptoms [57]. The reason for this reprieve is unknown.

In one study, over one-third of patients had constant burning or irritation in the vestibule, three-quarters had excessive vaginal discharge, and 10 percent had chronic urinary tract symptoms [29]. Constant burning or irritative symptoms are often misinterpreted as Candida infection and may be misinterpreted as originating in the vagina.

VBY is the leading cause of superficial dyspareunia in women under the age of 50 [58]. Deep dyspareunia and pelvic pain are not features of VBY, but may occur if interstitial cystitis or endometriosis is also present. Pain that interferes with sexual functioning is a cause of secondary depression [59]. It can also lead to emotional disequilibrium and distress, low self-esteem, and reduced social functioning [60].

DIAGNOSIS — The diagnosis of VBY is clinical, based on characteristic findings on history and physical examination. The presence of pain on vaginal penetration and tenderness provoked by local pressure of the vestibule are the cardinal signs and symptoms [61,62]. There are no unique histological findings associated with VBY so biopsy is unnecessary for diagnosis.

The huge sense of relief these patients feel upon receiving a concrete diagnosis cannot be underestimated. Confirmation that the pain is real and the condition is not malignant or communicable is also reassuring.

History — In addition to the clinical manifestations described above, patient comments suggestive of VBY are listed in the table (table 1). The diagnosis of VBY should not be made in women complaining of vestibular pain of only a few weeks' duration.

Primary VBY can often be diagnosed by history alone if the woman describes dyspareunia with first attempt at sexual activity or inability to use a tampon or tolerate a vaginal speculum.

Secondary VBY, developing after a period of comfortable sexual relations or vaginal procedures, may appear after childbirth, repeated infection (eg, recurrent candidiasis [28]), long-term vulvar dermatosis, or laser or chemical treatment of the vestibule.

A sexual history is essential to confirm that the relationship is loving and not abusive and that sexual technique is adequate. Nonreceptive and unlubricated intercourse could be the cause of the patient's pain, rather than VBY.

Chronic pain conditions that may be associated with VBY include trigonitis, chronic cystitis, interstitial cystitis, urethral syndrome, irritable bowel syndrome, fibromyalgia, migraines, depression, chronic fatigue syndrome, temporomandibular joint syndrome, and endometriosis.

Physical examination — The vulva is examined to confirm normal architecture and exclude dermatoses or other medical conditions. Erythema is often present and can be diffuse, in patches, or focal red spots near the minor vestibular gland openings. Fissuring, especially posteriorly at the 6 o'clock location, may occur.

The labia, perineum, and interlabial folds are palpated to determine if tender areas exist outside of the vestibule. With the labia minora gently parted, the examiner uses a moist cotton-tipped applicator to determine whether pain is provoked by pressure at one or more points around the vestibule (figure 2). Such tenderness is easily overlooked in general gynecology evaluations without careful exposure and Q-tip evaluation of the vestibule.

A bimanual exam should confirm that the examining hand does not elicit vaginal, cervical, or pelvic tenderness after it passes beyond the vestibule. Applying a small amount of a topical anesthetic to the

vestibule 30 to 60 minutes prior to the internal digital examination can help with this part of the evaluation. If there is tenderness over the bladder or upon palpation through the anterior vaginal wall, the patient should be asked whether she has pain upon bladder filling and/or emptying, which is one symptom of interstitial cystitis. (See "Clinical features and diagnosis of painful bladder syndrome/interstitial cystitis".)

We find colposcopy helpful in evaluating the vulva for epidermal abnormalities, but it is not required. Acetic acid significantly worsens vulvar pain. (See "Colposcopy".)

The mouth and skin should be checked for lesions suggestive of lichen sclerosus or lichen planus. (See "Vulvar lichen sclerosus" and "Lichen planus".)

Laboratory — A vaginal pH and wet mount should be performed to exclude vaginitis. A yeast culture should be obtained if microscopy is nondiagnostic for yeast infection. Tests for herpes, gonorrhea, and chlamydia should also be obtained, if appropriate. Paradoxically, although women with VBY complain of, and have, excessive vaginal discharge, they may also feel extremely dry. (See "Diagnostic approach to women with vaginal discharge or vulvovaginal symptoms".)

Differential diagnosis — Vulvovaginal candidiasis and vulvar dermatoses can cause vestibular pain, and should be excluded before making a diagnosis of VBY.

Differentiating Candida from VBY is problematic since both can produce irritative symptoms and tenderness in the vestibule. Yeast is best excluded by examining and culturing the woman when her symptoms are maximal and have not been treated by oral or topical antifungals in the preceding two weeks. PCR testing is an acceptable alternative to culture if Sabouraud's medium is not available. We swab both the vagina and the vestibule and plate them in one culture.

VBY should be considered if dyspareunia persists after treatment with antifungal medication and a confirmatory negative culture. If a woman has had recurrent yeast infections, her inflammatory symptoms will require at least six to eight weeks of antifungal suppression (eg, fluconazole 150 mg orally once per week) before regressing. (See "Candida vulvovaginitis".)

Vulvar lichen sclerosus and lichen planus result in characteristic lesions, synechiae, and introital narrowing, which can cause dyspareunia. Biopsy may be necessary to confirm the clinical diagnosis. VBY should be considered if the patient has ongoing vestibular tenderness after the dermatoses are controlled by ultrapotent topical steroids. (See "Vulvar lichen sclerosus" and "Vulvar lichen planus".)

TREATMENT — (see "Treatment of vulvar pain syndrome".

SUMMARY AND RECOMMENDATIONS

- Vestibulodynia (VBY) is a chronic vulvar pain syndrome characterized by: (1) severe pain upon vestibular touch or attempted vaginal entry, (2) tenderness to pressure localized within the vulvar vestibule, and (3) physical findings limited to vestibular erythema. It has no pathognomonic histological features. (See 'Introduction' above and 'Histology' above.)

- The cause of VBY is unknown. An insult to the mucous membrane of the vestibule appears to trigger chronic inflammation that ultimately results in neural sensitization so that the sensation of touch is transformed into that of pain (allodynia). (See 'Pathogenesis' above.)

- All women with VBY have introital pain when the vestibule is touched (eg, intercourse, speculum examination, tampon insertion, prolonged sitting, tight clothing, wiping). The pain is

localized to the vulvar vestibule and physical findings are limited to vestibular erythema. (See 'Clinical manifestations' above.)

- The diagnosis of VBY is clinical, based upon characteristic findings on history and physical examination. Biopsy is neither necessary nor diagnostic, given there are no unique histological findings. We suggest performing vaginal pH and wet mount to exclude vaginitis. A yeast culture should be obtained if microscopy is nondiagnostic for yeast infection. (See 'Diagnosis' above.)

- Differential diagnosis includes candidiasis and vulvar dermatoses involving the vestibule. These conditions typically display physical manifestations beyond simple vestibular erythema. VBY can also be associated with other pain syndromes. (See 'Differential diagnosis' above.)

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