Volume 61, Number 6
OBSTETRICAL AND GYNECOLOGICAL SURVEY

CME REVIEW ARTICLE 16

CHIEF EDITOR'S NOTE: This article is part of a series of continuing education activities in this Journal through which a total of 36 AMA/PRA category 1 credits™ can be earned in 2006. Instructions for how CME credits can be earned appear on the last page of the Table of Contents.

A Conceptual Model for the Pathophysiology of Vulvar Vestibulitis Syndrome

Denniz Zolnoun, MD, MPH,* Katherine Hartmann, MD, PhD,† Georgine Lamvu, MD, MPH,* Suzie As-Sanie, MD, MPH,‡ William Maixner, DDS, PhD,§ and John Steege, MD‖

*Assistant Professor, Division of Advanced Laparoscopy and Pelvic Pain, Department of Obstetrics and Gynecology, and Center for Women's Health Research, University of North Carolina, Chapel Hill, North Carolina; †Associate Professor, Departments of Obstetrics & Gynecology and Epidemiology, and Director of Center for Women's Health Research, University of North Carolina, Chapel Hill, North Carolina; ‡Lecturer, Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan; §Professor, Department of Endodontics, and Director of the Center for Neurosensory Disorders, School of Dentistry, University of North Carolina, Chapel Hill, North Carolina; and ‖Professor and Director, Division of Advanced Laparoscopy and Pelvic Pain, University of North Carolina, Chapel Hill, North Carolina

Vulvar vestibulitis syndrome (vestibulitis), the most common type of chronic vulvovaginal pain, impairs the psychologic, physical, and reproductive health of approximately 10% of women at some point in their lives. Research on the pathophysiology of vestibulitis suggests abnormalities in 3 interdependent systems: vestibular mucosa, pelvic floor muscles, and central nervous system pain regulatory pathways. To date, causes and relative contributions of these abnormalities to the development and maintenance of vestibulitis remain poorly understood. Research consistently supports the conceptualization of vestibulitis as a chronic pain disorder—akin to fibromyalgia, irritable bowel disorder, and temporomandibular disorder (TMD)—that is far more complex than vestibular hypersensitivity alone. Nevertheless, the clinical diagnosis of vestibulitis continues to rely on subjective report of pain during intercourse and vestibular sensitivity on clinical examination after exclusion of other gynecologic disorders. We propose that current diagnostic criteria, which are based on highly subjective patient and clinician measures, are not sufficient to describe and properly classify the heterogeneous clinical presentations of this disorder. To inform clinical care or research, we must be able to objectively characterize women with vestibulitis. This narrative review critically appraises current conceptualization of vestibulitis and presents a context for studying vestibulitis as a chronic pain disorder, emphasizing the need for objective assessment of clinical features.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader should be able to state that vulvar vestibulitis is common; recall that the disorder has three major pathophysiological pathways and that understanding of these pathways is important in selecting treatment options, and explain that the clinician must attempt to properly classify the clinical presentations of the disorder.

OVERVIEW

Although many women suffer in silence without seeking care and many go undiagnosed after seeking care, an estimated 200,000 women who receive a diagnosis of vestibulitis seek care each year in specialty clinics in the United States (1,2). Little is known about the etiology of vestibulitis, although it is thought to result from an exaggerated inflammatory response of the vulvar mucosa (vestibule) to injury. Clinical diagnosis remains one of exclusion. Before treatment for vestibulitis, patients have seen an average of 3 physicians (3) and had 5 years of pain (4,5). Vestibulitis is clinically defined by 3 subjective signs and symptoms: 1) entry dyspareunia; 2) tenderness to light touch (eg, cotton swab palpation) on the vestibule; and 3) presence of erythema (6–8). Treatment options continue to be empiric and of variable efficacy, with biofeedback and surgical resection being the 2 most commonly used modalities (9).

Vestibulitis, a functional versus organic disorder, is controversial. Proponents of vestibulitis as predominantly an organic disorder cite well-documented genetic differences in proinflammatory tendencies of the vestibular mucosa (10–19). In this model, commonly mentioned psychologic abnormalities and pelvic muscle dysfunction (spasm and difficulty with relaxation) are thought to result from a chronically inflamed and painful vestibular mucosa that causes reflexive guarding (20–25). On the other hand, others suggest that vestibulitis is a functional disorder. In this alternative model, psychosexual dysfunction is the antecedent to the development of vestibulitis. In support of this theory is the well-documented success of treatment with biofeedback or cognitive behavioral therapy (26–28). Neither theory sufficiently explains what we observe in clinical practice: a range of vestibulitis patients, those in whom central nervous system (CNS) dysfunction is more predominant and others in whom mucosal sensitivity is primary. That is, some women report improvement in pain only after interventions specific to pelvic floor muscles and psychosexual function, others report improvement only after interventions directed at decreasing sensitivity of the vestibular mucosa, whereas the majority respond to combination therapy (29–32).

We speculate that the proinflammatory tendencies of the mucosa may, in fact, be a "risk marker" for the development of vestibulitis, that is, a necessary component of the clinical syndrome that leads to symptoms only in the context of a greater dysfunction (eg, pelvic floor dyssynergia secondary to central dysregulation). Our theory is that vestibulitis is a group of conditions characterized by varying degrees of pain and dysfunction in the mucosa, underlying musculature, and associated dysfunction in pain-regulatory systems (Fig. 1). The clinical manifestations of vestibulitis may result from the convergence of a variety of pathophysiological mechanisms, including a predisposition of the mucosa toward heightened inflammatory response, pelvic muscle dysfunction, previous trauma (eg, childbirth, pudendal nerve injury, vaginitis), intrinsic CNS dysregulation, and modulation by psychologic traits.

This review appraises current literature in the pathophysiology of vestibulitis as it relates to peripheral (vestibular mucosa and pelvic floor muscles), central, and psychosocial factors in the manifestation of vestibulitis. The impetus behind this work is based on 2 fundamental principles: 1) conditions yielding persistent state of pain are too complex to be adequately diagnosed using a single axis (eg, anatomic location), and 2) concomitant assessment of biologic (peripheral and CNS) and psychologic (CNS) factors is necessary to identify subgroups with important pathophysiological differences (33,34). At the conclusion, we review the clinical implications of these observations and future directions for investigation of vestibulitis as a multidimensional pain disorder.

Is Vestibulitis a Disease of the Vestibular Mucosa?

Mucosal inflammation plays a central role in the clinical manifestations of vestibulitis (35–39). Histologic and biomolecular analyses of vestibular mucosa among women with vestibulitis demonstrate distinct alterations in biochemical and neuronal composition (15–19,40–42). In comparison to women without pain, women with vestibulitis tend to express genetic variants that result in more potent proinflammatory substances (eg, IL-1β, TNF-α) (18) and less potent antiinflammatory counterparts (eg, IL-1, RA) (15,19). Persistent inflammation is the natural consequence of this imbalance between the proinflammatory and antiinflammatory arms of the immune system (12).

The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

Dr. Zolnoun is a recipient of Grant/Research funding from Celgene Corporation. All other authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

This work was in part supported by the NIH Building Interdisciplinary Research Career in Women's Health (BIRCWH).

Reprint requests to: Denniz Zolnoun, MD, MPH, Department of Obstetrics and Gynecology, CB 7570, MacNider Building, University of North Carolina, Chapel Hill, NC 27599-7570. E-mail: zolnound@med.unc.edu

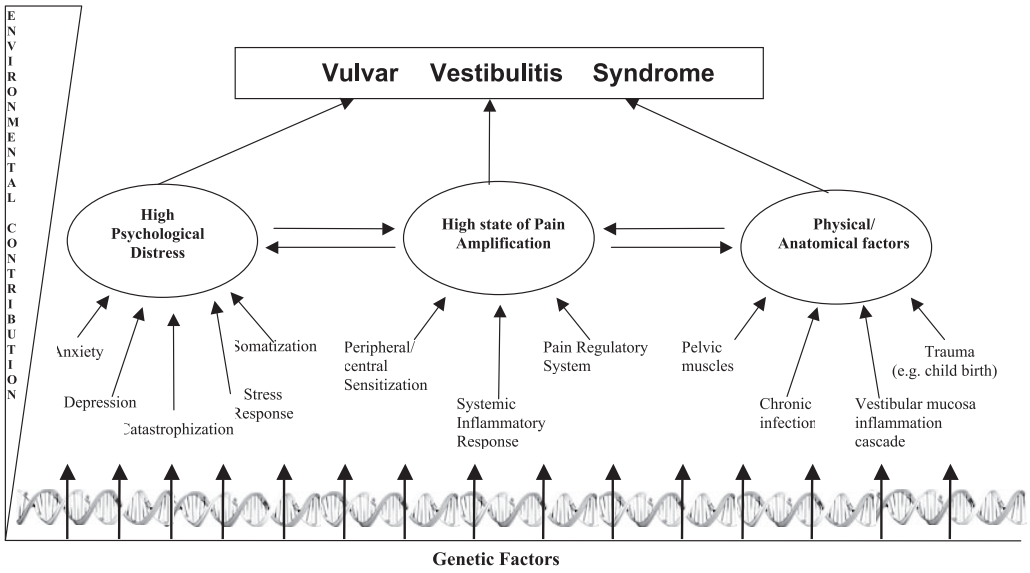

Fig. 1. Unifying conceptual model. This model displays the likely biologic and psychologic determinants that contribute to the odds of developing vestibulitis. These factors are influenced by genetic factors and environmental events that determine an individual's psychologic profile and pain amplification status.

Chronic inflammation results in proliferation of nociceptive nerve fibers (c-fibers) with altered receptor expression (41). Sustained inflammatory response in the vulvar mucosa promotes both neuronal proliferation and persistent elevation of proinflammatory substances (43–46). This, in turn, lowers the sensory threshold of vestibular mucosa. In this setting, a normally imperceptible and painless stimulus is felt as painful among women with vestibulitis (allodynia) (38,44). Consequently, even light touch can result in exaggerated release of proinflammatory substances by the sensitized nerve fibers. These proinflammatory substances, in turn, activate inflammatory cells (eg, neuroendocrine cells and mast cells) to release more proinflammatory substances. This self-perpetuating process of inflammation (neurogenic inflammation) is thought to play a key role in maintenance of the local inflammation in vestibulitis (12,20).

Inability to break this self-perpetuating cycle of inflammation can lead to changes in the CNS such that patients experience sensory and motor abnormalities at regions (eg, arm, deltoid) remote from the original site of inflammation. This phenomenon is known as "central sensitization" (47–49). Compared with women with no genital pain, women with vestibulitis have higher sensitivity to experimental pain stimuli at the nongenital regions. Central sensitization as described here is offered as the explanatory model. However, heightened sensitivity to nonpainful stimuli may occur independently and precede the development of chronic pain conditions such as vestibulitis (50). For example, harboring a less potent genetic variant of catecholamine-O-methyltransferase (COMT), an enzyme involved in catecholamine metabolism, is shown to be a risk factor for developing chronic myofascial pain disorder (eg, temporomandibular dysfunction); higher pain sensitivity to experimental pain is also observed among carriers of this less potent variant of COMT (50).

Is Vestibulitis a Disease of the Pelvic Floor Muscle?

Pelvic floor muscle dysfunction of varying severity is commonly observed in women with vestibulitis. Treatments targeting physical (ie, biofeedback) and volitional control (ie, cognitive behavior therapy) of pelvic muscle contraction are common modalities in management of vestibulitis (9,51). One of the few randomized treatment trials for vestibulitis assessed the efficacy of 3 commonly used approaches for the treatment of vestibulitis: biofeedback, cognitive–behavioral therapy, and vestibulectomy on a sample of 78 women. Across the 3 arms, the baseline pain was 5.45 to 6.34 on a Likert scale of zero (no pain) to 10 (worse imaginable pain), which decreased to 1.9 to 4.42 at 6-month follow up ($P < .01$) (9) with no meaningful difference across groups.

The importance of pelvic floor muscle dysfunction in women with vestibulitis is widely acknowledged (21). Most theories assume muscle dysfunction is secondary to chronic inflammation of the mucosa and, thus, reactive in nature (20–22,52). Some experts have

postulated that skin disturbance in vestibulitis destabilizes the pelvic floor muscles, resulting in high resting tone and poor voluntary control (29–32). Others have viewed it as a reflexive phenomenon secondary to ongoing pain with attempted intercourse, similar to involuntary muscle "splinting" seen in the setting of acute musculoskeletal pain (21,22). Neither theory fully explains the observed clinical efficacy of biofeedback in vestibulitis, which requires an explanatory model with pelvic floor muscle dysfunction as a primary pathologic process. It is plausible that in some women with vestibulitis, pelvic floor muscle dysfunction may act as an initiator of sensory changes in susceptible mucosa; whereas in others, muscle dysfunction may occur in response to mucosal inflammation. Well-established constructs in neurosensory research support this concept of muscle contraction as either an initiator or a consequence of skin inflammation or an ongoing component of sustained dysfunction (53).

Temporomandibular disorder (TMD) offers a model for muscle dysregulation as a primary process. Individuals with TMD have dysfunction in contraction and relaxation of the facial muscles that is associated with chronic orofacial pain (54). TMD muscle dysfunction has been traced to an imbalance between central inhibitory and excitatory pathways. The net result is loss of adequate inhibition from the CNS to the involved muscles. This disinhibition of motor signal is thought to cause some of the clinical manifestations (clenching, difficulty with voluntary jaw opening) in women with TMD. In this case, primary abnormalities in muscle function are intimately associated with the development of pain. Such dysfunction in inhibitory pathways is also seen in association with another syndromatic pain disorder (eg, fibromyalgia). Not surprisingly, there is a known comorbidity between fibromyalgia and TMD (55,56). In fact, our own data support a similarly high comorbidity between TMD and vestibulitis. Seventy-eight percent of women with vestibulitis recently studied in our clinic were found to have concomitant diagnosis of TMD: clinical (40%) and subclinical (38%) (submitted for publication).

Alternatively, pelvic muscle dysfunction may be the consequence of chronic inflammation in the overlying vestibular mucosa. An inflammatory insult of the mucosa may initiate hypersensitivity (hyperalgesia) in the underlying musculature (57). In animal models, as well as in human models, pain fibers (C-fibers and A-β fibers) that are sensitized by mucosal inflammation initiate, through polysynaptic spinal processes, hypersensitivity and contraction of the underlying musculature. Further sensitization of the muscle pain receptors may in turn, through a process of central sensitization, reduce sensory pain thresholds, resulting in a "vicious cycle" of inflammation and additional muscle contraction (53,58).

In summary, the pelvic floor muscle dysfunction commonly documented in women with vestibulitis, although clinically similar, could, in fact, be driven by distinctly different pathophysiological processes.

Does a State of Pain Amplification (Hypersensitivity in Nongenital Sites) Precede or Follow the Development of Vestibulitis?

Women with vestibulitis have measurable differences in sensory pain thresholds, a centrally regulated trait. A substantial proportion of women with vestibulitis shows hypersensitivity to several categories of pain (tactile, thermal, and pressure) at nongenital sites (25,48,59–61). The thermal pain threshold for women with vestibulitis (42.2 $\pm$ 2.5°C) is significantly lower than pain-free comparison groups (43.6 $\pm$ 1.9°C) ($P = .006$) (59). Similarly, high sensitivity to pressure pain in the upper thighs ($P = .004$) and deltoids ($P < .05$) is reported in this population (25). Collectively, these observations point to an abnormal state of pain amplification among women with vestibulitis. However, the relative contribution of a state of pain amplification in initiation and maintenance of vestibulitis is poorly understood. Some investigators attribute this pain sensitivity to chronicity of pain in vestibulitis (central sensitization) (25,62), whereas others view it as a reflection of inherent dysfunction in pain-regulatory mechanisms (61,63). Over the past 3 years, a growing body of literature suggests that an inherent biologic abnormality in pain processing (a state of pain amplification) may be present in some women with vestibulitis (25,47,48,59–62,64).

Subgroups of women with vestibulitis differ along the continuum of extragenital pain sensitivity (60). Women with vestibulitis are clinically divided into 2 subgroups: primary (women who have never had comfortable intercourse) and secondary (women who had no history of pain or dyspareunia until later into adult life). Women with primary onset of vestibulitis have greater pain sensitivity to thermal pain ($P = .019$) despite reports of intercourse-related pain that are similar to women with secondary onset of vestibulitis (60). These central regulatory differences suggest differences in underlying pathophysiological mechanisms (60). Women with secondary vestibulitis may experience a local disease (ie, peripheral

process), whereas those with primary onset may have dysfunction in pain-regulatory mechanisms in addition to the local vestibular and muscle pain. A one-dimensional clinical classification schema based on the history of the onset of pain (primary vs secondary) is unlikely to explain the varying contributions of central and peripheral factors. Nevertheless, the ability to see such differences using this crude classification emphasizes the magnitude of heterogeneity in this population. The involvement of central pain-regulatory mechanisms may help explain observed differences in clinical severity and treatment outcomes in subgroups of women with this condition (60). Poor treatment outcomes among women with extragenital pain sensitivity (marker for central dysregulation) (61) emphasize the need for a comprehensive multidimensional assessment of vestibulitis as a pain disorder.

Is Vestibulitis a Psychologic Disorder?

Specific psychologic traits may precede or be modified by chronic pain disorders. Little empiric attention has been given to the role of psychologic distress in vestibulitis with competing conceptualizations of the condition as either functional or organic (65). Surprisingly, evidence does *not* suggest that histories of abuse or assault are more prevalent in patients with vestibulitis (66–70). In fact, our own research team found that patients with vestibulitis tend to report less trauma and abuse than other populations of women in our chronic pelvic pain clinic (Leserman, *American Journal of Obstetrics and Gynecology*, in press). Nonetheless, anxiety, depression (65,71–76), and somatization (tendency to report a higher frequency of bodily complaints) are commonly observed psychologic features among women with vestibulitis (25,70,75,77). Granot and Lavee found more trait anxiety (standard difference [d] = 0.65, $P < .01$) and somatization ($d = 0.84$, $P < .01$) among women with vestibulitis compared with a vestibulitis-free comparison group (63).

Some investigators view vestibulitis as primarily a psychologic disorder (73,78), whereas others view psychologic dysfunction as a consequence of prolonged pain (74) and sexual dysfunction (69). Although research supports both constructs (79,80), the direction of these relationships remains unclear, and both pathways may be operative in vestibulitis.

Differences in severity of anxiety and somatization are also observed among subgroups of women with vestibulitis (60,81). Women conventionally considered to have primary vestibulitis experience higher levels of anxiety and somatization and are more refractory to treatment compared with women with secondary vestibulitis (60,81). Longer duration and more severe pain are commonly postulated reasons for the observed psychologic differences in cross-sectional or retrospective studies between primary and secondary vestibulitis.

Alternatively, some women with vestibulitis may have psychologic profiles that favor anxiety and somatization as risk factors for the development of the disorder and do not result from having the condition (although the traits may be amplified by symptoms). As outlined here, these individuals may have dysfunction in central pain-regulatory systems that promote psychologic traits that contribute to developing vestibulitis symptoms. This combination of psychologic abnormalities and pain sensitivity has been shown prospectively to be a risk factor for development of TMD among individuals who were asymptomatic at baseline (50).

Future Directions

Our current clinical diagnostic criteria and classification of vestibulitis are inadequate for understanding the differences in underlying pathophysiological processes. Consider the challenges presented by patient scenarios as divergent as 1) a 28 year old with pain since tampon use and an unconsummated marriage; 2) a 35 year old with no history of painful intercourse until childbirth; and, 3) a 28 year old with a lifelong history of occasional pain with intercourse, which spontaneously resolved but became chronic after a severe candidal infection. As clinicians, we are acutely aware of the different challenges each of these patients present. Furthermore, based on our experience, we often empirically use different first-line therapies. However, using our current classification schema, these women, despite distinct clinical differences, are classified together as having the same disorder. We purpose a multidimensional assessment akin to our daily clinical practice, which includes detailed exploration of the patient's history and clinical examination findings before diagnosis and treatment.

In essence, the current state of diagnoses and treatment of vestibulitis may be comparable to diagnosing severe headache without a context and a conceptual model to elicit pertinent historical and physical examination, critical for differentiating sinus, migraine, cluster, or tension-type headaches. In the absence of such knowledge, a diverse range of interventions (eg, antibiotic treatment, analgesics, surgery, and acupuncture) are likely to be found effective when the "symptom" is viewed as a "disorder." Only when a symptom is examined in the context of other associ-

ated signs and symptoms can we begin to decipher the differences in underlying pathophysiology.

Development of rational treatment interventions informed by the underlying pathophysiology is critically impaired in vestibulitis as a result of the lack of a conceptual model that examines the interplay between clinical variables. Reliable, reproducible, and comprehensive evaluation will be required to further advance study of vestibulitis pathophysiology, natural history, treatment efficacy, and long-term outcomes. To that end, we must: 1) objectively measure the clinical manifestation of vestibulitis as it relates to mucosal, pelvic floor muscle, psychologic, and central pain-processing mechanisms; 2) investigate the potential for distinctive subtypes; and 3) develop a conceptual framework informed by these measures to guide effective therapeutic interventions.

REFERENCES

1. Harlow BL, Stewart EG. A population-based assessment of chronic unexplained vulvar pain: have we underestimated the prevalence of vulvodynia? J Am Med Womens Assoc 2003; 58:82–88.
2. Reed BD, Crawford S, Couper M, et al. Pain at the vulvar vestibule: a web-based survey. J Low Genit Tract Dis 2004; 8:48–57.
3. Harlow BL, Wise LA, Stewart EG. Prevalence and predictors of chronic lower genital tract discomfort. Am J Obstet Gynecol 2001;185:545–550.
4. Hansen A, Carr K, Jensen JT. Characteristics and initial diagnoses in women presenting to a referral center for vulvovaginal disorders in 1996–2000. J Reprod Med 2002;47: 854–860.
5. Zolnoun DA, Hartmann KE, Steege JF. Overnight 5% lidocaine ointment for treatment of vulvar vestibulitis. Obstet Gynecol 2003;102:84–87.
6. Baggish MS, Miklos JR. Vulvar pain syndrome: a review. Obstet Gynecol Surv 1995;50:618–627.
7. Friedrich EG Jr. Vulvar vestibulitis syndrome. J Reprod Med 1987;32:110–114.
8. Friedrich EG Jr. Therapeutic studies on vulvar vestibulitis. J Reprod Med 1988;33:514–518.
9. Bergeron S, Binik YM, Khalife S, et al. A randomized comparison of group cognitive–behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. Pain 2001;91:297–306.
10. Babula O, Danielsson I, Sjoberg I, et al. Altered distribution of mannose-binding lectin alleles at exon I codon 54 in women with vulvar vestibulitis syndrome. Am J Obstet Gynecol 2004; 191:762–766.
11. Babula O, Bongiovanni AM, Ledger WJ, et al. Immunoglobulin E antibodies to seminal fluid in women with vulvar vestibulitis syndrome: relation to onset and timing of symptoms. Am J Obstet Gynecol 2004;190:663–667.
12. Bornstein J, Goldschmid N, Sabo E. Hyperinnervation and mast cell activation may be used as histopathologic diagnostic criteria for vulvar vestibulitis. Gynecol Obstet Invest 2004; 58:171–178.
13. Eva LJ, MacLean AB, Reid WMN, et al. Estrogen receptor expression in vulvar vestibulitis syndrome. Am J Obstet Gynecol 2003;189:458–461.
14. Foster DC, Hasday JD. Elevated tissue levels of interleukin-1 beta and tumor necrosis factor-alpha in vulvar vestibulitis. Obstet Gynecol 1997;89:291–296.
15. Foster DC ST, Stodgell CJ. Impact of genetic variation in interleukin-1 receptor antagonist and melanocortin-1 receptor genes on vulvar vestibulitis syndrome. J Reprod Med 2004;49:503–509.
16. Gerber S, Bongiovanni AM, Ledger WJ, et al. A deficiency in interferon-alpha production in women with vulvar vestibulitis. Am J Obstet Gynecol 2002;186:361–364.
17. Gerber S, Bongiovanni AM, Ledger WJ, et al. Defective regulation of the proinflammatory immune response in women with vulvar vestibulitis syndrome. Am J Obstet Gynecol 2002;186:696–700.
18. Gerber S, Bongiovanni AM, Ledger WJ, et al. Interleukin-1β gene polymorphism in women with vulvar vestibulitis syndrome. Eur J Obstet Gynecol Reprod Biol 2003;107:74–77.
19. Jeremias J, Ledger WJ, Witkin SS. Interleukin 1 receptor antagonist gene polymorphism in women with vulvar vestibulitis. Am J Obstet Gynecol 2000;182:283–285.
20. Graziottin A, Brotto LA. Vulvar vestibulitis syndrome: a clinical approach. J Sex Marital Ther 2004;30:125–139.
21. Reissing ED, Brown C, Lord MJ, et al. Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. J Psychosom Obstet Gynaecol 2005;26:107–113.
22. Reissing E, Binik Y, Khalifā S, et al. Vaginal spasm, pain, and behavior: an empirical investigation of the diagnosis of vaginismus. Arch Sex Behav 2004;33:5–17.
23. Masheb RM. Psychosocial Functioning in Women With Vulvodynia. New York: St. John's University, 1997.
24. Masheb RM, Nash JM, Brondolo E, et al. Vulvodynia: an introduction and critical review of a chronic pain condition. Pain 2000;86:3–10.
25. Pukall CF, Binik YM, Khalife S, et al. Vestibular tactile and pain thresholds in women with vulvar vestibulitis syndrome. Pain 2002;96:163–175.
26. Schover LR, Youngs DD, Cannata R. Psychosexual aspects of the evaluation and management of vulvar vestibulitis. Am J Obstet Gynecol 1992;167:630–636.
27. de Jong JM, van Lunsen RH, Robertson EA, et al. Focal vulvitis: a psychosexual problem for which surgery is not the answer. J Psychosom Obstet Gynaecol 1995;16:85–91.
28. Lamont J, Randazzo J, Farad M, et al. Psychosexual and social profiles of women with vulvodynia. J Sex Marital Ther 2001;27:551–555.
29. Glazer HI. Dysesthetic vulvodynia. Long-term follow-up after treatment with surface electromyography-assisted pelvic floor muscle rehabilitation. J Reprod Med 2000;45:798–802.
30. Glazer HI, Jantos M, Hartmann EH, et al. Electromyographic comparisons of the pelvic floor in women with dysesthetic vulvodynia and asymptomatic women. J Reprod Med 1998; 43:959–962.
31. Glazer HI, Marinoff SC, Sleight IJ. Web-enabled Glazer surface electromyographic protocol for the remote, real-time assessment and rehabilitation of pelvic floor dysfunction in vulvar vestibulitis syndrome. A case report. J Reprod Med 2002;47:728–730.
32. Glazer HI, Rodke G, Swencionis C, et al. Treatment of vulvar vestibulitis syndrome with electromyographic biofeedback of pelvic floor musculature. J Reprod Med 1995;40:283–290.
33. Pukall CF, Payne KA, Binik YM, et al. Pain measurement in vulvodynia. J Sex Marital Ther 2003;29(suppl 1):111–120.
34. Merskey H. Variable meanings for the definition of disease. J Med Philos 1986;11:215–232.
35. Warner TF, Tomic S, Chang CK. Neuroendocrine cell-axonal complexes in the minor vestibular gland. J Reprod Med 1996; 41:397–402.
36. Westrom LV, Willen R. Vestibular nerve fiber proliferation in vulvar vestibulitis syndrome. Obstet Gynecol 1998;91:572–576.
37. Prayson RA, Stoler MH, Hart WR. Vulvar vestibulitis. A histopathologic study of 36 cases, including human papilloma-

virus in situ hybridization analysis. Am J Surg Pathol 1995; 19:154–160.
38. Pukall CF, Strigo IA, Binik YM, et al. Neural correlates of painful genital touch in women with vulvar vestibulitis syndrome. Pain 2005;115:118–127.
39. Pyka RE, Wilkinson EJ, Friedrich EG Jr, et al. The histopathology of vulvar vestibulitis syndrome. Int J Gynecol Pathol 1988;7:249–257.
40. Scheinfeld N. The role of gabapentin in treating diseases with cutaneous manifestations and pain. Int J Dermatol 2003;42: 491–495.
41. Tympanidis P, Casula MA, Yiangou Y, et al. Increased vanilloid receptor VR1 innervation in vulvodynia. Eur J Pain 2004;8:129–133.
42. Masterson BJ, Galask RP, Ballas ZK. Natural killer cell function in women with vestibulitis. J Reprod Med 1996;41:562–568.
43. Bohm-Starke N, Falconer C, Rylander E, et al. The expression of cyclooxygenase 2 and inducible nitric oxide synthase indicates no active inflammation in vulvar vestibulitis. Acta Obstet Gynecol Scand 2001;80:638–644.
44. Bohm–Starke N, Hilliges M, Falconer C, et al. Increased intraepithelial innervation in women with vulvar vestibulitis syndrome. Gynecol Obstet Invest 1998;46:256–260.
45. Bohm-Starke N, Hilliges M, Blomgren B, et al. Increased blood flow and erythema in the posterior vestibular mucosa in vulvar vestibulitis. Obstet Gynecol 2001;98:1067–1074.
46. Bohm-Starke N, Hilliges M, Falconer C, et al. Neurochemical characterization of the vestibular nerves in women with vulvar vestibulitis syndrome. Gynecol Obstet Invest 1999;48:270–275.
47. Giesecke J, Reed BD, Haefner HK, et al. Quantitative sensory testing in vulvodynia patients and increased peripheral pressure pain sensitivity. Obstet Gynecol 2004;104:126–133.
48. Lowenstein L, Vardi Y, Deutsch M, et al. Vulvar vestibulitis severity—assessment by sensory and pain testing modalities. Pain 2004;107:47–53.
49. Gracely RH, Lynch S, Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. Pain 1992;51:175–194.
50. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14:135–143.
51. Bergeron S, Brown C, Lord MJ, et al. Physical therapy for vulvar vestibulitis syndrome: a retrospective study. J Sex Marital Ther 2002;28:183–192.
52. Reissing EDB, YM, Khalife S, et al. Etiological correlates of vaginismus: sexual and physical abuse, sexual knowledge, sexual self-schema, and relationship adjustment. J Sex Marital Ther 2003;29:47–59.
53. Graven-Nielsen T, Arendt-Nielsen L. Peripheral and central sensitization in musculoskeletal pain disorders: an experimental approach. Curr Rheumatol Rep 2002;4:313–321.
54. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6: 301–355.
55. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med 2000;160: 221–227.
56. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med 2001; 134:868–881.
57. Wesselmann U. Neurogenic inflammation and chronic pelvic pain. World J Urol 2001;19:180–185.
58. Svensson P, Graven-Nielsen T, Arendt-Nielsen L. Mechanical hyperesthesia of human facial skin induced by tonic painful stimulation of jaw muscles. Pain 1998;74:93–100.
59. Granot M, Friedman M, Yarnitsky D, et al. Enhancement of the perception of systemic pain in women with vulvar vestibulitis. BJOG 2002;109:863–866.
60. Granot M, Friedman M, Yarnitsky D, et al. Primary and secondary vulvar vestibulitis syndrome: systemic pain perception and psychophysical characteristics. Am J Obstet Gynecol 2004;191:138–142.
61. Granot M, Zimmer EZ, Friedman M, et al. Association between quantitative sensory testing, treatment choice, and subsequent pain reduction in vulvar vestibulitis syndrome. J Pain 2004;5:226–232.
62. Bohm-Starke N, Hilliges M, Brodda-Jansen G, et al. Psychophysical evidence of nociceptor sensitization in vulvar vestibulitis syndrome. Pain 2001;94:177–183.
63. Granot M, Lavee Y. Psychological factors associated with perception of experimental pain in vulvar vestibulitis syndrome. J Sex Marital Ther 2005;31:285–302.
64. Eva LJ, Reid WM, MacLean AB, et al. Assessment of response to treatment in vulvar vestibulitis syndrome by means of the vulvar algesiometer. Am J Obstet Gynecol 1999;181: 99–102.
65. Meana M, Binik I, Khalife S, et al. Affect and marital adjustment in women's rating of dyspareunic pain. Can J Psychiatry 1998;43:381–385.
66. Edwards L, Mason M, Phillips M, et al. Childhood sexual and physical abuse. Incidence in patients with vulvodynia. J Reprod Med 1997;42:135–139.
67. Bodden-Heidrich R, Kuppers V, Beckmann MW, et al. Psychosomatic aspects of vulvodynia. Comparison with the chronic pelvic pain syndrome. J Reprod Med 1999;44:411–416.
68. Dalton VK, Haefner HK, Reed BD, et al. Victimization in patients with vulvar dysesthesia/vestibulodynia. Is there an increased prevalence? J Reprod Med 2002;47:829–834.
69. Meana M, Binik YM, Khalife S, et al. Biopsychosocial profile of women with dyspareunia. Obstet Gynecol 1997;90:583–589.
70. Danielsson I, Sjoberg I, Wikman M. Vulvar vestibulitis: medical, psychosexual and psychosocial aspects, a case-control study. Acta Obstet Gynecol Scand 2000;79:872–878.
71. Gates EA, Galask RP. Psychological and sexual functioning in women with vulvar vestibulitis. J Psychosom Obstet Gynaecol 2001;22:221–228.
72. Meana M, Binik YM, Khalife S, et al. Psychosocial correlates of pain attributions in women with dyspareunia. Psychosomatics 1999;40:497–502.
73. Koblenzer CS, Bostrom P. Chronic cutaneous dysesthesia syndrome: a psychotic phenomenon or a depressive symptom? J Am Acad Dermatol 1994;30:370–374.
74. Nunns D, Mandal D. Psychological and psychosexual aspects of vulvar vestibulitis. Genitourin Med 1997;73:541–544.
75. Stewart DE, Whelan CI, Fong IW, et al. Psychosocial aspects of chronic, clinically unconfirmed vulvovaginitis. Obstet Gynecol 1990;76:852–856.
76. Jadresic D, Barton S, Neill S, et al. Psychiatric morbidity in women attending a clinic for vulval problems—is there a higher rate in vulvodynia? Int J STD AIDS 1993;4:237–239.
77. Van Lankveld JJ, Weijenborg PT, ter Kuile MM. Psychologic profiles of and sexual function in women with vulvar vestibulitis and their partners. Obstet Gynecol 1996;88:65–70.
78. Pucheu SJ. 'It itches, it burns': psychoanalytic approach to a case of vulvar burning syndrome. J Psychosom Obstet Gynaecol 1998;19:175–181.
79. Huang GJ, LeResche L, Critchlow CW, et al. Risk factors for diagnostic subgroups of painful temporomandibular disorders (TMD). J Dent Res 2002;81:284–288.
80. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. Pain 2003;106:127–133.
81. Bornstein J, Maman M, Abramovici H. 'Primary' versus 'secondary' vulvar vestibulitis: one disease, two variants. Am J Obstet Gynecol 2001;184:28–31.