



Vulvodynia: Strategies for Treatment

ANDREW T. GOLDSTEIN, MD,*
STANLEY C. MARINOFF, MD, MPH,†
and HOPE K. HAEFNER, MD‡

**Division of Gynecologic Specialties, Department of Gynecology and Obstetrics, Johns Hopkins School of Medicine, Baltimore, Maryland; †George Washington University School of Medicine and Health Sciences, Washington, DC; and ‡The University of Michigan Center for Vulvar Diseases, The University of Michigan Hospitals, Ann Arbor, Michigan*

Introduction

In 2003, the International Society for the Study of Vulvovaginal Disease (ISSVD) revised its definition of the frequently used and well-accepted term “vulvodynia.” The new classification acknowledges that vulvar pain can be attributed to diagnosable disorders such as infections, dermatologic disorders, neoplastic processes, and neurologic disorders. The other category is vulvodynia, pain not related to a specific, identifiable disorder. Vulvodynia is often described as a vulvar discomfort with sensations of burning, irritation, or rawness. In addition, the ISSVD further expanded its classification of vulvodynia into generalized and localized pain. These categories are further subdivided to provoked pain or unprovoked pain.

Correspondence: Hope K. Haefner, MD, Associate Professor, Director, The University of Michigan Center for Vulvar Diseases, The University of Michigan Hospitals, L 4000 Women's Hospital, 1500 E. Medical Center Drive, Ann Arbor, MI 48109. E-mail: haefner@umich.edu

Additionally, there is a category for pain that is both provoked and unprovoked (mixed). Vestibulodynia (previously termed vestibulitis) is a pain localized to the vestibule. The suffix “-itis” has been excluded from the recent ISSVD terminology because studies found a lack of association between excised tissue and inflammation. Other terminologies have classified vestibulodynia as primary or secondary; in the primary subset, the pain has been present since the first tampon use or intercourse, and with secondary vestibular pain, women have had painless tampon insertion or intercourse, then the vestibular pain develops at a later time.

Epidemiology

Until recently, the epidemiology of vulvodynia was largely unknown. The prevalence of vulvodynia has ranged from estimates of as low as 200,000 women in the United States¹ to as high as 15% of women based on a

report from a general gynecologic practice population.² A study from 1998 reported 1.3% in a female genitourinary medicine clinic population had vulvodynia.³ A more recent study by Danielsson and coworkers evaluated 3017 women aged 20 to 60 years participating in a screening program for cervical cancer who answered a questionnaire about possible painful coitus. The prevalence was 9.3% for the whole group (13% for women aged 20–29 and 6.5% for women aged 50–60).⁴ Women with pain localized to the vestibule (vestibulodynia) have been characterized as white, young (mean age, 32 years), and nulliparous.⁵ However, a recent study, performed in 2003, estimated the prevalence of chronic unexplained vulvar pain in an ethnically diverse population-based sample of women.⁶ Approximately 16% of respondents (4915 women) reported chronic burning, knife-like pain, or pain on vulvar contact that lasted for at least 3 months or longer. Chronic vulvar pain on contact decreased with increasing age, but the cumulative incidence of chronic burning and knife-like pain was similar across all ages. Contrary to earlier assessments, white and black women reported a similar lifetime prevalence. However, Hispanic women were 80% more likely to experience chronic vulvar pain than were white and black women. They concluded that as many as 14 million women in the United States may experience chronic vulvar pain during their lifetime. If only a small percentage of these women have true vulvodynia, the number of women with the problem is enormous. At least 30% will suffer without seeking medical care.⁷ Respondents in this ongoing study are being seen for a complete medical history and physical examination to confirm that the pain reported is vulvodynia.

Additionally, similar findings have been reported on a web-based survey.⁸ Between May 24, 2002, and June 6, 2002, 730 non-black women and 364 black women responded to an invitation to participate in a survey; 94.5% completed the survey. A history of pain at the vulvar vestibule was

reported by 288 women (27.9%), with 80 (7.8% of the initial 1032) reporting pain within the past 6 months, 31 (3.0%) reporting pain that lasted 3 or more months, and 18 (1.7%) reporting vestibular pain lasting 3 or more months that occurred within the past 6 months.

The Etiology of Vulvodynia

Exactly what causes vulvodynia is unknown, but it most likely occurs from a variety of sources. Proposed etiologies include abnormalities of embryologic development, increased urinary oxalate excretion, genetic and/or immune factors, hormonal factors (association with oral contraception use or menopause), infection (human papillomavirus [HPV] and candida), inflammation, and neuropathies. There may be several different diseases with similar symptoms that are related to vulvodynia.⁹

In the past decade, many of the early theories about vulvodynia have not been substantiated. The majority of recent studies do not support an association with HPV, particularly in pain that is localized to the vestibule.^{10–13} The role of candidiasis in this condition is uncertain. Similarly, the role that inflammation plays in the development of localized vulvar dysesthesia is unclear. Histopathologic specimens from patients with vestibulodynia have been compared with control subjects and similar findings have been found in each population. Many control subjects have nonspecific inflammation.¹⁴ Several papers that mention inflammation and inflammatory cytokines show inconsistent results. Bohm-Starke and colleagues found a low expression of the inflammatory markers cyclooxygenase 2 and inducible nitric oxide synthase in the vestibular mucosa of women with localized vestibular pain as well as in healthy control subjects.¹⁵ A few clinicians believe that vulvodynia occurs directly as a result of psychologic or sexual dysfunction. This viewpoint, however, is rejected both by most patients and by the majority of those working in the field.

On the other hand, almost all agree that the presence of chronic pain such as occurs in vulvodynia can secondarily affect a patient's psychologic well-being.

A consensus has been emerging among thought leaders (most recently at an National Institutes of Health [NIH]-sponsored conference on vulvodynia in April 2003) that generalized, nonprovoked vulvodynia is described most accurately when it is thought of as a complex regional pain syndrome (CRPS), similar to other CRPS such as fibromyalgia and interstitial cystitis.⁹

Like women with other CRPS, women with vulvodynia exhibit enhanced systemic pain perception, a process known as central nervous system sensitization.¹⁶ Second, women with vulvodynia are more likely to have other CRPS such as interstitial cystitis.¹⁷ This may be explained by another phenomenon common to CRPS known as "wind-up" in which there is a progressively increasing activity in dorsal horn cells of the spinal cord after repetitive activation of primary afferent C-fibers.¹⁸ Another study found a significant decrease in estrogen receptor expression in the vestibular mucosa of women with vestibulodynia.¹⁹

Treating Vulvodynia

Numerous treatments have been used for the various forms of vulvodynia, including vulvar care measures; topical, oral, and injectable medications; biofeedback and physical therapy; a low oxalate diet with calcium citrate supplementation; and surgical treatments. Other kinds of treatment include acupuncture, hypnotherapy, topical nitroglycerin, and botulinum toxin, but they are not discussed here. It is important to recognize that rapid resolution of vulvodynia is unusual even with appropriate therapy. Whereas a 100% improvement rate is desired in all patients, most women with vulvodynia do not reach that level. They report markedly less pain at follow up, although many are not cured. It is interesting to note that in a study by Peckham and colleagues. Approximately

one half of patients with vestibular pain experienced spontaneous improvement, and in approximately half of these patients, this occurred within 6 months.²⁰

We include a vulvodynia algorithm to guide practitioners in diagnosing and treating this common disorder (Fig. 1).

VULVAR CARE MEASURES

Common suggestions for minimizing irritation include the use of 100% cotton underwear during the day and not wearing underwear at night while sleeping. We counsel patients to avoid vulvar irritants and douching, and to use mild soap for bathing without applying soaps to the vulva. We recommend against using facecloths for washing; the interlabial sulci and vestibule can be cleaned easily with water and gentle touch. If menstrual pads are irritating, 100% cotton pads may be helpful. Adequate lubrication for intercourse is recommended. Many different lubricants exist with various bases such as Slippery Stuff (Wallace-O'Farrell, Inc., Puyallup, WA), Femglide (Medicool Inc., Torrance, CA), Astroglide (Biofilm Inc., Vista, CA), Femigel (Australian Bodycare, Denmark) (natural product from tea trees), K-Y Jelly (Personal Products Co., Skillman, NJ), Lubrin (Aurora Pharmaceuticals, Australia) (a suppository), Moist Again (Lake Pharmaceutical, Vernon Hills, IL), Replens (Lil' Drug Store Products, Cedar Rapids, IA) (generally used several times weekly), Sylk (Geneva Marketing Pty Ltd., Australia) (made of Kiwi fruit vine and purified water), Surgilube (Fougera, a division of Altana Inc., Melville, NY), Vielle (Futura Medical PLC, Guildford, Surrey), vitamin E oil, Crisco oil (J. M. Smucker, Co., Orrville, OH), and saliva. Some patients find the lubricants to be irritating, particularly some of the commercial lubricants. Many patients have an allergic reaction to lubricants that contain propylene glycol. Natural oils are also used by some patients (olive, sweet almond, sesame, rose hip, grape seed, and wheat germ). Ice packs or other forms of cold application are helpful in some patients, but these

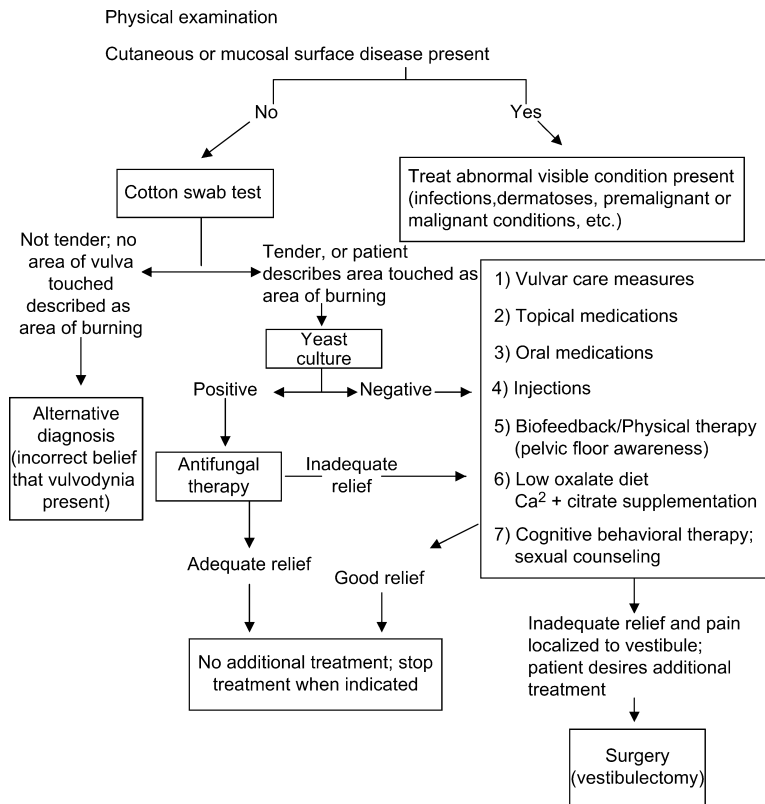


FIGURE 1. Vulvodynia algorithm depicts path of physical examination leading to diagnosis and treatment options. (Reprinted with permission from Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. *Journal of Lower Genital Tract Disease*. 2005;9:40–51.)

produce irritation when overused. Cool gel packs may be useful. Rinsing the vulva after urination may be helpful in some cases. The area then should be gently patted dry. The use of hair dryers is irritating and should be avoided. After bathing in a tub or shower, we advise patients to pat dry the genital area. If the skin is dry, emollients (such as vegetable oil or plain petrolatum) may be used topically to hold moisture and improve the barrier function.

TOPICAL THERAPIES FOR VULVODYNIA

Some patients find relief from vulvodynia with topical anesthetics (Table 1). All topical anesthetics may cause initial burning and stinging on application; the discomfort

lasts for a few minutes until the area is numb. The longer the ointment is on the area, the deeper the anesthesia.

The most commonly prescribed topical medication is lidocaine (Xylocaine) jelly 2% (AstraZeneca Pharmaceuticals, Ltd., Wilmington, DE) or ointment 5% (Ferndale Laboratories, Ferndale, MI). This can be applied as often as required for symptomatic relief and 30 minutes before sexual activity for those women with dyspareunia (ointment preferred). EMLA (AstraZeneca Pharmaceuticals LP, Wilmington, DE) (eutectic mixture of local anesthesia, comprising lidocaine and prilocaine) LMX 4 (Ferndale Laboratories, Ferndale, MI), and LMX 5 (Ferndale Laboratories, Ferndale, MI) (lidocaine 4% and 5%) are also used by some

TABLE 1. Topical Medications Used to Treat Vulvodynia

Topical Medication	Dosage	Side Effects*
5% lidocaine ointment (Ferndale Laboratories, Ferndale, MI)	Apply to skin as needed Dispense 30-g tube Do not use over 20 g of ointment in a 24-hour period	Erythema or edema; rare cases of purpura If ointment is present on skin during intercourse, the partner may experience numbness
EMLA cream (lidocaine 2.5% and prilocaine 2.5%) (AstraZeneca Pharmaceuticals LP, Wilmington, DE)	Apply to skin as needed; do not exceed 2.5 g over 20 to 25 cm ² of skin surface (for example, a 5 cm × 5-cm area) Dispense 30-g tube	Paleness, erythema, and swelling
L-M-X 4 formerly ELA-Max 4% cream (lidocaine 4%) (Ferndale Laboratories, Ferndale, MI)	Apply to skin as needed	Erythema and edema
L-M-X 5 formerly ELA-Max Anorectal 5% cream (lidocaine 5%) (Ferndale Laboratories, Ferndale, MI)	Dispense 30-g tube	
Estrogens	These can be used intravaginally or topically	Common reactions
Estrace [®] vaginal cream (estradiol vaginal cream 0.01%) (Bristol-Meyers Squibb Company, Princeton, NJ)	For treatment of vulvar and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible The usual dosage range is 2 to 4 g (marked on the applicator) daily for 1 or 2 weeks, then gradually taper	Vaginal bleeding, spotting, breast changes, nausea, vomiting, headache, fluid retention, mood changes, weight changes, rash
Premarin vaginal cream (conjugated estrogens 0.625 mg/g) (Wyeth-Ayerst Co., Philadelphia, PA)	Tube containing 1½ oz (42.5 g) with a calibrated plastic applicator for delivery of 1, 2, 3, or 4 g ½ to 2 g daily, intravaginally, depending on the severity of the condition; taper gradually to every other day, twice weekly, and so on Patients with an intact uterus should be monitored closely for signs of endometrial cancer, and appropriate diagnostic measures should be taken to rule out malignancy in the event of abnormal vaginal bleeding Each contains net wt 1½-oz (42.5-g) tube with one plastic applicator calibrated in ½-g increments to a maximum of 2 g; taper gradually	Serious reactions Thromboembolism, stroke, myocardial infarction, breast, endometrial changes, fibroid enlargement, gallbladder disease, cholestatic jaundice, pancreatitis, asthma worsening, depression, hypertension
Amitriptyline 2%/baclofen 2% in water-washable base (Elavil 2%/Lioresal 2% in water-washable base)	Topical amitriptyline 2% with baclofen 2% in water-washable base (WWB): squirt ½ cc from syringe onto finger and apply to affected area one to 4 times daily	Common reactions (amitriptyline)
Elavil (AstraZeneca Pharmaceuticals LP)	Dispense 30-day supply	Irritation, contact dermatitis, dry mouth, drowsiness, dizziness, constipation, weight gain, urinary retention, tachycardia, blurred vision, confusion

continued on next page

TABLE 1. Continued

Topical Medication	Dosage	Side Effects*
Liorsesal (Geigy Novartis Pharmaceuticals Corp., East Hanover, NJ)		Serious reactions (amitriptyline) Seizures, stroke, myocardial infarction, agranulocytosis, thrombocytopenia Common reactions (baclofen) Drowsiness, dizziness, weakness, nausea, confusion, hypotension, headache, insomnia, constipation, muscle weakness, rash, sweating, fatigue Serious reactions (baclofen) Depression, respiratory problems, ataxia, syncope, seizures, hallucinations, exacerbation of spasticity

* Generally the side effects of topical medications are less than when taken systemically.

(Reprinted with permission from Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. *Journal of Lower Genital Tract Disease*. 2005;19:40–51.)

patients. The sexual partner may experience numbness as well. When a topical anesthetic is used, the sexual partner should avoid oral contact.

The long-term use of overnight topical lidocaine has been suggested as a specific therapy for vulvodynia, with a theory that the regular application of lidocaine to interrupt the painful impulses may minimize feedback amplification of pain and allow for healing. The use of overnight lidocaine has been studied in an open label trial by Zolnoun and colleagues.²¹ Patients were instructed to apply a copious amount of 5% lidocaine ointment to the affected area at bedtime and were asked to place a cotton ball generously coated with the 5% lidocaine ointment in the vestibule to assure continuing overnight application. They were instructed to use the treatment nightly for 8 or more hours every night. Of 61 women with vestibulodynia, 76% were able to have intercourse after therapy as compared with 36% at baseline (mean, 7 weeks) with significantly less pain during sexual activity. Because lidocaine toxicity is a possibility, we carefully advise patients with regard to the correct dosage and frequency of the topical lidocaine use.²²

Benzocaine, which is the anesthetic in Vagacaine (Clay-Park Laboratories, Inc., Bronx, NY) and Vagisil (Combe Inc., White Plains, NY), is a sensitizer and can cause an allergic contact dermatitis, which is why we do not recommend their use in patients with vulvodynia. Similarly, diphenhydramine, Benadryl (Warner Wellcome, Morris Plains, NJ), is in many topical anesthetic and anti-itch preparations, and because it is another common sensitizer, we do not recommend it. Some patients benefit symptomatically from the application of plain petrolatum, Vaseline (Cheesborough-Ponds, Greenwich, CT), perhaps because it minimizes friction of skin folds.

Estrogen has been used both topically and in an intravaginal ring with variable results. Other topical medications that patients have used include capsaicin, atropine, nitroglycerine, and Traumeel (Heel Inc., Albuquerque, NM).

Some patients with specific point tenderness have responded to topical doxepin. For some patients with localized pain, a combination of topical amitriptyline 2% and baclofen 2% in a water-washable base has been useful.

Topical therapies that patients describe as not having significant benefit for vulvodynia are important to note to avoid possible local side effects and ultimate aggravation of symptoms. Although topical corticosteroids logically should improve the pain of vestibulodynia, they generally do not improve this condition. The use of chronic topical corticosteroids on the vulva occasionally produces steroid dermatitis, characterized by erythema and burning. Likewise, some clinicians have used topical testosterone for vulvodynia, thinking that a subclinical vulvar dermatosis is a possible causative factor. However, this medication is irritating to many and useful for very few. Topical antifungal medications are used empirically by many clinicians for presumed superimposed yeast because early theories as to the cause of vulvodynia included possible hypersensitivity to candida species. Topical antifungal therapy generally does not improve vulvodynia beyond the soothing properties of some vehicles, and superimposed irritant discomfort is more likely for women using it.

Oral Treatments for Vulvodynia

ANTIDEPRESSANTS

Antidepressants have been used for the treatment of many chronic pain conditions. A common treatment of vulvodynia is the use of an oral tricyclic antidepressant such as amitriptyline, Elavil (AstraZeneca Pharmaceuticals LP, Wilmington, DE), nortriptyline, Pamelor (Novartis Pharmaceutical Corp., Easthanover, NJ), and desipramine, Norpramin (Hoechst Marion Roussel for Aventis Pharmaceuticals, Bridgewater, NJ); all 3 have been used to treat many pain conditions thought to have a neuropathic etiology (Table 2). Whereas tricyclic antidepressants have traditionally been used for generalized vulvodynia, they are also useful in the treatment of localized pain. In a report of 33 women being treated at a vulvodynia clinic, 15 had a complete response to tricyclic antidepressants for the treatment of vulvodynia (both generalized and localized).²³ However,

this was not a randomized study and other interventions may have contributed to the success in treatment such as support and counseling. The mechanism of action is believed to be associated with blocking reuptake of norepinephrine and serotonin transmitters, although the mechanism may actually be from the anticholinergic effects. These drugs affect sodium channels and the N-methyl-D-aspartate (NMDA) receptor.

If a healthcare provider and patient choose this treatment of vulvodynia, it may be important to emphasize its effect on pain rather than its effect on depression to enhance patient compliance.

TRICYCLIC ANTIDEPRESSANT DOSAGE FOR VULVODYNIA

The dosages of tricyclic antidepressants used for vulvodynia are significantly less than those used for depression. Amitriptyline is often used as a first-line agent, although many healthcare providers prefer nortriptyline and desipramine, because they tend to have fewer side effects than amitriptyline (which include dry mouth, drowsiness, and constipation) (Table 2). All are dosed in a similar fashion. We recommend starting patients at a low dose and increasing the dosage slowly until a nightly dose is reached that relieves symptoms. Patients should take this medication approximately 2 hours before bedtime. It is started at 5 to 25 mg nightly (use 5–10 mg for elderly patients) and increased by 10 to 25 mg weekly, not to exceed 150 mg per night. Tricyclic medications are available as syrups so that very small doses can be used to start patients who are sensitive to these medications.

Should patients elect to stop taking these drugs, they should be weaned off them gradually and warned against stopping them too suddenly. This medication should not be used in patients with abnormal heart rates (tachycardia) or in patients taking monoamine oxidase (MAO) inhibitors.

Patients on tricyclic antidepressants should not be pregnant, intend to become pregnant, or breast feed while using these drugs;

TABLE 2. Oral Medications Used to Treat Vulvodynia*

Medication Category Medication	Dosage	Side Effects
Antidepressants Amitriptyline (Elavil) (AstraZeneca Pharmaceuticals LP Wilmington, DE)	<p>Initial amitriptyline prescription: Amitriptyline 10 mg or 25 mg Sig: 1 by mouth each night for 1 week; if symptoms persist, 2 by mouth each night for 1 wk.; if symptoms persist, 3 by mouth each night for 1 wk.; if symptoms persist, 4 by mouth nightly; maintain nightly dose that relieves symptoms; generally do not exceed 100 to 150 mg nightly</p> <p>Start at 10 mg in patients age 60 or older or in patients who have not been able to tolerate higher dosages; increase by 10 mg weekly; often other medications should be tried in the elderly population than amitriptyline</p> <p>Do not stop suddenly (ie, wean); wean by 25 mg every 3 to 4 days; discuss interaction with alcohol (no more than one drink per day); if patient is in the reproductive-age group, discuss contraception Same dosing as amitriptyline</p>	<p>Common reactions Dry mouth, drowsiness, dizziness, constipation, weight gain, urinary retention, tachycardia, blurred vision, confusion Serious reactions (amitriptyline) Seizures, stroke, myocardial infarction, agranulocytosis, thrombocytopenia</p>
Nortriptyline (Pamelor) (Novartis Pharmaceuticals Corp., East Hanover, NJ)	Same dosing as amitriptyline	<p>Common reactions Dry mouth, drowsiness, dizziness, constipation, urinary retention, tachycardia, blurred vision, weight gain, confusion Serious reactions Seizures, myocardial infarction, stroke, agranulocytosis, thrombocytopenia</p>
Desipramine (Norpramin) (Hoechst Marion Roussel for Aventis Pharmaceuticals, Bridgewater, NJ)	Same dosing as amitriptyline, except desipramine is often taken in the morning instead of the evening	<p>Common reactions Drowsiness, dizziness, blurred vision, dry mouth, constipation, tachycardia, urinary retention, diaphoresis, weakness, nervousness, rash, seizures, tinnitus, anxiety, confusion Serious reactions Seizures, sudden death, arrhythmias, stroke, myocardial infarction, arteriovenous block, thrombocytopenia</p>

TABLE 2. Continued

Medication Category Medication	Dosage	Side Effects
Venlafaxine (Effexor XR) Consider this in patients who do not respond to tricyclic antidepressants; often used in conjunction with an anticonvulsant (Wyeth Pharmaceuticals Madison, NJ)	It is started at 37.5 mg a day (in the morning) with an increase to 75 mg a day (in the morning) after 1 to 2 weeks; can increase gradually (dose changes every 1 to 2 weeks) to a maximum dose of 150 mg a day; when stopping the medication, wean by 75 mg/wk Well tolerated in the elderly population	Common reactions Headache, nausea, somnolence, weight loss, anorexia, constipation, anxiety, vision changes, diarrhea, dizziness, dry mouth, insomnia, weakness, sweating, hypertension Serious reactions Seizures, suicide ideation, depression
Other antidepressants are used to treat pain; these include: fluoxetine (Prozac) (Eli Lilly & Co., Indianapolis, IN) sertraline (Zoloft) (Pfizer Inc., New York, NY) paroxetine (Paxil) (GlaxoSmithKline, Research Triangle Park, NC) citalopram (Celexa). (Forest Laboratories Inc., New York, NY)	Gabapentin comes in 100-, 300-, 400-, 600-, and 800-mg tablet sizes; generally it is started at 300 mg by mouth daily for 3 days, then 300 mg by mouth twice daily for 3 days, then 300 mg by mouth 3 times a day; it can gradually be increased to 3600 mg total daily; ideally, gabapentin is given in a 3-times-a-day dosage, but if the patient is unable to comply with that, it can be given in a twice-daily dosage; however, if using higher doses, a 3-times-a-day regimen should be followed; do not exceed more than 1200 mg in a dose For the elderly population, do not exceed 2700 mg per day	Common reactions Somnolence, dizziness, ataxia, fatigue, nystagmus, tremor, diplopia, rhinitis, blurred vision, nausea, vomiting, nervousness, dysarthria, weight gain Serious reactions Leukopenia
Anticonvulsants Gabapentin (Neurontin) (Pfizer Inc.) Carbamazepine XR (Tegretol-XR) Novartis Pharmaceuticals Corp., East Hanover, NJ)	Start at 100 mg by mouth nightly; add 100 mg every 3 days, titrating with blood levels; requires serial blood tests (drug level, liver function tests, and complete blood count) For pain, the general dose is 200 to 400 mg by mouth twice daily; maximum dose is 1200 mg per day; comes in 100-, 200-, 400-mg tablets)	Common reactions Dizziness, drowsiness, unsteadiness, incoordination, nausea/vomiting, blurred vision, nystagmus, allergic rash, confusion, elevated liver transaminases, hyponatremia, ataxia Serious reactions Hypersensitivity reaction, seizures, arrhythmias, syncope, aplastic anemia, agranulocytosis, thrombocytopenia, leukopenia, pancytopenia, hepatitis, cholestatic jaundice, hyponatremia, water intoxication, porphyria, Steven's-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, pancreatitis

(continued on next page)

TABLE 2. Continued

Medication Category Medication	Dosage	Side Effects
Topiramate (Topamax) Ortho Pharmaceutical Corp., Raritan, NJ	Start at 25 mg daily to twice daily; if symptoms persist, 50 mg by mouth twice daily for 1 week; if symptoms persist, 75 mg by mouth twice daily for 1 week; if symptoms persist, 100 mg by mouth twice daily; maintain at doses above in which symptoms are controlled	Common reactions asthenia, fatigue, paresthesia, tremor, ataxia, confusion, difficulty with concentration or attention, dizziness, breast pain, dysmenorrhea, diplopia, myopia, acute and secondary angle closure glaucoma, nystagmus, memory problems, nervousness, psychomotor retardation, somnolence, nausea, speech or language problems
Other medications that have been used for vulvodinia Tramadol (Ultram) (Ortho Pharmaceutical Corp.)	In the elderly and chronically ill, or those with renal or hepatic dysfunction, start at lower dose and titrate more slowly This is a synthetic 4-phenylpiperidine analogue of codeine; studies have shown that it is effective for long-term pain management in the elderly population 50 to 100 mg by mouth every 4 to 6 hours; start at 25 mg by mouth in the morning then increase by 25 mg per day every 3 days to 25 mg 4 times a day, then increase by 50 mg per day every 3 days to 50 mg 4 times a day, then maintenance Do not stop suddenly Maximum does is 200 mg per day in the elderly population; up to 400 mg per day may be used in the general population	Serious reactions Hyperthermia, oligohidrosis, anemia (rare), leukopenia (infrequent), dyspnea (rare), hepatic failure, hepatitis, pancreatitis, renal calculi, renal tubular acidosis, hyperchloremic, nonanion gap metabolic acidosis Common reactions Dizziness, nausea, constipation, headache, somnolence, vomiting, pruritus, nervousness, confusion, euphoria, tremor, spasticity, emotional lability, vasodilation, visual disturbances, urinary retention, incoordination, anorexia, rash Serious reactions Seizures, respiratory depression, anaphylaxis, angioedema, bronchospasm, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypotension, orthostatic serotonin syndrome, hallucinations, suicidal ideation, dependency

*With all of the antidepressants discussed, adequate time for a treatment trial must be given before abandoning them as long as the side effects are tolerable. (Reprinted with permission from Haefliger HK, Collins ME, Davis GD, et al. The vulvodinia guideline. *Journal of Lower Genital Tract Disease*. 2005;9:40-51.)

appropriate contraception should be used for patients of reproductive age if they are sexually active. It is important to remember that these medicines will add to the effects of alcohol and other central nervous system depressants. Patients should avoid more than one drink of alcohol daily while on this medication.

Other antidepressants have been used for pain control. Many providers have prescribed selective serotonin reuptake inhibitors (SSRIs) for women with vulvodynia, but in general, SSRIs have not proven effective for pain relief for a majority of women. However, a newer class of medications called selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) have been effective in treating vulvodynia. These include venlafaxine, Effexor XR (Wyeth Pharmaceuticals, Madison, NJ), and duloxetine, Cymbalta (Eli Lilly, Inc., Indianapolis, IN).

Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethyl-venlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic cholinergic, H₁-histaminergic, or (alpha)₁-adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. It is started at 37.5 mg daily and increased to 75 mg daily, if needed. With all of the antidepressants discussed, adequate time for a treatment trial must be given before abandoning them, as long as the side effects are tolerable. Often, full pain relief response is not seen until 4 or more weeks of antidepressant use.

Cymbalta (Eli Lilly, Inc., Indianapolis, IN) is a newer medication that is early in its use for pain control. It is U.S. Food and Drug Agency (FDA)-approved for diabetic peripheral neuropathic pain as well as major depression. For pain control, it is started at 30 mg by mouth daily and gradually increased to 60 mg per day in a single

dose. For depression, it is started at 30 mg daily by mouth and gradually increased to 30 mg twice a day if needed. Reported side effects include nausea, dizziness, somnolence, and fatigue. When discontinuing this medication, gradual reduction in dosage is recommended.

ANTICONVULSANTS

Gabapentin (Neurontin) and carbamazepine (Tegretol) have been used to treat chronic pain conditions, including vulvodynia (Table 2). Gabapentin comes in 100-mg, 300-mg, 400-mg, 600-mg, and 800-mg tablet sizes. Generally, it is started at 300 mg orally per day × 3 days, then 300 mg orally twice a day × 3 days, and then 300 mg orally 3 times per day. It can gradually be increased to 3600 mg orally total daily. Ideally, gabapentin is given in a 3-times-a-day dose, but if the patient is unable to comply with that, it can be given in a twice-a-day dose. No more than 1200 mg of gabapentin should be given in a single dose. Gabapentin tends to have fewer side effects than the tricyclic antidepressants. The adverse effects of gabapentin include somnolence and dizziness and, less commonly, gastrointestinal symptoms and mild peripheral edema. Monitoring and dosage adjustment are required for these side effects, but usually the drug does not need to be discontinued. Gabapentin can cause or increase gait and balance problems in older patients, and may have an effect on cognitive impairment. For patients with renal insufficiency, we recommend a careful dose adjustment. It may take 3 to 8 weeks for gabapentin to become effective for pain control; like with antidepressants, it takes time to work and for patients to develop a tolerance to side effects from the drug. Topiramate, Topamax (Ortho Pharmaceutical Corporation, Raritan, NJ) and oxcarbazepine, Trileptal (Novartis Pharmaceutical Corp., Easthanover, NJ), also anticonvulsants, may also be used for treating vulvodynia instead of carbamazepine.

BIOFEEDBACK AND PHYSICAL THERAPY

Biofeedback and physical therapy are currently used in the treatment of vulvodynia, both for the patient with localized pain as well as the patient with generalized pain. Biofeedback can help patients devise strategies for confronting and reducing pain, especially if vaginismus is also present. This is a common finding in patients with vestibulodynia. Patients with vestibular pain in general have increased resting tone and decreased contraction tone of the pelvic floor muscles. With the aid of an electronic measurement and amplification system or biofeedback machine, an individual can view a display of numbers on a meter, or colored lights to assess nerve and muscle tension. In this way, it is possible to develop voluntary control over those biologic systems involved in pain, discomfort, and disease. The time required for physical therapy and biofeedback as well as the frequencies of visits will vary with each person. Success rates in the 60% to 80% range have been reported.

In our experience, physical therapists with experience in vulvodynia have often been helpful to our patients. Through a thorough evaluation and assessment of muscle tone, posture, mobility, and muscle strength, specific exercises can be prescribed, often with good results. A thorough musculoskeletal evaluation will determine whether some of the pain of vulvodynia is a result of pain in other areas of the body such as the back and hips. When assessing women with vulvodynia from a physical perspective, practitioners many times find abnormally high muscle tone or spasm, poor contraction/relaxation cycles, and instability within the muscular structure of the pelvic floor. Hartmann and Nelson retrospectively studied a group of women with chronic vulvar pain (15 with vulvodynia) who had undergone physical therapy care.²⁴ Of those treated by a physical therapist, 71% showed a greater than 50% improvement in overall symptom reduction, whereas 62% reported an improvement in sexual functioning and

50% reported an increase in quality-of-life issues. Bergeron and colleagues retrospective study also questioned women (n = 35) who had undergone physical therapy care and found that 71% of those treated experienced complete, great, or moderate improvement as a result of the care received.²⁵ They also showed an increase in intercourse frequency as well as a decrease in report of pain with intercourse and with gynecologic examination. In this study, physical therapy treatment included internal (vaginal and rectal) and external soft tissue mobilization and myofascial release, trigger-point pressure, visceral, urogenital and joint manipulation, electrical stimulation, therapeutic exercises, active pelvic floor retraining, biofeedback, bladder and bowel retraining, instruction in dietary revisions, therapeutic ultrasound, and home vaginal dilation.²⁵ The randomized outcomes study comparing cognitive-behavioral sex therapy/pain management, surface electromyography (sEMG) biofeedback, and vestibulectomy found that those in the biofeedback treatment group reported great improvement (35%) or complete relief (35%) from painful intercourse. These patients were less satisfied with this treatment protocol as compared with other experimental groups, however, perhaps because it involved long-term self-directed treatment at home and tended to be somewhat repetitive.²⁵

INTRALESIONAL INJECTIONS

Generally speaking, topical steroids do not help patients with vulvodynia, although occasionally, a trigger point injection may be beneficial. Trigger-point steroid and bupivacaine injections have been successful for some patients with localized vulvodynia. It is recommended that not over 40 mg triamcinolone acetonide be injected monthly. To administer this treatment, we suggest combining the steroid with bupivacaine (large-area use 0.25% bupivacaine; small-area use 0.5% bupivacaine), drawing the triamcinolone acetonide into the syringe before the bupivacaine to prevent contamination of the triamcinolone. Inject the combined

drugs into a specific area or use them as a pudendal block. Generally, patients do not tolerate more than 3 or 4 injections. Another regimen has been reported that uses submucosal methylprednisolone and lidocaine.

INTERFERON THERAPY

Interferon-alpha, a naturally occurring protein produced by leukocytes, improves the immune system, decreases inflammation, and inhibits mast cells. A study of 214 patients treated with a series of 12 intravestibular injections of 1.5 million units of interferon-alpha showed an overall 42% success rate. Patients were more likely to have success if they had secondary vulvar vestibulitis for less than 2 years. Very few patients with primary vulvar vestibulitis were improved.²⁶

LOW OXALATE DIET WITH CALCIUM CITRATE SUPPLEMENTATION

Oxalates are found in foods such as spinach, beets, wheat bran, peanuts, chocolate, and tea. Oxalate appears in the urine from eating these foods, but also by degradation

of microbes in the intestines, intestinal permeability, endogenous (internal) synthesis within the body by the liver and other tissues, and the kidneys' handling of oxalate. Although controversial, the use of oral calcium citrate along with a low oxalate diet may help some women. Because oxalate is an irritating substance, vulvar burning may be associated with elevated levels of oxalates in the urine.^{27,28} Hyperoxaluria has been treated with calcium citrate, which has a chemical structure similar to oxalate and competes with it in the tissues. The significance of oxalates to vestibulodynia has been questioned.²⁹

Surgical Treatment of Vulvodynia

VESTIBULECTOMY

The most important criterion for surgical success in treating vulvodynia is identifying the proper surgical candidate. Before vestibulectomy, it is important to evaluate the

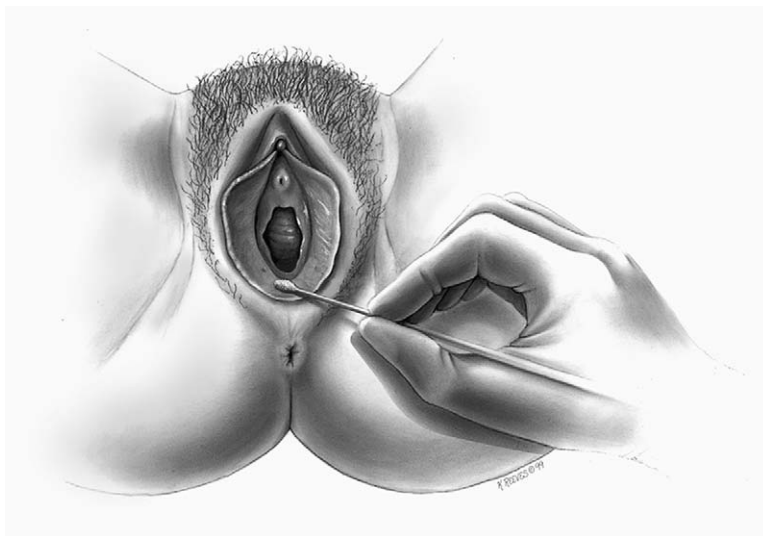


FIGURE 2. Diagnosing vestibulodynia: a cotton swab is used to test the vestibule for pain at 2:00, 4:00, 6:00, 8:00, and 10:00 positions, and to rate pain as mild, moderate, or severe. (Reprinted with permission from Haefner HK. Critique of new gynecologic surgical procedures: surgery for vulvar vestibulitis. *Clin Obstet Gynecol.* 2000;43:689–700.)

patient for vaginismus, which may occur in 50% to 60% of patients with vestibulodynia. Vaginismus, if present, should be treated before surgery, because surgery is generally less successful in this subgroup of patients. Treatment of vaginismus includes using vaginal dilators and different types of physical therapy. Sexual counseling may aid a patient's recovery by reducing vaginismus and improving poor sexual arousal, which can develop after long-term dyspareunia.

SURGICAL EXCISION

Surgical excision is generally thought of as the last treatment option for patients with vestibulodynia, but this opinion varies among specialists. Excision of the vulvar vestibule has had a variety of success rates.^{30,31} It is our opinion that although vestibulectomy has a high success rate in some studies, this surgery should be reserved for women with longstanding and severe localized vestibular pain when all other managements have not brought adequate pain relief, because many women find adequate relief with other less invasive treatments.

Surgical Techniques

Various surgical techniques are used for the treatment of vestibulodynia unresponsive to all other therapies.³⁰ We categorize surgical correction of introital dyspareunia of vestibulodynia into the 3 groups: 1) local excision, 2) total vestibulectomy, and 3) perineoplasty. Vestibuloplasty, which involves denervation of the vestibule using incision, undercutting, and closure of the mucosa without excision of the painful tissue or increasing the caliber of the introitus, has been found ineffective, most likely because either removal of the painful tissue or the generation of increased introital dimensions is required for relief of dyspareunia caused by vestibulodynia.³²

LOCAL EXCISION

This technique requires precise localization of small painful areas at the time of surgery, which are outlined with a marking pen

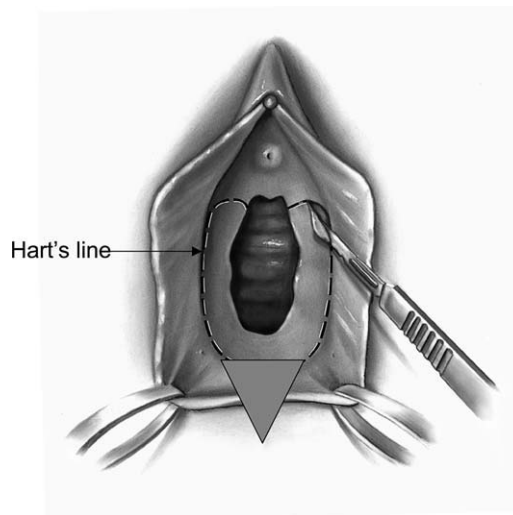


FIGURE 3. Sharp dissection with a 15-blade knife. This patient did not have periurethral pain so that area is not included in excision. Some patients will require excision of tissues adjacent to urethra. Care should be taken to avoid injury to the urethra as well as alteration of the urethral angle. At times, a portion of the perineum is removed (inverted triangle). (Adapted from Haefner HK. Critique of new gynecologic surgical procedures: surgery for vulvar vestibulitis. *Clin Obstet Gynecol.* 2000;43:689–700. Reprinted with permission.)

before administering anesthesia to the area. The tissue is then excised and closed in an elliptical fashion. It may be necessary to undermine the margins of contiguous tissue for sufficient closure.³³

TOTAL VESTIBULECTOMY

Vestibulectomy is most often performed under spinal or general anesthesia. The patient should undergo testing with a cotton swab before anesthesia while in the operating room to outline the areas of pain (Fig. 2). Often pain may be in the majority of the vestibule. The incision may need to approach the periurethral area and extend from the opening of Skene's ducts to the perineum (Fig. 3).³³ Excision of the periurethral area should occur with caution not to compromise the angle of the urethra (Fig. 4). The

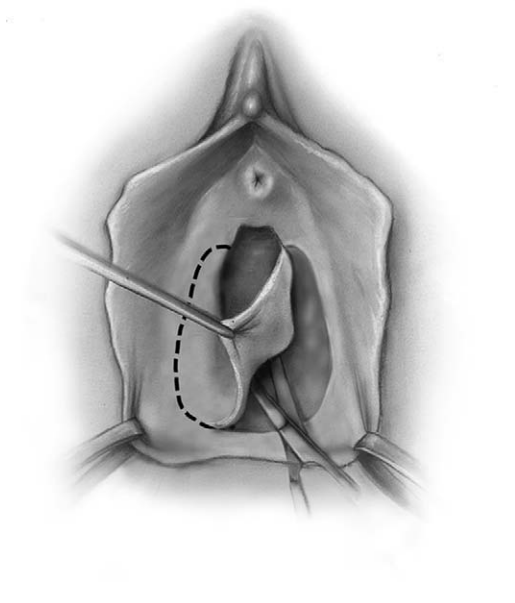


FIGURE 4. The tissue is removed (2–5 mm depth). (Reprinted with permission from Haefner HK. Critique of new gynecologic surgical procedures: surgery for vulvar vestibulitis. *Clin Obstet Gynecol.* 2000;43:689–700.)

incision is carried down laterally along Hart's line to the superior portion of the perineum. The incision should extend above the hymeneal ring. The intervening skin, mucous membrane, hymen, and adjacent tissue are removed. The minor vestibular glands are excised and Bartholin's ducts are traversed in the dissection (however, it is rare to see a cyst develop after vestibulectomy). The vagina is undermined, mobilized, and brought down to cover the defect (Fig. 5). The defect should be closed in 2 layers using absorbable 3-0 and 4-0 sutures (Fig. 6).³³

PERINEOPLASTY

In the perineoplasty procedure, the vestibulectomy is performed and includes removal of tissue on the perineum, usually terminating just above the anal orifice. Again, the vaginal mucosa is undermined and advanced to cover the defect.³³

Complications in vestibulectomies include blood loss, wound infection or separation,

granulation tissue, chronic fissuring, Bartholin's duct cyst formation, decrease in lubrication, and continued pain.³³

SURGERY FOR PUDENDAL NERVE ENTRAPMENT

When the pudendal nerve is entrapped, and the patient has failed guided nerve blocks, tricyclic antidepressants, anticonvulsants, and physical therapy, surgical treatment is an option. Because there are a variety of surgical approaches used for nerve entrapment, we recommend finding a surgeon with particular expertise in this procedure when surgery is indicated.

Psychologic Effects of Vulvodynia

The psychologic impact of chronic pain is well documented. Feelings of hopelessness,

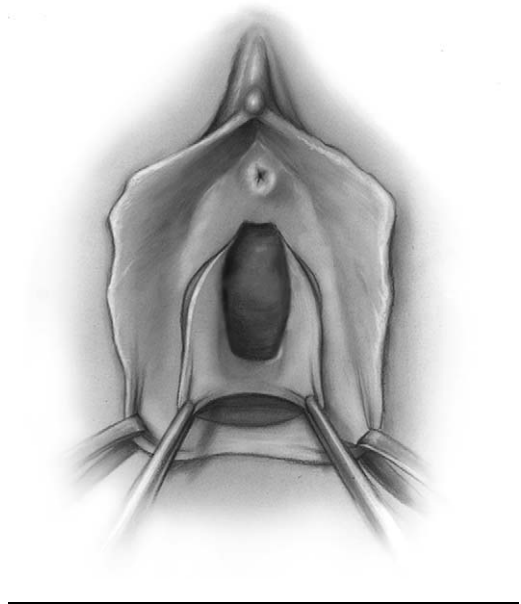


FIGURE 5. After the vestibular tissue and hymen are removed, vaginal tissue is dissected to cover the excision. It is important to have sufficient tissue to cover the area to avoid straining vaginal tissue. (Reprinted with permission from Haefner HK. Critique of new gynecologic surgical procedures: surgery for vulvar vestibulitis. *Clin Obstet Gynecol.* 2000;43:689–700.)

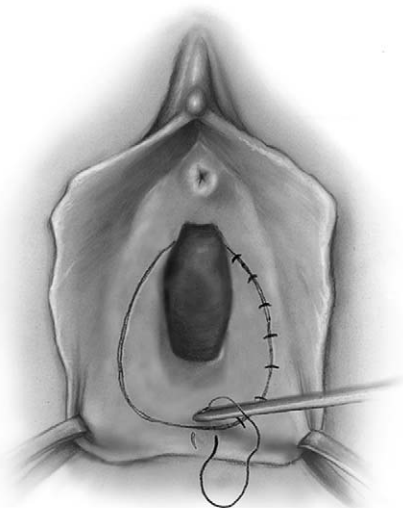


FIGURE 6. A running unlocked stitch with absorbable suture is used for closure. (Reprinted with permission from Haefner HK. Critique of new gynecologic surgical procedures: surgery for vulvar vestibulitis. *Clin Obstet Gynecol.* 2000;43:689–700.)

depression, and anxiety are common. These feelings are compounded in sexual pain disorders such as provoked vestibulodynia.³⁰ Unfortunately, even when vulvar pain resolves, the psychologic and sexual dysfunction often persists.³⁰ Therefore, in addition to treating the biologic processes of vulvar pain, it is imperative to concurrently treat the associated psychosexual and relationship dysfunction. At our institutions, the authors have found that it is essential to have a multidisciplinary team involving physicians, nurses, sex therapists, psychologists, and couple therapists to adequately treat the biologic, psychologic, and social aspects of vulvar pain.

Summary

The treatment of vulvodynia is confounded by the fact that the cause is unknown in a majority of cases. Additionally, whereas we tend to separate generalized from localized

vulvodynia, the characteristics of women with generalized vulvodynia are similar to those with localized pain. The 2 disorders may exhibit 2 presentations on a continuum of severity seen in generalized versus localized vulvodynia rather than 2 distinct entities.

Acknowledgment

The authors thank Julie Bedore for her editorial assistance.

References

1. Jones KD, Lehr ST. Vulvodynia: diagnostic techniques and treatment modalities. *Nurse Pract.* 1994;19:34, 37–46.
2. Goetsch MF. Vulvar vestibulitis: prevalence and historic features in a general gynecologic practice population. *Am J Obstet Gynecol.* 1991;164:1609–1614; discussion 1614–1616.
3. Denbow ML, Byrne MA. Prevalence, causes and outcome of vulvar pain in a genitourinary medicine clinic population. *Int J STD AIDS.* 1998;9:88–91.
4. Danielsson I, Sjöberg I, Stenlund H, et al. Prevalence and incidence of prolonged and severe dyspareunia in women: results from a population study. *Scand J Public Health.* 2003;31:113–118.
5. Boardman LA, Peipert JF. Vulvar vestibulitis: is it a defined and treatable entity? *Clin Obstet Gynecol.* 1999;42:945–956.
6. 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.
7. *Resident Population Estimates of the United States by Age and Sex, April 1, 1990–July 1, 1999.* Washington, DC: Population Estimates Program, Population Division, US Census Bureau; 2000.
8. Reed BD, Crawford S, Couper M, et al. Pain at the vulvar vestibule: a web-based survey. *Journal of Lower Genital Tract Disease.* 2004;8:48–57.
9. Edwards L. New concepts in vulvodynia. *Am J Obstet Gynecol.* 2003;189(Suppl):S24–S30.
10. Prayson RA, Stoler MH, Hart WR. Vulvar vestibulitis. A histopathologic study of 36 cases, including human papillomavirus in situ hybridization analysis. *Am J Surg Pathol.* 1995;19:154–160.
11. Bergeron C, Moyal-Barracco M, Pelisse M, et al. Vulvar vestibulitis. Lack of evidence for a human papilloma virus etiology. *J Reprod Med.* 1994;39:936–938.
12. Chadha S, Gianotten WL, Drogendijk AC, et al. Histopathologic features of vulvar vestibulitis. *Int J Gynecol Pathol.* 1998;17:7–11.
13. Morin C, Bouchard C, Brisson J, et al. Human papillomaviruses and vulvar vestibulitis. *Obstet Gynecol.* 2000;95:683–687.
14. Friedman M, Siegler E, Kerner H. *Clinical and histopathological changes of the vulvar vestibulum in healthy subjects and in patients with vulvar vestibulitis.* XII International Congress of the International Society for the Study of Vulvar Disease, Quebec City, Canada 1993, Abstracts p. 21.
15. 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.
16. Pukall CF, Binik YM, Khalife S, et al. Vestibular tactile and pain thresholds in women with vulvar vestibulitis syndrome. *Pain.* 2002;96:163–175.
17. Gordon AS, Panahian-Jand M, McComb F, et al. Characteristics of women with vulvar pain disorders: responses to a Web-based survey. *J Sex Marital Ther.* 2003;29(Suppl 1):45–58.
18. Eide PK. Wind-up and the NMDA receptor complex from a clinical perspective. *Eur J Pain.* 2000;4:5–15.

19. Eva LJ, MacLean AB, Reid WM, et al. Estrogen receptor expression in vulvar vestibulitis syndrome. *Am J Obstet Gynecol.* 2003;189:458–461.
20. Peckham BM, Maki DG, Patterson JJ, et al. Focal vulvitis: a characteristic syndrome and cause of dyspareunia. Features, natural history, and management. *Am J Obstet Gynecol.* 1986;154:855–864.
21. Zolnoun DA, Hartmann KE, Steege JF. Overnight 5% lidocaine ointment for treatment of vulvar vestibulitis. *Obstet Gynecol.* 2003;102:84–87.
22. Yamashita S, Sato S, Kakiuchi Y, et al. Lidocaine toxicity during frequent viscous lidocaine use for painful tongue ulcer. *J Pain Symptom Manage.* 2002;24:543–545.
23. Munday PE. Response to treatment in dysaesthetic vulvodynia. *J Obstet Gynaecol.* 2001;6:610–613.
24. Hartmann EH, Nelson C. The perceived effectiveness of physical therapy treatment on women complaining of chronic vulvar pain and diagnosed with either vulvar vestibulitis syndrome or dysaesthetic vulvodynia. *J Sect Womens Health.* 2001;25:13–18.
25. 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.
26. Goldstein A, Davies-Treene L, Hurtado S, et al. *Interferon alpha therapy for vulvar vestibulitis syndrome: a large retrospective trial.* Presented at the International Society for the Study of Women's Sexual Health Conference, Vancouver, BC, October 2002.
27. Solomons CC, Melmed MH, Heitler SM. Calcium citrate for vulvar vestibulitis. A case report. *J Reprod Med.* 1991;36:879–882.
28. Yount JJ, Solomons CC, Willems JJ, et al. Effective nonsurgical treatments for vulvar pain. *Women's Health Digest.* 1997;3:88–93.
29. Baggish MS, Sze EH, Johnson R. Urinary oxalate excretion and its role in vulvar pain syndrome. *Am J Obstet Gynecol.* 1997;177:507–511.
30. Haefner HK. Critique of new gynecologic surgical procedures: surgery for vulvar vestibulitis. *Clin Obstet Gynecol.* 2000;43:689–700.
31. Bornstein J, Zarfati D, Goldik Z, et al. Vulvar vestibulitis: physical or psychosexual problem? *Obstet Gynecol.* 1999;93:876–880.
32. Bornstein J, Zarfati D, Goldik Z, et al. Perineoplasty compared with vestibuloplasty for severe vulvar vestibulitis. *Br J Obstet Gynaecol.* 1995;102:652–655.
33. Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. *Journal of Lower Genital Tract Disease.* 2005;9:40–51.