Vulvodynia: Definition, Prevalence, Impact, and Pathophysiological Factors

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ABSTRACT

Introduction: Vulvodynia constitutes a highly prevalent form of chronic genital pain in women, and current information regarding its definition, prevalence, impact, and pathophysiologic factors involved is needed.

Aim: To update the scientific evidence published in 2010 from the Third International Consultation of Sexual Medicine pertaining to the definition, prevalence, impact, and pathophysiologic factors of women’s sexual pain.

Methods: An expert committee, as part of the Fourth International Consultation of Sexual Medicine, comprised of researchers and clinicians from biological and social science disciplines, reviewed the scientific evidence on the definition, prevalence, impact, and pathophysiologic factors related to chronic genital pain.

Main Outcome Measures: A review of the definition, prevalence, impact, and pathophysiologic factors involved in vulvodynia.

Results: Vulvodynia is a prevalent and highly impactful genital pain condition. Numerous factors have been implicated in its development and maintenance.

Conclusion: What is becoming increasingly apparent is that it likely represents the end point of different factors that can differ from patient to patient. Longitudinal research is needed to shed light on risk factors involved in the expression of vulvodynia, as well as in potential subgroups of affected patients, in order to develop an empirically supported treatment algorithm.


Key Words: Vulvodynia; Sexual Pain; Vestibulodynia; Prevalence; Definition; Pathophysiologic Factors; Dyspareunia

DEFINITION

Reports of sexual pain are highly prevalent in postmenarchal women, with pain sites including the vulvar, vaginal, cervical, and deep pelvic areas. Vulvodynia, or chronic vulvar pain, is a specific pain disorder that appears to have been reported by women for centuries. However, accurate descriptions of vulvar pain have only recently been defined. The most recent nomenclature (http://www.isswwh.org/news/190-2015-consensus-terminology-and-classification-of-persistent-vulvar-pain) was developed in April 2015 at a vulvar pain and vulvodynia consensus conference that was sponsored by the International Society for the Study of Vulvovaginal Disease, the International Society for the Study of Women’s Sexual Health, and the International Pelvic Pain Society. The new nomenclature (referred to as the “2015 classification”) proposes two main categories of chronic vulvar pain: vulvar pain related to a specific disorder (eg, inflammatory, neoplastic, traumatic) and vulvodynia, which is idiopathic vulvar pain of at least 3 months’ duration. The 2015 classification also uses a pain-based system to characterize vulvodynia based on pain location (eg, localized, generalized, mixed), situations that elicit the pain (ie, upon contact, spontaneous, or mixed), temporal pattern (eg, intermittent or constant), and onset (ie, primary or secondary). The 2015 classification adds a list of potential associated factors for
vulvodynia (eg, musculoskeletal, neuro-proliferation, associated comorbidities, psychosocial factors) that act to acknowledge that vulvodynia is likely not one disease but a constellation of symptoms of several (sometimes overlapping) disease processes.

The importance of using a pain-based system to characterize vulvodynia is evident in research. For example, information regarding pain location and eliciting situations has led to the appreciation of different subtypes of vulvodynia. For example, provoked vestibulodynia (PVD; formerly called vulvar vestibulitis syndrome, focal vestibulitis, vestibular adenitis, and focal vestibulitis vulvae) is characterized as localized provoked pain at the vaginal vestibule, whereas generalized vulvodynia (formerly termed essential or dysesthetic vulvodynia and burning vulva syndrome) is characterized by unprovoked, diffuse vulvar pain affecting the entire vulvar area. At this point, it is not known whether provoked and unprovoked vulvar pain have overlapping or distinct pathophysiologies; however, there is agreement in the literature that vulvodynia can be caused by different factors. In addition, studies on PVD have indicated that pain onset might be an important factor to consider. The issue of whether the pain has been present since the patient’s first episode of vaginal penetration (ie, lifelong or primary PVD, referred to as PVD1) or after a period of pain-free activities (ie, acquired or secondary PVD, referred to as PVD2) can influence pain sensitivity (eg, Sutton et al) and treatment outcome (eg, Heddini et al; for a review of distinct and overlapping factors in PVD1 and PVD2, see Pukall et al).

In this article, genital pain refers to the report of any kind of genital or abdominal pain (eg, from vulvodynia, chronic pelvic pain, or undiagnosed conditions); vulvodynia refers to the general condition of idiopathic, chronic vulvar pain; provoked vestibulodynia refers to provoked vestibular pain; and dyspareunia describes a common symptom of many genital pain conditions (including, but not limited to, vulvodynia; eg, chronic pelvic pain and pain during penetrative sexual activities).

PREVALENCE

Prevalence studies of vulvodynia have indicated that it is prevalent, with lifetime estimates ranging from 10% to 28% in reproductive-aged women in the general population. A recently published study by Harlow et al indicated that 8% of women 18 to 40 years old reported a history of vulvar burning or pain upon contact that persisted longer than 3 months and that limited or prevented intercourse. These researchers also replicated previous work demonstrating that women of Hispanic origin were more likely to develop vulvar pain symptoms compared with white women.

IMPACT

A recent non-probability survey indicated the costs of vulvodynia in the United States to be 31 to 72 billion dollars annually. This staggering amount includes direct health care costs (eg, insurance payments and out-of-pocket expenses), direct non-health care costs (eg, transportation), and indirect costs (financial loss owing to medical leave from work and employer payments to patients for medically related work loss). However, this figure does not take into account the very significant psychological burden of vulvodynia.

PATHOPHYSIOLOGIC FACTORS

Numerous factors have been suggested to play a role in the initiation and/or maintenance of vulvodynia (Table 1). These factors are interdependent and likely act within a cyclical model; however, the direction of causality is not clear given the lack of prospective, longitudinal studies.

Vulvar (Neuro-Proliferative) Factors

Although hypersensitivity of the vulvar vestibule is one of the defining characteristics of vulvodynia—in particular PVD—the underlying mechanism of this allodynia was not elucidated until 1998. In that year, Weström and Willén and Bohm-Starke et al used immunohistochemical (IHC) staining to visualize an increase in the density of nerve endings in the vestibular endoderm of women with PVD who had undergone vulvNSectomy compared with controls. Bohm-Starke et al followed up their original research with an additional study that identified these increased nerve endings as nociceptors. They postulated that the neuro-proliferation of these nociceptors could explain the perceived allodynia. Other research teams have since confirmed the findings of these initial studies (eg, Tympanidis et al, Halperin et al, Leclair et al, Goetsch et al). Increased innervation has implications for increased sensitivity, and the phenomenon of increased sensitivity has been documented in women with PVD. For example, a quantitative sensory testing study conducted by Pukall et al found that women with PVD were more sensitive to punctate tactile and pain stimuli applied to four vestibular sites compared with control women. A similar pattern of findings in response to various forms of stimulation (eg, thermal and pressure pain) has been reported by this and other groups (eg, Bohm-Starke et al, Gieseker et al, Pukall et al, Sutton et al, Smith et al, Heddini et al). Interestingly, the heightened sensitivity does not appear to be limited to static stimuli or the vestibule (eg, forearm). Research conducted by Heddini et al implicated

Table 1. Pathophysiologic Factors

<table>
<thead>
<tr>
<th>Vulvar (neuro-proliferative)</th>
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<tr>
<td>Comorbid conditions</td>
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<td>Central nervous system</td>
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<td>Genetics</td>
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<td>Myofascial and muscular</td>
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<td>Hormonal</td>
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<td>Embryologic and congenital</td>
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<td>Inflammatory</td>
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the serotonin receptor gene (5HT-2A) polymorphism in this heightened non-vulvar sensitivity, thereby implicating the serotonergic system as playing a role in the pathophysiology of PVD. This pattern of results coincides with more frequent reports of painful conditions (eg, Pukall et al, Heddini et al) and comorbidities (eg, irritable bowel syndrome) in women with vs without PVD.

Indeed, numerous studies have documented increased comorbid pain conditions in women with vulvodynia, in particular, interstitial cystitis, orofacial pain, fibromyalgia, and irritable bowel syndrome. A recent study indicated a low probability of women with vulvodynia endorsing no comorbidities or a single comorbidity; rather, analyses demonstrated that at least two comorbid conditions were likely to be endorsed by at least 50% of affected women, with fibromyalgia and irritable bowel syndrome being the most common comorbidities. The results of increased non-genital sensitivity, increased pain reports, and increased comorbidities suggest that the central nervous system is involved in the expression of PVD (for a review, see Pukall and Cahill).

**Central Nervous System Involvement in Vulvodynia**

Functional and structural brain imaging techniques are popular methods with which to study neural correlates of pain; however, only five studies published to date have examined neural correlates of pain in women with vulvodynia. Pukall et al were the first to examine neural correlates of touch and pain in women with and without vulvodynia using functional magnetic resonance imaging. The results of that study indicated that women with PVD exhibited evidence of augmented neural activity in response to painful vestibular stimulation in areas involved in pain modulation, such as the somatosensory, insular, and anterior cingulate regions—areas that are commonly activated in patients with other pain conditions. In addition, non-painful pressure led to significant activation levels in insular, frontal, and somatosensory regions in women with PVD. The results of that study suggest that women with PVD have an increased perception of non-painful and painful stimulation to the vestibule. Augmented sensory processing also has been reported in response to slightly intense thumb pressure in women with vulvodynia (some of whom had PVD) compared with control women, and in women with vulvodynia and fibromyalgia in response to painful thumb pressure compared with control women. Other imaging studies have reported alterations in the intrinsic connectivity in regions comprising sensorimotor, salience, and default mode resting-state networks in women with vulvodynia compared with healthy control women and women with irritable bowel syndrome. Greater gray matter density in several brain areas (eg, para-hippocampus, hippocampus, and basal ganglia) in women with PVD compared with the control group, and heightened activation in areas important for pain processing in women with PVD1 compared with those with PVD2. Structurally, gray matter density also differed in women with PVD1 vs PVD2, with women with PVD1 showing significant decreases in gray matter throughout pain processing areas compared with women with PVD2.

**Genetic Involvement**

Several studies have suggested that some women might have a genetic predisposition to the development of PVD (eg, Babula et al, Lev-Sagie et al, Foster et al, Gerber et al, Goldstein et al) and that the contribution of genetic factors might be greater in women with PVD1 vs PVD2 (eg, Babular et al). Genetic studies have focused on three possible (but potentially overlapping) mechanisms: genetic polymorphisms that increase the risk of candidiasis or other infections (eg, Lev-Sagie et al), genetic changes that permit prolonged or exaggerated inflammation (eg, Gerber et al), and increased susceptibility to hormonal changes caused by oral contraceptive pills.

**Myofascial and Muscular Factors**

There is a wide range of etiologies for pelvic floor hypertonic dysfunction and overactivity, and the events implicated in the development of pain in any given case might not be easy to identify. Changes in the physiology and biomechanics of the pelvis can result from such singular events as acute vaginal or urinary infection, trauma, vaginal childbirth, and abdominal or pelvic surgery and from insidious factors such as prolonged sitting, poor posture, or muscle bracing in reaction to fear, pain, or altered gait patterns. These changes can cause lasting imbalances and functional modifications in the pelvic floor musculature and neural tissue. Causes of pelvic floor disorders include dysfunctional voiding in adulthood and childhood, neuropathic pain, past or current abuse (psychological, physical, and/or sexual), and inflammatory conditions such as endometriosis, interstitial cystitis, or inflammatory bowel disorders. In inflammatory conditions, viscerosomatic reflexes have been postulated to activate nociceptive and visceral afferent neurons and contribute to myospasticity and palpable tissue texture changes. The result is somatic dysfunction and potential neuropathic upregulation. Pelvic scarring and adhesions are often coincident findings in overactive and shortened pelvic floor muscles. Such biomechanical abnormalities as foraminal narrowing, scarring of a nerve canal, myofascial trigger points, and connective tissue restrictions at the introitus or around nerves can leave the pelvic floor muscles dysfunctional.

The discomfort inherent in chronic vulvar pain conditions (eg, PVD) also can be associated with pelvic floor muscle overactivity. Prolonged holding patterns can result in decreased tissue perfusion, muscle overactivity, shortening of sarcomeres and connective tissues, altered neurodynamics, and the development of myofascial trigger points (ie, a hyperirritable spot in skeletal muscle associated with a palpable nodule in a taut band). When pressure is applied to a myofascial trigger point, the result is referred, localized, or radiating pain and/or intense tenderness. With chronic symptoms, altered neurodynamics and neural tension can result in tissue hypoxia and can manifest as
sensations of itching, burning, tingling, cold, or sharp and shooting pain. For example, hypertonicity (overactivity) of the muscles that insert at the posterior vestibule—the puboccygeus, puborectalis, and superficial transverse perineum—can lead to allodynia (as seen in PVD) in the posterior vestibule. Hypertonicity of deeper muscles (eg, ileococcygeus and obturator internus) can lead to vaginal or deep thrusting dyspareunia. In addition, overactivity of the bulbocavernosus and ischiocavernosus has been associated with clitorodynia.

Hormonal Factors
It has been recognized for decades that the tissues of the vulva and vagina are responsive to and dependent on sex steroids (hormones) for proper health and function, and that a deficiency in circulating estrogen leads to anatomic and physiologic changes in the vagina. There are many causes of decreased sex steroids, natural and iatrogenic, that can lead to the physiologic changes and symptoms mentioned earlier. By far the most common cause of decreased sex steroids in women is menopause. Other natural causes include anovulation secondary to lactation or owing to anorexia, hypothalamic amenorrhea secondary to biologic stressors such as excessive physical activity or physiologic stress, and hyperprolactinemia. Iatrogenic causes of decreased circulating sex steroids include surgical factors, such as oophorectomy and hysterectomy (without oophorectomy), and commonly prescribed medications, such as combined hormonal contraceptive pills (CHCs; oral contraceptives that contain an estrogen and a progestin), which have been used by 82% of North American women at some time in their lives. CHC use leads to a decrease in serum estradiol and free testosterone by decreasing ovarian production of estrogen and total testosterone and by inducing the liver to produce increased levels of SHBG. In addition, some CHCs contain synthetic progestins that act as testosterone antagonists at the androgen receptor. It has been demonstrated that CHCs induce morphologic changes in the vestibular mucosa, increasing its vulnerability to mechanical strain. Furthermore, CHC use has been associated with decreases in mechanical pain thresholds and with decreases in clitoral size, labial thickness, and introital diameter. In addition, this latter prospective, randomized, pilot study by Battaglia et al demonstrated decreased orgasm, decreased sexual frequency, decreased lubrication, and increased dyspareunia associated with CHCs.

Given their effects on sex steroids, it is perhaps not surprising that studies have associated CHCs with symptoms consistent with PVD. Bazin et al showed, in a case-controlled study, that women who used CHCs before 17 years of age had a relative risk of 11 of developing PVD. In addition, Bouchard et al and Harlow et al confirmed (in case-controlled studies) that early CHC use significantly increases the risk of developing PVD. Greenstein et al reported that the use of CHCs that contain ethinyl estradiol at a dose no higher than 20 μg significantly increases the risk of developing PVD. In addition, Burrows and Goldstein described a case series of 50 consecutive women who developed PVD while on CHCs and who were successfully treated with topical estradiol and testosterone. Goldstein et al identified a polymorphism in the androgen receptor that significantly increased the risk of developing CHC-induced PVD. Conversely, three studies found no association between CHCs and vulvodynia. Studies by Arnold et al and Reed et al showed no association, possibly because of the reliance on self-reported vulvodynia symptoms in these studies (although the study by Reed et al was population-based and prospective in nature). Surprisingly, Foster and Woodruff reported, in an early case-control study, that CHCs actually decreased the risk of vestibulodynia. However, the CHCs used by the women in that study likely had higher doses of ethinyl estradiol and more androgenic progestins than patients in later studies.

Embryologic and Congenital Factors
Vulvodynia has been described in young girls with and without concurrent interstitial cystitis and painful bladder syndrome. One possible explanation of the coexistence of vulvodynia and interstitial cystitis is that the two disorders could represent a congenital disorder of urogenital sinus-derived endothelium. Possible evidence to support this idea is that women with PVD1 have exhibited umbilical hypersensitivity compared with women with PVD2 and non-affected women. Embryologically, the vestibule is derived from the primitive urogenital sinus, which is contiguous with the allantois (which further differentiates to form the urachus and then the umbilicus). Anomalies, such as urachal cysts and urachal diverticulum, represent congenital abnormalities in these tissues. Some cases of PVD1 may be associated with a congenital defect of neuronal hyperplasia in this tissue.

Inflammatory Factors
The methods and approaches used in studying the connection between vulvodynia and inflammation can be categorized as presented in Table 2.

IHC and Histologic Studies
Based on the lack of diagnostic cues of the cardinal signs of inflammation in surgical pathology, the microscopic presence of inflammatory cell infiltrate is equated with “inflammation,” although inflammatory cell infiltrate is a histopathologic surrogate. Vulvodynia research using standard histopathologic and in situ immunopathologic methods comprises a relatively large proportion of vulvodynia publications. Epidemiologically, women with vulvodynia are two to three times more likely to report a history of hives before the onset of their vulvar pain. Researchers have sought to determine whether mast cells, a recognized mediator of cutaneous urticaria, also might be a trigger for small nerve fiber sensitization and mucocutaneous chronic pain development. The earliest study of the connection between mast cells and vulvodynia was published by Pyka et al in 1988. They found an increased inflammatory infiltrate (predominantly lymphocytic), and more mast cells in painful

vestibular regions, in women with vulvodynia vs control women. Chaim et al\textsuperscript{76} reported a significant difference in the surgical specimens of 16 women with PVD compared with control women without pain after colporrhaphy. They suggested a possible inflammatory link between interstitial cystitis and PVD, each of which has been associated with mast cell activation.

These results have been replicated and extended by several research groups; however, it is clear that inflammatory infiltrates in general and mast cell infiltration in particular have not been found consistently increased by all vulvodynia studies (see, eg, Halperin et al\textsuperscript{17}). Thus, most, but not all, studies have reported increases in inflammatory cell infiltrate within painful regions of the vulvar vestibule. In research specifically staining for mast cells, more than half the studies have found an increased mast cell presence in regions of vestibular pain.

Assessment of Proinflammatory Tissue Milieu: Neurokine, Cytokine, and Chemokine Levels

The pathogenesis of neuroinflammation involves neurokines (eg, cacitonin gene-related peptide [CGRP]), a host of proinflammatory cytokines (eg, interleukin [IL]-1\textbeta, tumor necrosis factor [TNF]-\alpha, and IL-6), and proinflammatory chemokines (eg, chemokine receptor-2) associated with pain development.\textsuperscript{27} Hypothetically, regional changes in the biochemical milieu from changes in cytokine, neurokine, chemokine, or prostanoid signaling could alter signal transduction and/or facilitate neural activity within the peripheral preterminal axon.\textsuperscript{78} This process could lead to a lowering of the mechanical, thermal, or chemical threshold in primary nociceptors. There have been mixed results in this sphere of research. In the first cytokine study, Foster and Hasday\textsuperscript{79} found that IL-1\textbeta and TNF-\alpha were elevated in vulvar regions in pain in women with PVD compared with control women. In contrast, Bohm-Starke et al\textsuperscript{80} found no significant difference of cyclooxygenase-2 or inducible nitric oxide synthase women with and without PVD. However, another study by the same research team found elevated neurokine IHC\textsuperscript{\textast} CGRP in biopsy samples of women with vulvodynia compared with controls, suggesting a neuro-inflammatory process.\textsuperscript{15} Eva et al\textsuperscript{81} performed in situ IHC studies of proinflammatory cytokines TNF-\alpha, and IL-1\beta from representative vestibular biopsy samples of 35 PVD cases and 16 pain-free controls. Using formalin-fixed specimens, only an epidermal cytokine signal could be identified, and the investigators reported no difference in TNF-\alpha or IL-1\beta IHC\textsuperscript{\textast} signal in cases and controls. From this IHC analysis, the researchers concluded that vulvodynia was not an inflammatory condition.

Hormonal Studies Connected to Inflammation

Goetsch et al\textsuperscript{82} demonstrated that mechanical pain to light touch was localized to the vestibule in women with hypoestrogenic breast cancer. Although these participants did not fulfill the formal diagnosis of vulvodynia, cotton-swab testing found the vulvar vestibule to be the localized region of hyperalgesia and allodynia similar to that seen in PVD. This observation provided evidence that contradicted the prevailing clinical impression that symptoms of pain and dryness found in “atrophic vaginitis” arose from the hypoestrogenic vagina. In an additional study of menopausal and premenopausal vulvodynia cases by the same group, Leclair et al\textsuperscript{83} found that lymphoid and mast cell inflammatory infiltrates were greater in the menopausal vulvodynia cases compared with premenopausal cases but that neural hyperplasia was less. The results suggest that the hypoestrogenic state might promote location-specific vestibular inflammation and pain.

Studies of Systemic Immune Challenges and Associated Proinflammatory Genetics

Gerber et al\textsuperscript{84} published a series of reports using systemic assays for inflammation by way of stimulated whole blood cultures from vulvodynia cases and controls. The research team hypothesized that systemic proinflammatory hyperresponsiveness, particularly innate immune responsiveness, would be connected to genetic carrier status for specific proinflammatory polymorphisms. They found a pattern of results supporting the idea that a proinflammatory trend might be based on a particular genotypic variable number tandem repeat polymorphism of the IL-1\beta product (IL1RN\textsuperscript{\textast}2), and that this inability to downregulate the proinflammatory cytokine activity might contribute to the pathophysiology of vulvodynia.\textsuperscript{84} Heightened systemic inflammatory response also has been demonstrated by dermatology researchers using a topical cutaneous challenge with yeast in vulvodynia cases compared with controls. After a patch test challenge to a standard series of allergens in addition to select series of other pathogenic antigens, women with vulvodynia were found to be particularly reactive to Candida albicans antigen, particularly at lower dose challenges (0.4%), compared with women with a history of contact or atopic dermatitis.\textsuperscript{85} The researchers hypothesized that the C. albicans antigen might be interacting with the innate immune system, among other possibilities.

Studies of Blood Flow Change (Rubor) as a Sign of Inflammation

In a study of the diagnostic reliability of the Friedrich criteria, Bergeron et al\textsuperscript{86} found that the diagnostic criterion of erythema
demonstrated poor reliability and concluded that erythema was not a useful criterion. This observation raises the question of whether vulvodynia lacks one of the major clinical signs (rubor) of inflammation. However, optics technology has helped recognize localized erythema in vulvodynia and thereby supports an inflammatory pain pathogenesis. Bohm-Starke et al. performed the earliest work using laser Doppler perfusion imaging to map superficial blood flow in the vestibular mucosa of women with and without PVD. Significantly higher levels of perfusion by Doppler flow were found in the posterior region of the vestibular mucosa. Visible erythema did not correlate with that determined by laser Doppler. In addition, cases and controls appeared to show vasoconstriction to a similar degree after regional injection with noradrenalin. In a later study, a novel enhanced visualization technique (Syrus v600; Syrus Scientific, LLC, Gray, ME, USA) used cross-polarized light to detect subsurface mucocutaneous erythema to study women with vulvitis, PVD, lichen sclerosus, and combined lichen sclerosus and PVD. The cross-polarized light system found enhanced blood flow (erythema), often below levels of detection by clinical assessment, in all cases compared with controls. Particularly in the PVD cases, the erythema was found to be relatively diffuse in regions of the vulva, vagina, and cervix, suggesting a “regionalizing” phenomenon exceeding the anatomic bounds of pain manifestation. Increased peripheral blood flow (rubor) was found in the vestibule of vulvodynia-affected cases compared with controls. The phenomenon of erythema, a hallmark of inflammation, was greatest in the vestibule (introitus) of all women and significantly greater in the introitus of vulvodynia-affected women compared with pain-free controls.

Animal Model Development

Two animal models have been developed to induce a vulvodynia-like condition in mice. The two models differ in the specific proinflammatory stimulus, one being based on infection and the other induced by an allergic response. The first animal model for vulvodynia was reported by Farmer et al. Female CD-1 mice were subjected to vaginal C. albicans inoculation or genital submucosal zymosan injection. After the yeast challenge, von Frey testing of a hairless vulvar region was assayed for a “jump” response (interpreted as mechanical allodynia). Non-inoculated mice and hind paw-inoculated mice served as controls. Farmer et al reported the development of prolonged (>32-day) genital mechanical allodynia after multiple (three) rounds of C. albicans genital inoculation but with absence of genital yeast at time of testing. Of interest, no difference in microscopic identification of an inflammatory infiltrate of could be recognized in inoculated vs control mice. The researchers also found an increase in positive protein gene product-9.5 and positive CGRP-immunoreactive nerve fibers after the development of allodynia. A single extended duration (14-day) infection regimen resulted in a similar allodynia state as the multiple (three) inoculation regimens. Zymosan vulvar injections resulted in allodynia but with greater variability.

A second animal model was reported by Martinov et al of sensitizing female ND4 Swiss mice to oxazolone followed with a one to three labial challenges on days 5 to 7 after sensitization. With a single challenge, mice developed a “hyperalgesia” response for up to 24 hours after the challenge. Labial neutrophil influx remained up to 48 hours after the challenge. With a three-session challenge, the hyperalgesia response lasted up to 5 days. Neural hyperplasia was demonstrated by CGRP IHC + and positive protein gene product-9.5 fibers. Total RNA extraction was followed by quantitative real-time polymerase chain reaction analysis for proinflammatory mRNA products: chemokine ligand-2 160-fold over controls, IL-6 75-fold over controls, IL-1β 30-fold over controls, and chemokine ligand-1 15-fold over controls. TNF-α and interferon-gamma showed little to no change. The investigators concluded that they had developed the first “allergy-based” induction of mechanical hyperalgesia in rodents. Comparing the two animal models shows a difference in the initial stimulus (infectious vs allergenic) but an ultimate response that is remarkably similar: an early inflammatory response, followed by location-specific, long-term allodynia development and location-specific neural hyperplasia, in the absence of long-term inflammatory cell infiltrate.

In Vitro Model Development

The research team of Foster et al. has been working toward the development of an in vitro model of vulvodynia in the hope of facilitating a better understanding of vulvodynia pathogenesis and facilitating new drug development. The team has been testing the hypothesis that the vulvar vestibule of all women possesses unique inflammatory and immunologic responsiveness and that vulvodynia pain reflects an extreme example of a natural phenomenon. After screening a panel of 10 proinflammatory cytokines and chemokines and stimulating with yeast products, Foster et al reported that fibroblasts from the vulvar vestibule vs the external vulva in cases and controls produced elevated proinflammatory cytokine levels of IL-1β, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and interferon-gamma after stimulation by prevalent irritants, such as yeast and yeast breakdown products. Cytokine IL-6 and prostanoid prostaglandin E2 were found to be particularly responsive and elevated in association with allodynia. In later work, an in vitro model for vulvodynia was developed. Primary vestibular fibroblasts were found to be valuable in modeling vulvodynia, in part because they abundantly produce proinflammatory mediators, participate in the immune response, and maintain their relevant phenotypes in culture. After fibroblast culture challenge by several live yeast species including more pathogenic C. albicans and Candida glabrata, the research team found the amount of proinflammatory mediators IL-6 and prostaglandin E2 produced by isolated fibroblast strains was highly predictive of clinically measured pain thresholds previously measured at sites of future biopsy sampling. In general, the more robust the inflammatory response mounted by site-specific fibroblasts, the lower the pain threshold was at that site. These observations provide evidence that proinflammatory mediator production is associated with the evolution of pain in vulvodynia.
reported dyspareunia and 138 controls, Pazmany et al103 found that those with dyspareunia showed that they were more likely to report a history of sexual abuse and fear of physical abuse compared with sexually active adolescent girls from a control group.105 The extent to which antecedents of childhood victimization also contribute to the maintenance and modulation of current vulvodynia symptomatology is not clear. In a study conducted in a sample of women with self-reported dyspareunia, victims of childhood sexual abuse reported significantly lower levels of sexual functioning and psychological well-being compared with women reporting no sexual abuse. The two groups did not differ on pain severity.112 More research is needed to further the understanding of the mechanisms (psychologic and biologic) by which childhood victimization can contribute to the onset of vulvodynia.

Sexuality
Controlled studies published in the past two decades and conducted in clinical and non-clinical samples have indicated that women with vulvodynia report significantly less sexual desire, arousal, and satisfaction, more difficulty reaching orgasm, lower

Table 3. Psychosocial Factors Generally Considered as Risk Factors For, and Correlates or Consequences of, Vulvodynia

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<thead>
<tr>
<th>Psychological factors</th>
<th>Mood, childhood sexual or physical abuse, sexuality</th>
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<tr>
<td>Social and relational factors</td>
<td>Partner and relationship, peers and others, health care community</td>
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<td>Other factors</td>
<td>Comorbid conditions</td>
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It is hoped that the in vitro design will help to delineate the mechanisms by which pain is generated, informing us of potential inhibitory products that might serve as future therapy.

Summary
The preceding review leaves little doubt that the pathophysiology of vulvodynia is likely to involve multiple factors. Discussed below are psychosocial factors that generally have been considered correlates or consequences of vulvodynia (outline presented in Table 3), although longitudinal studies have indicated that some of these factors might precede the development of the pain. Vulvodynia is likely multicausal in nature, with multiple biopsychosocial etiologic pathways leading to the development and persistence of vulvodynia.

PSYCHOLOGICAL FACTORS

Mood
The past decade of research has suggested that psychosocial factors could contribute to the onset and maintenance of chronic vulvar pain. Several controlled studies conducted in different clinical samples have indicated that women with vulvar pain report higher depression scores than controls,95–99 although three other controlled studies have found no such difference.100–102 Such contradictory findings could be explained by the fact that the latter studies were conducted in community samples, which might be less distressed. However, in an online survey involving a community sample of 192 women with self-reported dyspareunia and 138 controls, Pazmany et al103 found that those with dyspareunia reported significantly more depressive symptoms than controls. It is noteworthy that, in many of these studies, women with vulvar pain have reported depressive symptoms that are not necessarily within the clinical range.

Many controlled studies also have found that these women display more state and trait anxiety than controls in clinical and general population samples. A community-based epidemiologic study has suggested that anxiety and depression might be antecedent and consequent to vulvodynia. Khandler et al107 found that the odds of vulvodynia were four times more likely in women with antecedent mood or anxiety compared with women without, and that vulvodynia was associated with a new or recurrent onset of mood or anxiety disorder, suggesting a bidirectional relation among anxiety, depression, and vulvodynia. Furthermore, psychological factors might maintain and exacerbate vulvodynia and its associated sexual impairment.

Psychological factors associated with greater pain intensity or sexual dysfunction include pain catastrophizing, fear of pain, hypervigilance to pain, lower self-efficacy, negative attributions about the pain, avoidance, anxiety, and depression.108,109 According to the fear-avoidance model, an initial pain experience might be interpreted as threatening (catastrophizing), leading to fear of pain and to avoidant behaviors, which in turn lead to hypervigilance followed by disability (sexual dysfunction) and disuse (decrease in sexual repertoire).110,111 In a 2-year prospective study involving 222 women with PVD, Davis et al112 found that their results did not support the fear-avoidance model. Only increases in pain self-efficacy—the degree to which a woman believes she can manage the pain effectively—were associated with decreases in pain intensity. The relation between changes in self-efficacy and changes in pain was mediated in part by changes in avoidance (more intercourse attempts). The same pattern of results was found for changes in sexual satisfaction as the outcome. In conclusion, psychological factors play a significant role in the experience of vulvodynia and might require targeted interventions.

Childhood Sexual and Physical Abuse
Childhood victimization can be a risk factor for the development of vulvodynia. In a population-based study, pre- and postmenopausal women with vulvodynia were 4.1 times more likely to have reported severe physical abuse and 6.5 times more likely to have reported sexual abuse.113 Another population-based study showed that women with vulvodynia had almost three times the odds of reporting experiences of severe physical and sexual abuse and of living in fear of abuse compared with women without vulvodynia.114 Similarly, a large-scale cross-sectional study of sexually active adolescent girls with dyspareunia showed that they were more likely to report a history of sexual abuse and fear of physical abuse compared with sexually active adolescent girls from a control group.105 The extent to which antecedents of childhood victimization also contribute to the maintenance and modulation of current vulvodynia symptomatology is not clear. In a study conducted in a sample of women with self-reported dyspareunia, victims of childhood sexual abuse reported significantly lower levels of sexual functioning and psychological well-being compared with women reporting no sexual abuse. The two groups did not differ on pain severity.112 More research is needed to further the understanding of the mechanisms (psychologic and biologic) by which childhood victimization can contribute to the onset of vulvodynia.
frequencies of intercourse, more negative attitudes toward sexuality, and more sexual distress than pain-free controls. Laboratory studies using vaginal photoplethysmography have shown no significant differences between women with vulvodynia and controls relative to their physiologic level of sexual arousal when exposed to an erotic stimulus, although women with pain tended to report more negative feelings toward the stimulus. However, another study using laser Doppler imaging to examine physiologic sexual arousal in women with PVD found that they displayed lower genital responsiveness to an erotic stimulus compared with controls. More research is needed to shed light on the phenomenon of sexual arousal in women with vulvodynia and its role in the experience of pain.

More recently, studies have shown that women with vulvodynia report more distress about their body image and a more negative genital self-image than controls. Two studies showed that women with PVD present with more anxiety and self-awareness with exposure of their bodies during sexual activity compared with women with PVD controls. Two controlled studies indicated that partners of women with vulvodynia also report sexual difficulties, including more erectile problems and lower sexual satisfaction than men from a control group, although the issue of “cause and effect” in this association is not clear. In conclusion, women with vulvodynia experience significant impairments with and distress about their sexuality, and new data suggest their partners do, too.

SOCIAL AND RELATIONAL FACTORS

Partner and Relationship Factors

A systematic review examined whether women with vulvodynia report more relationship distress than women without this problem. Most controlled studies have suggested that affected couples do not experience lower relationship satisfaction compared with control groups or scale norms on validated measurements, whereas a handful of studies have found significantly lower relationship adjustment in women with vulvodynia than controls. However, samples in many of these studies were heterogeneous, which could explain in part the discrepant findings. Relationship satisfaction also might be too global a construct: finer aspects of the relationship nevertheless might be affected by the pain and potentially play a role in its experience. In recent years, more specific relational variables have been associated with sexuality and pain outcomes in women with vulvar pain complaints.

The most studied relationship factor to date is partner responding. Partner responses to women’s genital pain can be solicitous (providing attention and sympathy), negative (demonstrations of hostility), and facilitative (encouraging adaptive coping). In a series of cross-sectional and dyadic daily diary studies, Rosen et al found that women’s perceptions of partner solicitous responses were associated with their own worse pain and sexual function, and that male partners’ self-reports of solicitous responding were associated with their own worse sexual function and satisfaction and with women’s worse pain, sexual function, and sexual satisfaction. Women’s perception of partner negative responses were associated with their own worse pain, sexual function, sexual satisfaction, and depressive symptoms, whereas male partners’ reports of negative responding were associated with their own worse sexual function and satisfaction. Women’s perception of partner facilitative responses were associated with their own better sexual function, sexual satisfaction, and relationship satisfaction, whereas male partners’ reports of facilitative responding were associated with their own better relationship satisfaction and women’s lower pain. In summary, solicitous and negative responses might be detrimental to women’s pain and couples’ sexual well-being, and facilitative responses might be beneficial to women and their partners. These findings are in line with those from the chronic pain literature associating solicitous and negative responses with greater pain intensity, supporting cognitive-behavioral conceptualizations of pain. Despite their usefulness, cognitive-behavioral models have been criticized for their restricted conceptualization of interpersonal processes, because they tend to neglect the affective dimensions of couple interactions.

Thus, recent studies have focused on intimacy, communication, emotion regulation, and attachment in couples coping with genital pain. In a cross-sectional study of women diagnosed with PVD and their partners and controlled for partners’ intimacy, women’s greater sexual intimacy was associated with their greater sexual satisfaction, sexual function, and pain self-efficacy. In addition, women’s greater relationship intimacy was associated with their higher sexual function. In an observational study involving 50 couples in which the woman was diagnosed with PVD, both partners’ greater empathic response was associated with their better sexual satisfaction and lower sexual distress. Both partners’ greater disclosure was associated with their better sexual satisfaction. Findings from these two studies suggest that self-disclosure and empathy—two components of intimacy—could facilitate couples’ adaptive coping with vulvar pain. Similarly, Pazmany et al found that better dyadic sexual communication was associated with higher levels of sexual function and dyadic adjustment and lower levels of sexual distress in women with dyspareunia.

Ambivalence overemotional expression is defined as the extent to which a person is comfortable with the way she or he expresses emotions. In a sample of 254 couples with vulvar pain, those in which both members were found to be low in ambivalence overemotional expression reported significantly better sexual function and satisfaction, less depressive symptoms, and better dyadic adjustment than couples in which both were high in ambivalence overemotional expression or in which one member was high and the other was low. Another study indicated that anxious and avoidant attachment styles were associated with lower sexual satisfaction in women with vulvodynia and their partners. Only attachment avoidance predicted lower sexual function in women. Further, women’s sexual assertiveness mediated the relation among their attachment dimensions, sexual function, and satisfaction. Although cross-sectional, taken together, these findings suggest...
that couples who can be intimate and communicate more openly about sexuality, coregulate emotions effectively together, and hold a secure attachment bond could experience less pain-related detrimental effects on their sexuality, relationship, and mood.

An important question that remains to be answered is why women with vulvodynia continue to engage in sexual activities involving vaginal penetration. Although some avoid sexual activity altogether, more than 80% have reported engaging in regular penetrative activities with a partner. In their conceptual model, Crombez et al suggested that motivation might be an important element to consider in understanding the behavioral aspects of genital pain. In qualitative studies, women with vulvodynia have reported reasons such as wanting to feel closer to their partner and wanting to avoid losing their partner. A recent quantitative study showed that women with self-reported dyspareunia endorsed more goals for engaging in intercourse that were associated with wanting to protect or keep their partner and concerns about duty and pressure compared with control women. They found that when women had higher avoidance goals for sexual activity or wanted to engage in sexual activity to avoid negative repercussions, they reported lower sexual and relationship satisfaction and higher levels of depressive symptoms. When women had higher approach goals for sexual activity or wanted to engage in sexual activity to achieve positive outcomes (e.g., feeling closer to their partner), they reported higher sexual and relationship function. In summary, although the motivations underlying sexual behavior in women with vulvodynia do not appear to affect their pain per se, they could contribute to women’s psychological and sexual adjustment to the pain. Engaging in sexual activity that is unwanted could indeed result in negative consequences for women’s sexual well-being.

Peers and Others

Many women with vulvar pain have reported feelings of shame, inadequacy, and low self-esteem. In a qualitative study involving 14 young women with self-reported dyspareunia, Donaldson and Meana identified a sequence of experiences that began with confusion about the onset of pain and a relatively fruitless search for what might be causing their symptoms. Then, women attempted to self-manage the problem using cognitive and behavioral strategies, with little relief. Negative consequences on sexual function, well-being, and relationships ensued, and women reported several barriers to seeking help. Further, up to 45% of women with vulvodynia reported a comorbid pain condition, and having a comorbid condition was associated with increased feelings of isolation and invalidation. In addition, women with PVD and concurrent chronic pain were found to be more likely to report a longer duration of pain, pain radiating to parts of the vulva other than the vestibule, and more pain interference than women with PVD alone; they also were more likely to report having consulted with more gynecologists, tried more therapies, and have more allergies and skin sensitivities than women with PVD alone.

A population-based study conducted by Nguyen et al showed that women with chronic vulvar pain were more likely to believe that people judged their condition as an excuse to avoid intercourse. Although half the women with chronic vulvar pain did not seek medical care for it, women who actually sought care (45.1%) were more likely to feel stigmatized by physicians. Further, in a study examining whether women with vulvar pain were comfortable talking about their problem within their social circle, Nguyen et al found that 67% of women with a partner were comfortable discussing their pain with him or her, 39% were comfortable with a family member, and 26% were comfortable with women friends. This body of research highlights women’s sense of feeling alone to deal with their vulvodynia and their difficulties in finding appropriate health care.

Health Care Community

Vulvodynia represents a unique intersection of the specialties of chronic pain and sexuality. These two topics are challenging to manage separately. Research has shown several barriers to physicians’ ability to work with patients with chronic pain, such as lack of training and knowledge in the area of pain management, a dearth of pain assessment strategies and tools, and the practical difficulties in creating a multimodal treatment plan. It is no surprise that physicians report low satisfaction with currently available treatment options and low confidence in their ability to treat chronic pain, which could contribute in part to a negative attitude toward patients with chronic pain (e.g., Dobscha et al). With respect to vulvodynia, the pain manifests in the genitals and likely during sexual activity; issues of genitai and sexuality can be uncomfortable topics for health professionals and patients to raise. When this discomfort is combined with possible negative attitudes surrounding the management of patients with chronic pain, the feelings of uneasiness, lack of expertise, and embarrassment in the relationship between the patient and the health care professional are potentially compounded. In a study examining university-age students, participants indicated a preference for receiving information about sexual health through conversations initiated by their health care professional; however, only approximately half the medical students indicated that they felt adequately trained to take a sexual history, and approximately 38% felt adequately trained to address and treat sexual concerns. Supporting the probable issues with initiating discussions surrounding intimate topics, a survey of obstetrics and gynecology residents in the United States found an overall feeling of dissatisfaction with training on female sexual function and dysfunction: 43% were mostly or very dissatisfied with the training they had received, and none of the 234 participants had received more than five didactic sessions on the topic.

Not surprisingly, chronic genital pain that affects sexual (and other) function can magnify the difficulty that health professionals—and patients—have in raising the issue. Indeed, in some studies, many women with chronic vulvar pain were silent sufferers,
with only approximately 60% of them consulting health care professionals\textsuperscript{8,143}; of these, 61% received a diagnosis, with only 9% diagnosed with chronic vulvar pain.\textsuperscript{9} Furthermore, in another study, 57% of participants consulted at least three physicians before receiving a diagnosis, a pattern echoed in other research.\textsuperscript{31} Similarly, Reed et al\textsuperscript{10} found that fewer than 50% of women meeting criteria for vulvodynia sought treatment, and only 1.4% of those women had received an appropriate diagnosis. It has been well established that women with vulvodynia are apprehensive to speak about their pain with others,\textsuperscript{144} and feelings of isolation and invalidation of their pain are common.\textsuperscript{141} Anecdotal evidence suggests that women with vulvodynia receive little validation for their symptoms in health care settings, with many women being told their pain is “all in their heads” owing to the absence of visible pathology (eg, Amalraj et al\textsuperscript{1}). However, the patient-physician relationship is an integral part of the social context of someone suffering from a chronic illness (see Nicassio and Smith\textsuperscript{152}). This dyadic interaction can affect treatment compliance and health outcomes (see Di Blasi et al\textsuperscript{155}), such as the ability to self-manage pain.\textsuperscript{154} Women with chronic genital pain also might decrease their efforts to seek help from other sources of support, such as family and friends. One study demonstrated that although 67.6% of women with chronic vulvar pain were comfortable discussing their pain with their partner, only 26.9% of women reported feeling comfortable discussing their pain with women acquaintances.\textsuperscript{144} This pattern of results indicates that education and comfort are two major areas to target in future research.

CONCLUSIONS

Vulvodynia is a prevalent and highly impactful genital pain condition. Numerous factors have been implicated in its development and maintenance. What is becoming increasingly apparent is that it likely represents the end point of different factors that can differ from woman to woman. Longitudinal research is needed to shed light on risk factors involved in the expression of vulvodynia, as well as in potential subgroups of affected patients, in order to develop an empirically supported treatment algorithm.

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