

Women's Sexual Pain and Its Management

Willibrord Weijmar Schultz, MD, PhD,* Rosemary Basson, MD,^{†,‡} Yitzchak Binik, PhD,[§]
David Eschenbach, MD,[¶] Ursula Wesselmann, MD,^{**} and Jacques Van Lankveld, PhD^{††}

*Department of Gynecology and Obstetrics, University of Groningen Medical Center, Groningen, the Netherlands;

[†]Department of Psychiatry and [‡]Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada;

[§]Department of Psychology, McGill University and McGill University Health Center (RVH), Montréal, Québec, Canada;

[¶]Department of Obstetrics and Gynecology, University of Washington Medical Center, Seattle, USA; ^{**}Department of

Neurology, Johns Hopkins University, Baltimore, USA; ^{††}Department of Medical, Clinical and Experimental Psychology, University of Maastricht, the Netherlands

Corresponding Author: Willibrord Weijmar Schultz, MD, PhD, Department of Gynecology, Groningen University Medical Center, Hanzeplein 1, PO Box 30.001, 9700 RB, Groningen, the Netherlands. Tel: +31 50 3616161; Fax: +31 50 3611694; E-mail: w.c.m.weijmar.schultz@og.umcg.nl

ABSTRACT

Introduction. Approximately 15% of women have chronic dyspareunia that is poorly understood, infrequently cured, often highly problematic, and distressing. Chronic dyspareunia is an urgent health issue.

Aim. To provide recommendations/guidelines concerning state-of-the-art knowledge for the assessment and management of women's sexual pain disorders.

Methods. An international consultation, in collaboration with the major sexual medicine associations, assembled over 200 multidisciplinary experts from 60 countries into 17 committees. One six-member committee focused on women's sexual pain disorders, developing recommendations over a 2-year period.

Main Outcome Measure. Expert opinion was based on grading of evidence-based medical literature, widespread internal committee discussion, public presentation, and debate.

Results. There is increasing evidence for the role of neuropathic pain mechanisms in the pathophysiology of sexual pain disorders. Empirical literature has demonstrated the comorbid presence of clinical psychopathology. With regard to the pathophysiologic role of the pelvic floor and sexual pain disorders, studies reveal that (i) differentiation between vaginismus and dyspareunia using clinical tools is difficult; (ii) vaginal spasms have not been identified; (iii) physical therapists can differentiate vaginismic women from matched controls based on muscle tone/strength differences; (iv) the traditional treatment of vaginismus with vaginal "dilatation" plus psycho-education, desensitization, and so forth is not evidence-based; (v) pelvic floor muscle tone/strength measures for women suffering from vulvar vestibulitis syndrome are intermediate between those of women with vaginismus and no-pain controls; and (vi) the pelvic floor musculature is indirectly innervated by the limbic system and highly reactive to emotional stimuli and states. Pelvic floor therapies for dyspareunia may be effective.

Conclusion. Recommendations include (i) revising the definitions of vaginismus and dyspareunia; (ii) integration of treatment approaches; (iii) validation of nonspecific treatment effects; (iv) controlled studies to test interventions; and (v) sexuality education to help prevent sexual pain.

Key Words. Female Sexual Pain Disorders; Vulvar Vestibulitis Syndrome; Dyspareunia; Vaginismus

Introduction

Treatment for sexual pain disorders in the healing professions has always been a tricky matter. This is well illustrated by a comment made by Robert Latou Dickinson in 1933:

The surgeon thinks of difficult coitus in terms of a knife passed through muscles in spasm; the psychiatrist thinks of dyspareunia as a mental knot to be disentangled by analysis; the gynecologist who is weary of patching—poor and late patching—begins to think in terms of prevention through routine premarital examination and instruction [1].

This article will review pathophysiology, psychopathology, treatments, and prognostic factors in sexual pain disorders, but interestingly there are no studies on prevention. Everyone who regularly encounters the complaint of dyspareunia knows that women are inclined to continue with coitus, if necessary, with their teeth tightly clenched. The repercussions on the woman—sexually and emotionally—plus the distancing and misunderstanding between the partners can make the treatment of sexual pain disorders difficult and frustrating for patients and clinicians.

Characteristics of Women's Sexual Pain at Variance with the ICD-10 and the DSM-IV-TR

This review highlights the clinical presentation of two categories of sexual pain disorders, dyspareunia and vaginismus. The ICD-10 and the DSM-IV-TR view sexual dysfunction as involving either psychological or somatic components or a combination of both, suggesting these are separate entities and that etiologies are usually known [2,3]. However, sexual function is a supreme example of the mandatory blending of mind and body. Moreover, the precise etiology of dysfunction is often unclear. Frequently, sexual pain is or becomes associated with lack of subjective arousal (and orgasm) and lack of desire or interest. Reduced genital congestion is frequently reported but is as yet not scientifically documented [4]. Whereas a lack of sexual arousal is one certain etiologic factor, other factors are currently extremely unclear. Therefore, we do not recommend the specification of a biologic or psychological etiology.

Current diagnostic systems also rely heavily on the sexual response cycle. However, the categories of pain disorders, vaginismus and dyspareunia, are not part of the sexual response cycle. Also, the assumption that dyspareunia and vaginismus are distinct types of sexual pain disorders has recently been challenged [5–8].

Recommended Definitions of Women's Sexual Pain

Despite the foregoing, in this review the independent existence of dyspareunia, vulvar vestibulitis syndrome (VVS), and vaginismus is *a priori* accepted to allow the use of the existent scientific literature based on this nosological distinction. For the present review on the etiology of sexual pain disorders, dyspareunia is defined as recurrent or persistent genital pain associated with sexual intercourse. It can be subdivided into deep and superficial pain. In the case of superficial (introital) pain, dyspareunia may or may not be identified as VVS. Vaginismus has been defined as recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, causing personal distress.

As knowledge of etiology and treatment of sexual pain disorders advances, these definitions are being modified. An international consensus committee recently recommended the following definition for vaginismus [9]: persistent or recurrent difficulties of the woman to allow vaginal entry of the penis, a finger, and/or any object, despite her expressed wish to do so. There is variable (phobic) avoidance, involuntary pelvic muscle contraction, and anticipation/fear/experience of pain. Structural or other physical abnormalities must be ruled out or addressed. As for dyspareunia, the recommended definition is persistent or recurrent pain with attempted or complete vaginal entry and/or penile vaginal intercourse.

Prevalence of Sexual Pain

Prevalence estimates for dyspareunia range from 3% to 43% and varies not only with culture (the lower estimates are from Northern European countries, whereas the higher ones are from the United States), but also with the setting (3–18% in the general population, 3–46% in the general practice, 0–30% in sexuality clinic settings, and 10–20% in gynecologic clinics) and the gynecologist's initiative to bring up the matter. Several authors found a major difference in the incidence of sexual complaints between self-reported data by the patients and data obtained during a discussion about sexuality initiated by the gynecologist [10–12]. Therefore, in order to detect sexual problems and sexual dysfunctions, explicit questions will have to be asked.

Prevalence rates for vaginismus are scant, without the benefit of multiple studies on specific populations. Prevalence estimates for vaginismus range from 1% to 6% [13].

Chronic Pain Physiology and Sexual Pain Disorders

There is experimental evidence from several psychophysical studies suggesting that neuropathic pain mechanisms might be involved in VVS [14–16]. There is a general consensus today that both peripheral and central nervous system mechanisms play a role in neuropathic pain [17]. Briefly, neuropathic pain is typically characterized by spontaneous paresthesias, dysesthesias and pain, and by evoked pain (e.g., pain evoked by mechanical stimuli, such as the pain evoked by tampon insertion or sexual intercourse in patients with VVS). Under normal conditions pain is experienced when impulses reach the brain via A-delta-fiber or C-fiber nociceptive afferents. Minor tissue injuries can cause a reduction in the threshold of nociceptors, resulting in “peripheral sensitization.” This change in threshold is caused by the release of chemical inflammatory mediators into the tissue. Sensitized nociceptors respond to weak, non-noxious stimuli—a clinical phenomenon called “allodynia.” Further, noxious stimuli result in an exaggerated pain response—“hyperalgesia,” thus the pain sensation no longer matches the painful stimulus. The clinical phenomena of allodynia and hyperalgesia can also be due to abnormal signal amplification in the central nervous system (CNS), a process called “central sensitization.” In the presence of central sensitization, signals entering the CNS via non-nociceptive A-beta touch afferents may evoke pain. The cause of increased descending excitatory signals and/or decreased inhibitory signals to allow this central sensitization of dorsal horn cells is unclear. Nevertheless, the typical initiation and exacerbations of VVS after times of severe stress fit this model of central sensitization. Various medical regimens (tricyclic antidepressants, anticonvulsants—usually carbamazepine or gabapentin) have aimed therapy at nerve hyperesthesia. Some offer pain relief, but total pain resolution with these drugs appears infrequent [18].

Psychological Aspect of Sexual Pain Disorders

With regard to the role of psychological factors in the possible etiology (causation and/or maintenance) of sexual pain disorders, a distinction is made between women with VVS, women with dyspareunia not identified as VVS, and women with vaginismus (Table 1).

In women with VVS, elevated rates of comorbid psychopathology were found (depression and anxiety disorders). However, the self-report findings on psychological characteristics were not

unequivocally found to support psychopathology findings. Both more problematic psychological functioning and unaffected functioning have been reported, possibly reflecting differences in study samples and instrumentation or true heterogeneity of women with VVS.

However, increased trait anxiety in women with VVS has been found in two studies and may represent a stable characteristic. Single-study findings of women with VVS included elevated rates of shyness; perfectionism; the temperament trait of harm avoidance; increased tendency to have catastrophizing thoughts and negative feelings toward sexual interaction; erotophobia; and problems with subjective sexual arousal and lubrication during sexual interaction with partner, but not during masturbation. Psychopathology and impaired psychological functioning may be cause, as well as effect, of vulvar vestibulitis. Women with VVS have been found to be more sensitive to thermal and tactile stimulation, reflected in lowered thresholds for sensitivity and the experience of pain on stimulation. An etiological element may be the attentional bias of hypervigilance for pain-related stimuli. These latter experimental findings have not yet been replicated.

Women with dyspareunia not further clarified are found to have elevated rates of clinically relevant comorbid depression and anxiety disorders. Sexual traumatization appears not to play a significant role in etiology. Self-report measurement of psychological characteristics corroborates the presence of depressive and anxious symptoms, both on the experiential and the behavioral level. Experiential and behavioral signs of hostility and psychotic symptoms also appear to be more frequently present. As to sexual functioning, women with dyspareunia are found to be more erotophobic, reflecting negative and conservative attitudes toward sex, and aversion to engage in sex. They have more problems with experiencing sexual arousal. Relationship discord is found to be increased in women with dyspareunia. Impairment of genital responding was found to be produced by specific sexual stimulation (audiovisual representation of penile–vaginal intercourse) during laboratory investigation. This effect has thus far not been replicated.

Women with vaginismus were found to have significantly increased comorbid anxiety disorder, while depression rates were not found to be increased. The role of childhood sexual trauma is unclear, as different frequency rates were found, and the presence of increased rates of post-

Table 1 Overview of psychological aspects of sexual pain disorders [19]

		Dyspareunia	VVS	Vaginismus
Clinical psychopathology	Anxiety disorder*	++	+	++
	Depression	++	++	
Psychological characteristics assessed with psychometric instruments	Neuroticism	+	--	+/-
	Depression	++	+ +/-	+ +/-
	State anxiety	++	+ +/-	+ +/-
	Trait anxiety		++	
	Phobic anxiety	++	+/-	+ +/-
	Obsessive-compulsive behavior	++	+/-	+/-
	Shyness		+	
	Interpersonal sensitivity (social anxiety)	++	+ +/-	+ +/-
	Hostility	++	+/-	+ +/-
	Psychoticism	+	+/-	+/-
	Extraversion		-	--
	Somatization	+	+ +/-	+/-
	Hysterical personality			+
	Perfectionism		+	
	Low self-esteem			+
	Harm avoidance		+	
	Erotophobia	+	+	
	Positive sexual self-schema		-	+
	Negative sexual self-schema		-	-
	Catastrophizing thoughts		+	
Marital problems	++	--	-	
Aspects of sexual functioning	Sexual trauma	--		+/-
	Less sexual self-stimulation		+	+
	Sexual desire problem		+	+
	Sexual arousal problems (with partner contact)	++	++	+
	Lubrication problems (with partner contact)		++	
	Sexual arousal problems (with masturbation)		-	
	Lubrication problems (with masturbation)		-	
	Lack of sexual pleasure		+	+
Psychological factors in etiology (results of controlled comparisons/experimental manipulation)	Negative feelings about sexual interaction	+	+	
	Lower heat pain threshold		+	
	Lower tactile pain threshold		+	
	Depression	+		
	Anxiety		+	
	Marital adjustment		+	
	Attentional bias toward pain stimuli		+	
	Lower genital arousal associated with intercourse	+		
	Attribution of pain to psychosocial factors	+		
Deficient pelvic muscle control			- [†]	
Pelvic muscle contractions in response to threat			-- [†]	

* Clinical diagnosis of anxiety disorder includes agoraphobia without panic disorder, generalized anxiety disorder, simple phobia, obsessive compulsive disorder, social phobia; [†] No higher than healthy controls.

+, significant; ++, more than one study; -, not significantly different from healthy controls; --, more than one study; +/-, found in one/some studies, but not in other(s).

VVS = vulvar vestibulitis syndrome.

traumatic stress disorder has not been investigated as yet. Psychological characteristics, measured with self-report instruments, do not unequivocally corroborate the presence of anxiety disorders. Personality traits found to be more often present in this group suggest the presence of self-focused attention and negative self-evaluation in the etiology or maintenance of vaginismus. Sexual functioning may be impaired with regard to sexual desire and arousal response during sexual activity. Experimental evidence thus far documented the role of experienced threat in increased pelvic floor muscle tension but did not discriminate between women with and without vaginismus. Therefore,

causation and maintenance of vaginismus by psychological factors remain unresolved, although fear of penetration and associated attentional bias may play a role.

Pelvic Floor and Sexual Pain Disorders

Almost all the research regarding the contribution of pelvic floor muscle physiology to dyspareunia is linked to the work of Howard Glazer, who has focused primarily on the use of vaginal electromyographic biofeedback ("Glazer protocol") as a treatment modality for VVS/vulvodynia. The discussion will focus on two questions: (i) Are

there demonstrable pelvic floor muscular differences in women with dyspareunia? and (ii) Are pelvic floor-focused therapies for dyspareunia effective?

In a series of uncontrolled consecutive patient outcome studies using vaginal electromyographic feedback, the investigator has reported impressive pain reduction/return to intercourse results for women suffering from VVS and vulvodynia [20–23]. As a result, the author has suggested that changes in resting pelvic muscle tone and contractility may characterize these disorders. Another study also examined this issue using a Glazer-based vaginal electromyography (EMG) protocol and structured physical therapist palpation [24]. Their EMG data confirm differences in muscle strength but not in muscle tone between VVS sufferers and matched controls. However, for physical therapist-based palpation data, the authors found increased pelvic floor tonicity and lowered muscle strength in women with VVS compared with normal matched controls. Combined with the findings from vaginismus women, there does appear some indication that pelvic floor muscle tone and strength measures for women suffering from VVS are intermediate between those of women with vaginismus and no-pain controls.

Bergeron et al. have carried out a prospective, randomized controlled treatment outcome study that compared the Glazer treatment protocol with cognitive-behavioral group pain management and vestibulectomy [25]. Glazer-type biofeedback resulted in significant clinical improvement when compared with baseline, and an approximately 40% reduction in pain. The same authors have also carried out an uncontrolled retrospective consecutive case investigation of whether pelvic floor physical therapy including, but not limited to biofeedback was useful in the treatment of VVS [26]. The pelvic floor physical therapy typically lasted 6–8 sessions and included a variety of manual techniques, biofeedback, electrical stimulation, and homework exercises designed to stretch, strengthen, relax, and heighten awareness of the pelvic floor muscles. Approximately 50% of the patients reported complete to great improvement and another 20% reported moderate gains.

Because all previous definitions of vaginismus were based on the concept of vaginal spasm and because the differential diagnosis of vaginismus from dyspareunia is questionable, there is reason to suspect that the diagnosis of vaginal muscle spasm may also not be reliable. In fact, the general

validity of the concept of muscle spasm has been called into question [27]. As far as we are aware, only one study has directly investigated whether muscle spasm specifically characterizes vaginismus [24]. The results of this study strongly suggest that vaginal muscle spasm does not characterize vaginismus and that different professionals diagnose spasm very differently. Interestingly, less than a quarter of the women in the vaginismus group attributed their difficulties with intercourse to vaginal spasm.

Four studies have investigated this issue using a variety of measurement techniques including vaginal and nonvaginal EMG, pelvic floor physical therapist, and gynecologist ratings [24,27–29]. EMG pelvic floor measurements were taken in response to (i) film stimuli displaying erotic, neutral, sexually-, and nonsexually-threatening situations; (ii) gynecologic examinations; and (iii) instructions to consciously contract and relax vaginal/pelvic muscles. In only one of the studies [24] did EMG measures differentiate vaginismus women from matched controls. Such studies are intrinsically problematic. Women with typical/severe “vaginismus” have never been able to tolerate the insertion of a finger, a tampon, a penis, or an speculum and, before any therapy, would not be likely to comply with these protocols. Indeed, in the above study, over half the women suffering from vaginismus refused to insert the EMG sensor for one of the two testing sessions. However, there were consistent data from this study indicating that a structured protocol of manual measurement of the pelvic floor musculature carried out by physical therapists is reliable and can differentiate women with vaginismus from matched normal controls.

Since Masters and Johnson, most therapies for vaginismus have used vaginal “dilatation” as a major treatment intervention. Initially, the woman becomes accustomed to self-touch to the introitus and insertion of her own finger though the introitus and part way into her vagina. She then places the first of a series of inserts of gradually increasing diameter into her vagina. In reality of course there is no “dilation” but a gradual reduction of reflex protective involuntary tightening. Although this intervention is generally acknowledged to be highly effective and necessary for treating vaginismus [30], there has never been a randomized controlled treatment study examining it or any other therapy protocol. Although there are numerous poorly or semicontrolled therapy outcome studies for vaginismus, the overall quality of the evidence

is quite poor. These studies will not be reviewed here as there have been several recent comprehensive and critical reviews of this literature [31–33]. Despite the differing evaluation methodologies used in these reviews, and despite strong clinical support for these approaches, the reviews conclude that the insert treatment and psycho-education, desensitization, and so forth have not been scientifically proven as effective treatments. There is also concern over the appropriate criterion for success in these therapies. While the traditional criterion is vaginal penetration, several recent authors criticized this criterion and suggested that the experience of penetration alone without pleasure is not adequate [34,35]. It has also been suggested that vaginismus symptoms sometimes serve the function of maintaining a dyadic emotional equilibrium. If this is indeed the case, then outcome criteria must take into account the removal of this coping mechanism and subsequent emotional and physical adjustments [36]. Clinical experience but not as yet scientific study confirms frequent comorbidity in the partner—the history of sexual hesitancy generally (relatively infrequent self-stimulation and a certain degree of emotional comfort with the sexual infrequency with the partner), or specifically avoidance of sexual intimacy with his partner.

It is remarkable that there is no empirical evidence to support the 500-year-old definition of vaginismus as related to spasm of the muscles of the pelvic floor. The existing evidence directly contradicts it. While there is some indication of differences in resting muscle tone or strength between vaginismus, dyspareunia, and no-pain controls, these are not well established and could equally well be the result of, or the expectation of pain rather than the cause. In fact, there is accumulating basic research to support the idea that the pelvic floor musculature, like other muscle groups, is indirectly innervated by the limbic system and therefore highly reactive to emotional stimuli and states [37–39].

Mucous Membranes and Sexual Pain Disorders

Sexual pain disorders of genital skin and mucus membranes are common. Most of these painful disorders are transient and are caused by inflammation from acute genital infection. Acute infections that most commonly cause vulvo-vaginal inflammation include acute episodes of candidiasis, trichomoniasis, genital herpes, furuncles, and infection of the greater vestibular glands. The

cause of acute inflammation is usually readily discernible by the clinician, and treatment usually resolves both the inflammation and the pain.

Chronic genital pain is more problematic because the causes are often difficult to discern. A recent review provides a systematic approach to vulvar disease and offers a comprehensive list of diseases to consider [36]. Treatment often does not totally remove pain. In many cases, treatment is not standard and does little to even substantially reduce pain. Unfortunately, iatrogenic inflammation of the vulvar skin is common from self-treatment or contact with irritants. Nearly all women with chronic vulvar symptoms first use over-the-counter antifungal medication. However, candida was found by physicians in only one-third of such patients. This self-treatment may be associated with increased duration of symptoms, which suggests a detrimental effect from the medication [40]. Some chronic genital pain is constant even without intercourse, but intercourse usually causes an exacerbation of the pain, often to the point where intercourse is avoided or stopped totally.

Types of Mucous Membrane Disease

Vulvodynias

When signs of VVS or other diagnoses are absent, and biopsies and culture are negative, the term dysesthetic vulvodynia is used. Here all the vulval structures are of normal appearance, and the woman describes vulvar burning and pain (vulvodynia) as severe enough to cause sexual and psychological distress [18]. The syndrome is difficult to treat. Topical treatment of any kind usually increases the amount of pain. Oral therapy using tricyclic antidepressants or anticonvulsants offers a reduction, but not a total resolution of pain [18].

Chronic Vulvar Dermatoses

A wide variety of chronic vulvar skin conditions can cause sexual pain both intermittently and continuously. While not common in the general population, lichen simplex chronicus, lichen sclerosis, and lichen planus can cause chronic vulvar inflammation and hence vulvar pain [36,41,42]. The diagnosis of these conditions can be more easily discerned by experienced clinicians. Lichen simplex chronicus results when chronic scratching produces inflammation of the skin and results in an itch-scratch cycle. The cycle can be interrupted by topical steroid and oral antihistamine therapy [43]. Lichen sclerosis is an indolent chronic con-

dition of unknown etiology where thinning of the epidermis occurs, resulting in a parchment-paper appearance of the skin. Underlying subepithelial inflammation can result in mild to intense itching that is possible to reduce better with topical steroid therapy than with topical testosterone [44]. Lichen planus results in superficial ulcers of the superficial epithelium, often resulting in intense pain. Patients can have concomitant vaginal mucosal inflammation that results in a profuse irritating vaginal discharge. Often, patients with lichen planus have evidence of inflammation in other mucus membrane areas such as ulcers of the gums, esophagus, or bowel in a Behcet-like syndrome. Prolonged topical steroid, topical tacrolimus (an inhibitor of interleukin-1), or other anti-inflammatory therapies are needed for the ulcerated and inflamed areas [45].

Raised vulvar lesions usually do not cause pain but must be accurately diagnosed and treated.

VVS

One of the most common causes of genital pain and pain with intercourse is VVS. Pain usually is noticed with attempted vaginal penetration during intercourse, although in more severe cases pain will be present with other activities such as sitting or running. Besides pain, vulvar burning and itching are common. Together, these symptoms cause physical, sexual, and psychological distress [46]. Community studies suggest vulvar pain is common, but the prevalence has varied widely, from 3% to 18% [47,48]. VVS has been described in up to 15% of gynecologic outpatients [49] and was thought to primarily affect white women [50,51]. A recent survey of ethnically diverse women gave similar lifetime prevalences of chronic vulvar burning or pain on contact [52].

Although VVS is easy to diagnose for the experienced clinician, the mean time between the onset of symptoms and diagnosis usually reaches 2 years or longer. A triad of conditions are necessary to diagnose VVS: (i) pain with penetration during vaginal intercourse; (ii) tenderness of the vestibular area upon even light touch with a cotton applicator; and (iii) erythema of the vestibular area [53]. The areas of allodynia (sensation of pain from light touch stimulus) are typically between 4 and 8 o'clock on the introitus, just exterior to the hymeneal ring but may involve the skin around the openings of the Skene's ducts. However, the whole introital ring may be involved. The area of tenderness, allodynia, and erythema can be difficult to locate because they are usually hidden in folds of

the vulva—presumably explaining the typical long time between the onset and diagnosis.

Inflammation in VVS

The etiology of VVS is unknown, but VVS may represent a chronic local inflammatory condition with a wide variety of etiologic causes. T cell lymphocytes make up most of the inflammatory cells present in vulvar biopsies obtained from those with VVS [53,54]. Plasma cells indicative of ongoing chronic infection are present, but not in large numbers. Mast cells and eosinophils indicative of an allergic condition are less common. The vulvar tissue of patients with VVS contains elevated tissue levels of interleukin 1- β (IL-1 β) and tumor necrosis factor alpha (TNF- α), but these proinflammatory mediators are actually at higher levels in the surrounding vulvar tissue than in the area of inflammation, confirming the clinical finding of a wider area of involvement beyond the area of erythema [55].

Genetics of VVS

Recent work on the etiology of VVS points to a possible genetic involvement. In fact, as is common for inflammatory conditions, allele 2 of the IL-1 β gene was found in significantly more women with VVS (40%) than in controls (25%) [56]. Leukocytes in blood from women with VVS also produce less interleukin-1 receptor antagonist, which suggests a failure in downregulation of inflammation [57]. Allele 3 of the gene encoding the interleukin-1 receptor antagonist was present in the homozygous form in 53% of women with VVS as against 8.5% of control women [58].

Possible Antigens Involved in VVS

The presence of a high T lymphocyte concentration and increased levels of proinflammatory mediators point to a chronic immunologic-induced inflammatory response to some antigen [59].

The antigen that induced VVS for an individual could still be present in vulvar tissues in a small concentration, or the antigen could have stimulated the inflammation but be gone by the time patients usually present with VVS. The most likely antigen candidate would be from microbes that commonly affect the vulva. Human papilloma virus (HPV) was first considered, but in multiple studies HPV was as common in controls as women with VVS [60–62]. Herpes simplex virus (HSV) is also a common vulvar infection, but to date HSV does not appear to cause VVS [63]. Candida is an

antigen present in the vulva more frequently than HPV or HSV. Up to 80% of women develop symptomatic candidiasis during their lifetime. Patients with VVS have a frequent history of candidiasis, often recurrent [64,65]. A modest prevalence of recovery from candida occurs in women with VVS [66,67]. Undoubtedly, other microbial antigens from bacteria, viruses, or other microbes or nonmicrobial antigens are present in the environment, and chemicals that come in contact with vulvar skin could also cause VVS.

Candida is infrequently identified by potassium hydroxide wet mounts, which require about 10^5 microbes to be positive. Candida frequently is isolated on culture from women with VVS, although extensive comparisons with control groups are lacking [64,65]. Some patients with chronic recurrent vulvo-vaginitis candidiasis (VVC) are noted to develop VVS when they are prospectively followed. Further, some women relate the onset of VVS to an acute episode of VVC, and patients cured of VVS often develop recurrent genital pain when another episode of VVC occurs.

Immunologic Model of VVS

The immunologic response that results in cutaneous T lymphocyte cell pathology is well described for other examples of disease with chronic T lymphocyte infiltration [59]. The innate immune system acts to arrange for cutaneous skin immune surveillance by the identification of antigens in the skin and the translation of antigen signal to memory T lymphocytes. Certain memory T cells contain a cell surface adhesion molecule called cutaneous lymphocyte antigen (CLA). T cells with CLA circulate preferentially in the skin as opposed to circulating in internal organs. Antigens in the vulvar skin initially are identified by dendritic cells with macrophage-like characteristics. As an example, macromolecules from candida antigens are efficiently internalized by dendritic cells, which in turn migrate to the regional lymph node.

In the lymph node, dendritic cells meet continuously circulating naive T cells. When a naive T cell encounters and interacts with the candida antigens in a dendritic cell, it becomes activated. Activation of the T cell in the lymph node produces a memory T cell and the expression of CLA provides this cell with the keys that, when it migrates out of the lymph node and into blood, allows it to escape the blood and circulate only in skin.

Thus, activated T cells have the molecular keys that allow their exit from the blood through the

vascular endothelium in skin. The adhesion molecule property of CLA allows tethering to occur of activated memory CLA-positive T cells traveling in postcapillary venules to the endothelium of these venules. The specific venule is identified by the expression of intracellular adhesion molecules and vascular-cell adhesion molecules on the inner endothelial surface. These adhesion molecules tether and slow travel of the T cell in the venule, which allows it to slide between endothelial cells into the local skin tissue [59]. The adhesion molecules are expressed in the endothelial cells by the action of nuclear factor- κ B (NF- κ B) which is formed in the local skin. The identification of antigens such as candida by dendritic cells and especially by activated T cells produces IL-1 β and TNF- α , which in turn activate the NF- κ B pathway. The persistence of candida or any antigen in the skin further activates memory CLA T cells and produces a further acceleration in the production of IL-1 β and TNF- α . The IL-1 β and TNF- α signal produces even more NF- κ B results in a circle effect of even more local inflammation, more activation of T cells, more adhesion molecule expression, and an increased collection of activated T cells [59].

Clinical Relevance of Immunologic and Neurogenic Inflammatory Theories

In this model, it is proposed that repetitive antigen stimulation or the prolonged presence of antigen markedly upregulates the local inflammation. The presence of a high concentration or a persistence of chronic proinflammatory molecules such as IL-1 β and TNF- α , in addition to serotonin, bradykinin, and histamine could sensitize local C nerve fibers [68]. Inflammation also increases the synthesis of sensory neuropeptides [such as calcitonin gene-related peptide (CGRP) and substance P] from activated C fibers. These substances themselves have a proinflammatory effect [69]. Prolonged C fiber firing reduces the threshold of pain and results in hyperalgesia. Further, transport of CGRP and substance P to the dorsal horn of the spinal cord sensitizes cord neurons with the end result that touch is perceived as pain (allodynia). A significant increase in the number of intraepithelial nerve endings occur in women with VVS compared with controls [70,71]. The nerve endings appear to be nociceptors [70], and it has been suggested that the erythema results from a neurogenic rather than an inflammatory source [71]. This chronic pain may lead to hypertonicity of the pelvic muscles. The reduced pain threshold and

pelvic muscle hypertonicity in turn causes more pelvic pain than one might expect.

It is unclear why surgery improves the local pain and decrease pain with intercourse in some subjects with VVS, but it is possible that surgery removes the target tissue of skin containing proinflammatory molecules and the local vascular epithelium to which CLA T cells home.

Establishing the Diagnosis

Table 2 summarizes various conditions that may be associated with varying degrees of chronic dyspareunia.

Gynecologic complaints, diagnostic procedures, and/or treatment may have consequences on the sexual functioning of the patient and on her experience of sexuality (and that of her partner). Therefore, it seems advisable for physicians addressing gynecologic concerns to ask each (new) patient about the existence of sexual problems and possible negative sexual experiences before administering any procedure or treatment. It is very important that the physician makes it clear to the patient in the way he/she formulates his/her questions that he/she is not making any *a priori* assumptions about the existence of a sexual relationship, not expressing a heterosexual preference, or making judgements about various aspects of sexuality, sexual behavior, or sexual experience. Sexual problems are embedded in a somatic, psychological, relational, and social context, which must be assessed in order to make adequate decisions regarding diagnosis, treatment, or referral.

In order to detect or exclude physical illness or abnormalities that cause pain on (attempted)

Table 2 Physical conditions associated with chronic dyspareunia

Superficial	Deep
Vulvitis, vulvovaginitis	Estrogen deficiency
Bartholinitis	Vaginitis
Condylomata	Mechanical or chemical irritation
Atrophia	Changed vaginal profile
Dermatologic diseases	Scarification
Noninfectious inflammations	Endometriosis exterior/interior
Epithelial defects	Vaginal septum
Large labia minora	Urethritis, cystitis
VIN	Uterus in r/vf
Vulvar vestibulitis syndrome	Fibroid uterus
Scarification	Ovarian tumor
Size of the penis	Ovarian remnant syndrome
Urethritis, cystitis	Chronic abdominal pain
Anatomic variations	Abdominal wall pain
Hymenal remnants	Irritable bowel syndrome
Episiotomy/rupture/neurinoom	Hemorrhoids
Radiation	

VIN = vulvar intraepithelial neoplasie; RVF = uterus in retroversion.

Table 3 Questions on pain that can be asked when taking a general sexual history (freely adapted from Ter Kuile and Weijnenborg [72])

1. Pain
 Where does it hurt? How would you describe the pain?
 Is the pain with penile contact to the opening of your vagina, once the penis is partially in, with full entry, after some thrusting, after deep thrusting, with your partner's ejaculation, after withdrawal, with subsequent micturition?
 Do you find your body is tensing when you or your partner attempts to insert his penis? What are your thoughts and feelings at this time?
 How long does the pain last? Does touching elsewhere in the genital area cause pain? Does it hurt when you ride your bicycle or when you wear tight clothes? Do other forms of penetration hurt (tampons, fingers)?

2. Pelvic floor muscle tension
 Do you recognize the feeling of pelvic floor muscle tension during sexual contact?
 Do you recognize the feeling of pelvic floor muscle tension in other (nonsexual) situations?

3. Arousal
 Do you feel subjectively excited when you attempt intercourse?
 Does your vagina become sufficiently moist? Do you recognize the feeling of drying up?

4. Consequences of the complaint
 What do you do when you experience pain during sexual contact? (Continue/stop intercourse/continue to make love without intercourse?)
 Do you currently continue to include intercourse or attempts at intercourse, or do you use other ways to make love instead?
 If so, are you both clear intercourse will not be attempted?
 What consequences does the pain have on the rest of your relationship?

5. Biomedical antecedents
 When and how did the pain start? What tests have been done?
 What treatment have you received.

vaginal entry, the nonphysician and physician will have to work together (Table 3). Especially in the case of dyspareunia or vaginismus, it is not always desirable or practical to perform a medical examination straight away. The patient and care provider together must make decisions about timing, who should be present, and the extent of the examination.

Educational Gynecological Sexological Examination

The examination technique to search for the cause of dyspareunia is more detailed and requires much more finesse than a routine pelvic examination. When conducted correctly, it can be highly therapeutic. This is especially true when the sexual partner is also present. Often referred to as an "educational gynecological sexological examination," the patient watches in the mirror as the doctor gathers information and tells the patient about her genital anatomy, clarifying normal (or abnormal) structures. This can correct misinformation and resultant negative self-image, and can

clarify how any physical changes relate to sexual problems. If not precluded by her pain, additional transvaginal sonographic assessment for deep dyspareunia increases both the sensitivity and specificity of the exam, especially any ovarian abnormality [73].

It is extremely important that the patient knows in advance that she has total control over the situation, knows exactly what is going to happen and decides who is going to be there and who is not, and that she knows that during the examination her personal boundaries will be respected and safeguarded [74]. Through this examination, the foundations are laid for a meaningful discussion afterwards, in which all the findings are explained and at which time further sexual complaints may come to light. This is recommended to lessen the common occurrence of women having to seek multiple health care providers before an accurate diagnosis is made.

When a component of vaginismus is indicated by the history, the patient is told ahead of time that the use of speculum or other means of internally examining the pelvis will not be part of this examination. It is recommended to ask the woman if there is anything she can think of that will facilitate the exam and to impart to her a sense of control on what is happening. The physician is seated comfortably on a low stool and the examination couch adjusted for the woman to be sitting on so she may see in a hand mirror, but her wish not to will be respected. Verbally checking how the woman is coping with the exam from time to time is recommended. Nonverbal communication—the patient's behavior and that of her partner during the examination—are noted, and the physician, too, must be aware of his or her nonverbal signals.

Permission is asked to gently spread the vulva, or the patient is asked to spread the vulva herself with her fingers. This enables her to observe the consequences of pelvic floor muscle activity. By bearing down or coughing, she is able to see the introitus becoming larger. The vulva is carefully inspected, including the labia minora, majora and the crease between the clitoral hood and clitoris, the posterior fourchette, vestibule, hymen, and hymenal edge. For women with introital dyspareunia, sites of allodynia are investigated with a cotton bud (Q-tip), applying the stimulus of touch along the outer edge of the hymen, which is also the inner edge of the inner surfaces of the labia minora. The skin at the opening of Skene's ducts must also

be tested for allodynia as it is commonly involved in vulvar vestibulitis.

It may be possible to proceed to the internal exam on this first visit when the characteristic features of vaginismus were not present in the history and are not present during this exam. With the woman bearing down, the insertion of physician's finger or, if necessary, something smaller such as Q-tip, with her permission, confirms vaginal entry without any pain. (Even with VVS, if the woman is opening the introitus and the finger is carefully placed without pressure on the edge, especially the posterior fourchette, the procedure is painless.)

Measurement of Allodynia

The cotton swab test is widely used [53,75]. As the Q-tip is repeatedly placed on the edge of the vestibule in a clockwise fashion, the woman's verbal and physical reactions are noted, and she may be asked to grade the pain (e.g., out of 1–4). However, the cotton swab test is prone to measurement error when used for experimental purposes or to measure treatment outcomes [15]. Therefore, a new simple mechanical device, the vulvalgesiometer, has been developed [76]. The vulvalgesiometer is cost- and time-effective and easy to use. It can be used as a diagnostic tool capable of differentiating among women with different types of genital pain, and because of its large range of exertable pressures, it may aid in quantifying the severity of pain (mild, moderate, severe) experienced by these women. This device also has applications in quantifying changes in vestibular sensitivity as a result of treatment.

Assessment of the Pelvic Floor Muscle Tone

Involuntary contraction on the gynecology couch does not indicate that this is also necessarily present at home. Conversely, some women can undergo a gynecologic examination without any problem but with vaginistic reactions in other circumstances, depending on what they find threatening. In many cases, the pelvic floor muscles are chronically contracted and feel like "steel cables."

Physician assessment of pelvic floor muscle tone is imprecise but still of some value. The physician places his or her finger between the woman's labia, just in front of the vaginal opening, and applies very gentle pressure. The woman is asked to bear down while the physician slowly moves the finger inside, keeping it dorsally curved to feel the pelvic floor muscle without touching painful areas

at the vestibular margin. At the end of the examination the finger is slowly withdrawn again as the patient is down. The use of a lubricant will facilitate the examination and also prevent tissue damage.

Questionnaire Assessment of Patients with Dyspareunia

It is worthwhile to administer a questionnaire before and after treatment. With the aid of such a measurement instrument, possible comorbidity can be detected and the effect of the intervention can be evaluated. Questionnaires in the English language have the advantage that they are well-known in the international literature, which facilitates comparisons of international publications, and that they have been used often in research, which facilitates comparisons between results and populations. However, for local use these questionnaires have to be translated and validated again, but this is recommended because of cultural differences. A simple and effective instrument to obtain measurement data is the visual analog scale. From time to time during the treatment, the woman marks a score on a sliding scale to represent the amount of progress that has been made.

Management of Women's Sexual Pain

Sexual pain disorders are heterogeneous, multisystemic, and multifactorial disorders that should be treated in a multimodal way according to etiologic factors, risk profile, and context. An algorithm of management of sexual pain disorders (Figure 1)

with three distinctive characteristics meets these requirements.

General Recommendations

1. *A multidimensional and multidisciplinary approach.* Specific attention is given to six areas, i.e., the mucous membrane, the pelvic floor, the experience of pain, sex and partner therapy, the emotional profile, and genital mutilation/sexual abuse. There is no "one size fits all" approach and no "or-or" approach but an "and-and" approach.
2. *Individualized treatment.* After careful listening to her story and after she has been well informed about the illness and its natural course and possible treatments or ways of handling it, a treatment plan is made.
3. *Patient-focused approach.* It is up to the woman and her partner to decide which treatment they wish to embark on. If the careful assessment of psychological function has shown some psychopathology, this should be treated first with psychotherapy. By involving the woman in the decision process regarding the specific treatment of the pain, she and her partner share the responsibility for treatment choice, and this is known to have a positive effect on the treatment outcome [78].

Shifts in preference for a certain approach will depend on the country in question, women's attitudes regarding psychosexual therapy vs. surgery, individual health care systems, cost-effectiveness

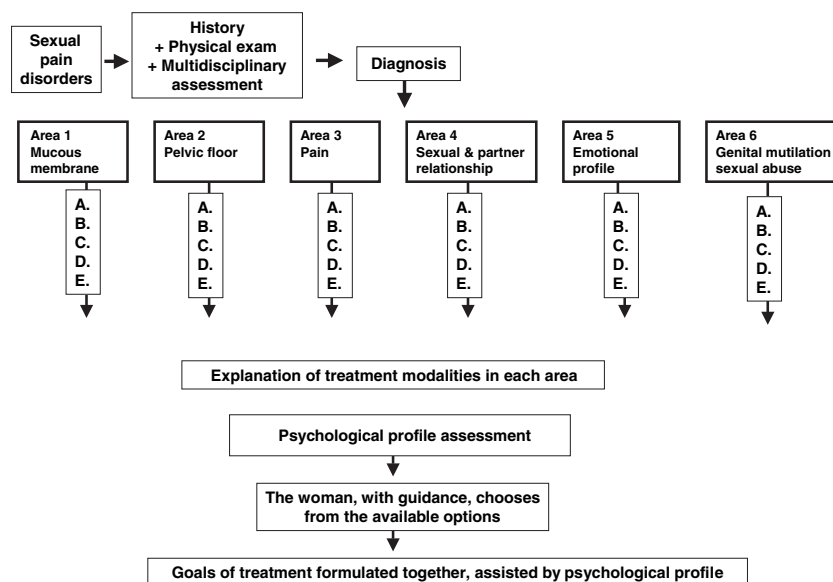


Figure 1 Algorithm of management of sexual pain disorders [77].

of the various modalities, e.g., for VVS, the options include surgery, cognitive behavioral therapy, biofeedback, or a combination of any of these methods.

A Counseling Model

This approach implies that the health care provider has to be familiar with the counseling model. He or she is advisor and counselor and takes care that the woman is in full command of the situation. This is a treatment that is very time-consuming, requires great patience, great empathy, sensitivity to nonverbal signals, and insight into relational interactions. The health care provider must be able to identify the woman's ambivalent feelings regarding coitus, sex, her partner, her own body, her desire to have children. He or she must be able to bring to light serious relational problems or severe traumatic experiences (sexual violence), and he or she has to realize that being able to have sex does not automatically mean that the coitus is enjoyed. It is highly recommended that the health care provider receive suitable training.

Therapeutic Options

The various treatment modalities for VVS are presented by area.

Medical Intervention

On medical intervention for VVS there are only two published studies that are methodologically correct: Fluconazole and Cromolyn [79,80]. Both interventions prove to be no more effective than placebo. One confounding factor is a consistent improvement of 20–30% of patients with VVS when treated with placebo or with no therapy [78]. In spite of this, many clinicians continue to include in their biopsychosexual therapeutic approaches medical interventions of unknown efficacy. Unless part of a randomized controlled trial, topical medication should be restricted to inert creams. (Possibly, repeated touch at subthreshold pain levels provides therapeutic benefit.)

Tricyclic antidepressants, venlafaxine, and anti-convulsants—usually carbamazepine or gabapentin—offer some pain relief, although total pain resolution with these drugs appears infrequent. The starting dose of amitriptyline and other tricyclic antidepressants is low, 10 mg, but can be gradually increased to 40–60 mg daily as tolerated.

Similar doses used to treat essential (dysesthetic) vulvodynia [81] have augmented the treatment of the pain in women with VVS [18].

Hygiene Measures

Preventive hygienic measures include no soap, no vaginal douching, no nylon underwear (“ventilation”), no panty liner (mini pads), fluids to produce 1,500 mL urine daily, and toilet hygiene. Hydration with sitz baths may help reduce inflammation and symptoms.

Recommendations on Sexual Activity

For protection of the mucous membrane, no vulvar penetration with penis, finger, or tongue should be advised, and no semen in the vulva. Some women feel very guilty and some men feel very frustrated about this. Persistent lack of sexual desire in spite of significant improvement in sexual frequency has been observed [25]. Therefore, normalizing, reframing, and encouragement of non-penetrative sex is needed because healing usually takes many months. It is recommended the couple aim at pleasurable and relaxing sex (with orgasms for both partners as desired) without guilt feelings for the woman and without negative sexual tension for the man.

Vaginal EMG Biofeedback, Pelvic Floor Physical Therapy, Cognitive Behavioral

Therapy and Vestibulectomy

There is preliminary information to suggest that vaginal EMG biofeedback, pelvic floor physical therapy, cognitive behavioral therapy, and vestibulectomy may all be useful interventions for VVS [20,82–84]. Treatment results are very similar. This may indicate a nonspecific treatment effect in terms of attention, validation of her pain, and the patient's feeling of control and competence. The active constituents seem to be effective on a meta-level rather than on a content level: how you are doing it may be more important than what you are doing. This phenomenon deserves further study.

Prognostic Factors and Surgery for VVS

A detailed recent critique of gynecologic/surgical procedures for VVS suggest that the following indicate better prognosis [85]: lack of any characteristics of vaginismus before the surgery; acquired rather than lifelong introital dyspareunia; very small amount of surface area involved with allo-

dynia; lack of involvement of the Skene's duct openings; lack of vulvodinia, i.e., only introital dyspareunia; and willingness to have sex therapy if offered.

One problem with many of the studies in this review is that the follow-up was short-term or unspecified. Clinical experience is that benefit from surgery is often temporary, with symptoms returning at about 18–36 months. However, longer follow-up with remaining good outcome is reported by some investigators [86–88].

Conclusions

Ideally, a multidimensional, multidisciplinary approach for sexual pain is recommended, with attention to the following areas: the experience of pain; the emotional/psychological profile; any context of past mutilation or sexual abuse; the genital mucous membrane; the pelvic floor; and sex and partner therapy. The evidence is that the syndromes of vaginismus and VVS overlap, as do the syndromes of vaginismus and dyspareunia not due to VVS. Treatment should be individualized for each woman and/or partner, whenever possible with their input. Psychological issues (as well as interpersonal issues) should be addressed early on with psychotherapy. Although many clinicians define vaginal penetration as the goal of therapy, in the future outcome measures should be broader to include sexual pleasure.

Summary of Committee. For the complete report please refer to *Sexual Medicine: Sexual Pain and Its Management*, edited by T.F. Lue, R. Basson, R. Rosen, F. Giuliano, S. Khoury, and F. Montorsi, Health Publications, Paris 2004.

Conflict of Interest: None.

References

- Dickinson RL. Human sex anatomy, a topographical hand atlas, 2nd edition. London: Baillière, Tindall & Cox; 1949.
- World Health Organization. The ICD-10 classification of mental and behavioral disorders: Clinical descriptions and diagnostic guidelines. Geneva, Switzerland; 1992.
- American Psychiatric Association. Diagnostic and statistical manual for mental disorders, 4th edition (text revised). Washington, DC: American Psychiatric Press; 2000.
- Wouda J, Hartman P, Bakker R, Bakker JO, van de Wiel HBM, Weijmar Schultz WCM. Vaginal plethysmography in women with dyspareunia. *J Sex Res* 1998;35:141–7.
- Reissing ED, Binik YM, Khalifé S. Does vaginismus exist? A critical review of the literature. *J Nerv Ment Dis* 1999;187:261–74.
- Meana M, Binik YM, Khalifé S, Cohen D. Dyspareunia. Sexual dysfunction or pain syndrome? *J Nerv Ment Dis* 1997;185:561–9.
- Van Lankveld JJ, Brewaeys AM, Ter Kuile MM, Weijnenborg PThM. Difficulties in the differential diagnosis of vaginismus, dyspareunia and mixed sexual pain disorder. *J Psychosom Obstet Gynaecol* 1995;16:201–9.
- Kruiff de MD, Ter Kuile MM, Weijnenborg PThM, Van Lankveld JJDM. Vaginismus and dyspareunia: Is there a difference in clinical presentation? *J Psychosom Obstet Gynaecol* 2000;21:149–55.
- Basson R. Lifelong vaginismus: A clinical study of 60 consecutive cases. *J Soc Gynecol Obstet Can* 1996;3:551–61.
- Frenken J, Van Tol P. Seksuele problemen in de gynaecologische praktijk. *Med Contact* 1987;42:150–4.
- Bachmann GA, Leiblum SR, Grill J. Brief sexual inquiry in gynecologic practice. *Obstet Gynecol* 1989;73:425–7.
- Wijma B, Schei B, Swahnberg K, Hilden M, Offerdal K, Pikarinen U, Sidenius K, Steingrimsdottir T, Stoum H, Halmesmäki E. Emotional, physical, and sexual abuse in patients visiting gynecology clinics: A Nordic cross-sectional study. *Lancet* 2003;361:2107–13.
- Lewis RW, Fugl-Meyer KS, Bosch R, Fugl-Meyer AR, Laumann EO, Lizza E, Martin-Morales A. Definitions, classification, and epidemiology of sexual dysfunction. In: Lue TF, Basson R, Rosen R, Giuliano F, Khoury S, Montorsi F, eds. *Sexual medicine: Sexual pain and its management*. Paris: Health Publications; 2004:48.
- Bohm-Starke N, Hilliges M, Brodda-Jansen G, Rylander E, Torebjörk E. Psychophysical evidence of nociceptor sensitization in vulvar vestibulitis. *Pain* 2001;94:177–83.
- Pukall CF, Binik YM, Khalifé S, Amsel R, Abbott FV. Vestibular tactile and pain thresholds in women with vulvar vestibulitis syndrome. *Pain* 2002;96:163–75.
- Sonni L, Cattaneo A, De Marco A, De Magnis C, Carli P, Marabini S. Idiopathic vulvodinia clinical evaluation of the pain threshold with acetic acid solutions. *J Reprod Med* 1995;40:337–41.
- Devor M, Seltzer Z. Pathophysiology of damaged nerves in relation to chronic pain. In: Wall PD, Melzack R, eds. *Textbook of pain*, 4th edition. New York: Churchill Livingstone; 1999:129–64.
- McKay M. Dysesthetic (essential) vulvodinia. Treatment with amitriptyline. *J Reprod Med* 1993;37:9–13.

- 19 Basson R, Weijmar Schultz WCM, Binik YM, Brotto LA, Eschenbach DA, Laan E, Utian WH, Wesselman U, Van Lankveld J, Wyatt G, Leiblum S, Althof SE, Redmond G. Women's sexual desire and arousal disorders and sexual pain. In: Lue TF, Basson R, Rosen R, Giuliano F, Khoury S, Montorsi F, eds. *Sexual medicine: Sexual pain and its management*. Paris: Health Publications; 2004:937–46.
- 20 Glazer HI, Rodke G, Swencionis C, Hertz R, Young AW. The treatment of vulvar vestibulitis syndrome by electromyographic biofeedback of pelvic floor musculature. *J Reprod Med* 1995;40:283–90.
- 21 Glazer HI, Jantos M, Hartmann EH. Dysthetic vulvodynia: Long-term follow-up after treatment with surface electromyography-assisted pelvic floor muscle rehabilitation. *J Reprod Med* 2000;45:798–802.
- 22 Glazer HI, Jantos M, Hartmann EH, Swencionis C. Electromyographic comparisons of the pelvic floor in women with dysesthetic vulvodynia and asymptomatic women. *J Reprod Med* 1998;43:959–62.
- 23 White G, Jantos M, Glazer H. Establishing the diagnosis of vulvar vestibulitis. *J Reprod Med* 1997;42:157–60.
- 24 Reissing ED, Binik YM, Khalifé S, Cohen D, Amsel R. Vaginal spasm, pain and behavior: An empirical investigation of the diagnosis of vaginismus. *Arch Sex Behav* 2004;33:5–17.
- 25 Bergeron S, Binik YM, Khalifé S, Pagidas K, Glazer HI. A randomized comparison of group cognitive-behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. *Pain* 2001;91:297–306.
- 26 Bergeron S, Brown C, Lord MJ, Oala M, Binik YM, Khalifé S. Physical therapy for vulvar vestibulitis syndrome: A retrospective study. *J Sex Marital Ther* 2002;28:183–92.
- 27 Johnson EW. The myth of skeletal muscle spasm. *Am J Phys Med Rehabil* 1989;68:1–2.
- 28 Van der Velde J, Everaerd W. Voluntary control over pelvic floor muscles in women with and without vaginistic reactions. *Int Urogynecol J* 1999;10:230–6.
- 29 Van der Velde J, Everaerd W. The relationship between involuntary pelvic floor muscle activity, muscle awareness and experienced threat in women with and without vaginismus. *Behav Res Ther* 2001;39:395–408.
- 30 Maurice WL. Intercourse difficulties in women: Pain, discomfort and fear. In: Maurice WL, ed. *Sexual medicine in primary care*. Toronto: Mosby; 1999:277–97.
- 31 Heiman JR, Meston CM. Empirically validated treatment for sexual dysfunction. *Ann Rev Sex Res* 1997;8:148–94.
- 32 van de Wiel HBM, Jaspers JPM, Weijmar Schultz WCM, Gal J. Treatment of vaginismus; A review of concepts and treatment modalities. *J Psychosom Obstet Gynecol* 1990;11:1–18.
- 33 O'Donohue W, Dopke CA, Swingen DN. Psychotherapy for female sexual dysfunction: A review. *Clin Psych Rev* 1997;17:537–66.
- 34 Kleinplatz PJ. Sex therapy for vaginismus. A review, critique and humanistic alternative. *J Humanistic Psych* 1998;38:51–81.
- 35 Drenth JJ. Vaginismus and the desire for a child. *J Psychosom Obstet Gynecol* 1988;9:125–37.
- 36 Foster DC. Vulvar disease. *Obstet Gynecol* 2002;100:145–63.
- 37 Holstege G. The emotional motor system in relation to the supraspinal control of micturition and mating behavior. *Behav Brain Res* 1998;92:103–9.
- 38 Blok BFM, Sturms LM, Holstege G. A PET study on cortical and subcortical control of pelvic floor muscles. *J Comp Neurol* 1997;389:535–44.
- 39 Blok BFM, Sturms LM, Holstege G. Brain activation during micturition in women. *Brain* 1998;121:2033–42.
- 40 Silvo S, Ahonen R, Mikander H, Hemminki E. Self-medication with vaginal anti-fungal drugs: Physicians' experiences and women's utilization patterns. *Fam Prac* 2000;17:145–9.
- 41 McKay M. Subsets of vulvodynia. *J Reprod Med* 1988;33:695–8.
- 42 Hansen A, Carr K, Jensen JT. Characteristics and initial diagnoses in women presenting to a referral center for vulvovaginal disorders in 1996–2000. *J Reprod Med* 2002;47:854–60.
- 43 Virgili A, Bacilieri S, Corazza M. Managing vulvar lichen simplex chronicus. *J Reprod Med* 2001;46:343–6.
- 44 Bornstein J, Heifetz S, Kellner Y, Stolar Z, Abramovici H. Clobetasol dipropionate 0.05% versus testosterone propionate 2% topical application for severe vulvar lichen sclerosis. *Am J Obstet Gynecol* 1998;178:80–4.
- 45 Lewis FM. Vulval lichen planus (review). *Br J Dermatol* 1998;138:569–75.
- 46 Paavonen J. Vulvodynia—a complex syndrome of vulvar pain. *Acta Obstet Gynecol Scand* 1995;74:243.
- 47 Denbow ML, Byrne MA. Prevalence, causes and outcome of vulvar pain in a genito-urinary medicine clinic setting. *Int J STD AIDS* 1998;9:88–91.
- 48 Harlow BL, Wise LA, Stewart EG. Prevalence and predictors of chronic lower genital tract discomfort. *Am J Obstet Gynecol* 2001;185:545–50.
- 49 Goetsch MF. Vulvar vestibulitis: Prevalence and historic features in a general gynecologic practice population. *Am J Obstet Gynecol* 1991;164:1609–14.
- 50 Nunn D, Higin SP, Mandal D. National vulvodynia questionnaire. *Int J STD AIDS* 1995;6:366–7.

- 51 Baggish MS, Miklos JR. Vulvar pain syndrome: A review. *Obstet Gynecol Surv* 1995;50:618–27.
- 52 Harlow BL, Stewart EG. A population-based assessment of chronic unexplained vulvar pain: Have we underestimated the prevalence of vulvodynia? *J Am Med Assoc* 2003;285:82–8.
- 53 Pyka RE, Wilkinson EJ, Friedrich EG, Croker BP. The histopathology of vulvar vestibulitis syndrome. *Int J Gynecol Pathol* 1988;7:249–57.
- 54 Chadha S, Gianotten WL, Drogendijk AC, Weijmar Schultz W, Blindeman LA, van der Meijden WI. Histopathologic features of vulvar vestibulitis. *Int J Gynecol Pathol* 1998;17:7–11.
- 55 Foster DC, Hasday JD. Elevated tissue levels of interleukin-1 β and tumor necrosis factor- α in vulvar vestibulitis. *Obstet Gynecol* 1997;89:291–6.
- 56 Gerber S, Bongiovanni AM, Ledger WJ, Witkin SS. Interleukin-1 beta gene polymorphism in women with vulvar vestibulitis syndrome. *Eur J Obstet Gynecol Reprod Biol* 2003;104:74–7.
- 57 Gerber S, Bongiovanni AM, Ledger WJ, Witkin SS. Defective regulation of the proinflammatory immune response in women with vulvar vestibulitis syndrome. *Am J Obstet Gynecol* 2002;186:696–700.
- 58 Jeremias J, Ledger WJ, Witkin SS. Interleukin 1 receptor antagonist gene polymorphism in women with vulvar vestibulitis. *Am J Obstet Gynecol* 2000;182:283–5.
- 59 Robert C, Kupper TS. Inflammatory skin diseases, T cells and immune surveillance. *New Engl J Med* 1999;341:1817–28.
- 60 Bornstein J, Shapiro S, Rahat M, Goldshmid N, Goldik Z, Lahat N, Abramovici H. Polymerase chain reaction search for viral etiology of vulvar vestibulitis syndrome. *Am J Obstet Gynecol* 1996;175:139–44.
- 61 Sjoberg I, Lundqvist EN. Vulvar vestibulitis in the north of Sweden. An epidemiologic case-control study. *J Reprod Med* 1997;42:166–8.
- 62 Wilkinson EJ, Guerrero E, Daniel R, Shah K, Stone IK, Hardt NS, Friedrich EG. Vulvar vestibulitis is rarely associated with human papillomavirus infection types 6, 11, 16 or 18. *Int J Gynecol Pathol* 1993;12:344–9.
- 63 Bazin S, Bouchard C, Brisson J, Morin C, Meisels A, Fortier M. Vulvar vestibulitis syndrome: An exploratory case-control study. *Obstet Gynecol* 1994;83:47–50.
- 64 Sarma AV, Foxman B, Bayirli B, Haefner H, Sobel JD. Epidemiology of vulvar vestibulitis syndrome: An exploratory case-control study. *Sex Transm Infect* 1999;75:320–6.
- 65 Mann MS, Kaufman RH, Brown D Jr, Adam E. Vulvar vestibulitis: Significant clinical variables and treatment outcome. *Obstet Gynecol* 1992;79:122–5.
- 66 Witkin SE, Gerber S, Ledger WJ. Differential characterization of women with vulvar vestibular syndrome. *Am J Obstet Gynecol* 2002;287:589–94.
- 67 Nyirjesy P. Vulvar vestibulitis syndrome: A post-infectious entity? *Curr Infect Dis Rep* 2000;2:531–5.
- 68 Meyer RA, Davis KD, Cohen RH. Mechanically insensitive afferents (MIAs) in cutaneous nerves of the monkey. *Brain Res* 1991;561:252.
- 69 Levine J, Taiwo Y. Inflammatory pain. Textbook of pain, 3rd edition. Edinburgh: Churchill Livingstone; 1994:45.
- 70 Bohm-Starke N, Hilliges M, Falconer C, Rylander E. Neurochemical characterization of the vestibular nerves in women with vulvar vestibulitis syndrome. *Gynecol Obstet Invest* 1999;48:270.
- 71 Bohm-Starke N, Hilliges M, Blomgren B, Falconer C. Increased blood flow and erythema in the posterior vestibular mucosa in vulvar vestibulitis. *Obstet Gynecol* 2001;98:1067–74.
- 72 Ter Kuile MM, Weijenborgh PhTM. Oppervlakke dyspareunie bij de vrouw. In: Hengeveld MW, Brewaeyns A, editors. *Behandelingsstrategieën bij seksuele disfuncties*. Houten: Bohn Stafleu Van Loghum; 2001.
- 73 Carter J, Fowler L, Carlson J, Twigg LB. How accurate is the pelvic examination as compared to transvaginal sonography? A prospective, comparative study. *J Reprod Med* 1994;39:32–4.
- 74 Basson R. Sexuality and sexual disorders. *Clin Updates Women's Health Care* 2003;11:1–94.
- 75 Friedrich EG Jr. Vulvar vestibulitis syndrome. *J Reprod Med* 1987;32:110–5.
- 76 Pukall CF, Payne KA, Binik YM, Khalifé S. Pain measurement in vulvodynia. *J Sex Marital Ther* 2003;29(s):111–20.
- 77 Gianotten WL, Van Lankveld JJ, Weijmar Schultz WCM. Algorithm of management of sexual pain disorders. Presented at ISSWSH, Vancouver, October 12, 2002.
- 78 Haynes RB, Taylor DW, Sackett DL. Compliance in health care. Baltimore, MD: John Hopkins University Press; 1979.
- 79 Bornstein J, Zarfati D, Goldik Z, Godik H, Abramovici H. Vulvar vestibulitis: Physical or psychosexual problem? *Obstet Gynecol* 1999;93(5 Part):876–80.
- 80 Nyirjesy P, Sobel JD, Weitz MV, Leaman DJ, Small MJ, Gelone SP. Cromolyn cream for recalcitrant idiopathic vulvar vestibulitis: Results of a placebo controlled study. *Sex Transm Infect* 2001;77:53–7.
- 81 McKay M. Dysesthetic (“essential”) vulvodynia. *J Reprod Med* 1984;29:457.
- 82 Brotto LA, Basson R, Gehring D. Psychological profiles among women with vulvar vestibulitis syndrome: A chart review. *J Psychosom Obstet Gynecol* 2003;24:195–203.
- 83 Weijmar Schultz WCM, Gianotten WL, Van der Meijden WI, Van de Wiel HBM, Blindeman B, Chada S, Drogendijk AC. Behavioural approach with or without surgical intervention for the vulvar vestibulitis syndrome: A prospective randomized

- and non-randomized study. *J Psychosom Obstet Gynecol* 1996;17:143–8.
- 84 Bergeron S, Binik YM, Khalifé S, Pagidas K, Glazer HI, Meana M, Amsel R. A randomized comparison of group cognitive-behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. *Pain* 2001;91:297–306.
- 85 Haefner HK. Critique of new gynecologic surgical procedures: Surgery for vulvar vestibulitis. *Clin Obstet Gynecol* 2000;45:689–700.
- 86 Bergeron S, Bouchard C, Fortier M, Binik Y, Khalifé S. The surgical treatment of vulvar vestibulitis syndrome a follow-up study. *J Sex Marital Ther* 1997;23:317–25.
- 87 Foster DC, Butts C, Shah KV, Woodruff JD. Long term outcome of perineoplasty for vulvar vestibulitis. *J Women's Health* 1995;4:669–75.
- 88 Goetsch MF. Simplified surgical revision of the vulvar vestibule for vulvar vestibulitis. *Am J Obstet Gynecol* 1996;174:1701–5.