Vulvodynia

A State-of-the-Art Consensus on Definitions, Diagnosis and Management

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Vulvodynia is a prevalent and highly distressing disorder, with major consequences for interpersonal and psychologic well-being. Due to the high level of psychologic distress commonly associated with the disorder, as well as the absence of evidence-based guidelines for clinical practice, a multinational consensus conference on the topic of vulvodynia was convened. The first National Institutes of Health (NIH)–sponsored conference on this topic was held in 1997, shortly after which a program of funded vulvodynia research was initiated. A second NIH meeting was convened in 2003 to present an overview of the science and epidemiology of vulvodynia with a focus on the fundamental mechanisms of this pain disorder. The meeting on which this article is based was held in October 2004 in association with the Third Annual Meeting of the International Society of Women's Sexual Health. The areas that were addressed included the definition of vulvodynia, comorbid conditions, disease progression, diagnosis and workup of the patient with vulvodynia, clinical management and research needs. The overall goals of the conference were to critically assess available data on vulvodynia and related syndromes, to develop a consensus paper on vulvodynia that included recommendations for research (basic and clinical) and to consider future needs of this patient population. (J Reprod Med 2006;51:0000–0000)

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Vulvodynia is a chronic disorder in women, characterized by provoked or constant vulvar pain of

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varying intensity without obvious concomitant clinical pathology. Two subsets of vulvodynia are recognized: generalized and localized pain subtypes, the latter currently referred to as *vestibulodynia* or *vestibulitis*. This condition has been shown to affect 15–20% of women in the United States either currently or previously.[1] As well as vulvar pain there is typically burning and, less often, itching. Pathologic findings include chronic inflammation (thought to be due to up-regulation of local mast cells), proliferation of local pain fibers (indicating up-regulation of the local pain system) and contraction of the levator ani muscle in response to pain (indicating up-regulation of pelvic muscle tone). Despite the high prevalence and significant burden of distress associated with this disorder, few large-scale surveys of vulvodynia have been conducted, and laboratory models of the disorder are lacking.

Several new methods, some validated and others not, have been developed for assessment and measurement of vulvar pain. Most self-report questionnaire methods in use today for assessing sexual function and quality of life (including mood state) and aspects of vulvar pain have been validated. Clinical evaluation currently includes detailed history and careful examination of the vulva and introitus, physiologic testing, general medical examination, laboratory evaluation, and psychologic and sexual assessment. Imaging methods, as well as genetic, immunologic, hormonal, neurogenic, muscular and inflammatory markers also have been employed in vulvar pain assessment, but none have been standardized or widely adopted. Recent multidimensional treatment approaches have been described but await prospective evaluation in well-controlled clinical trials. Although treatment for all medical disorders should be directed, if possible, at the underlying etiology or pathophysiologic processes involved, this is difficult to achieve with vulvodynia in view of the uncertainty of the etiology and the heterogeneity of pathophysiologic mechanisms thought to be involved. Indeed, vulvodynia may be a final result or common pathway for several pathologic processes such that any 1 management strategy may not be adequate for all women with complaints of vulvar pain. Treatment interventions, given sequentially or in combination, have ranged from psychotherapy and behavioral counseling, pharmacologic interventions and pelvic floor physiotherapy to surgical removal of portions of the affected vestibule. Management guidelines have been proposed by specific professional organizations, although these have yet to be broadly adopted.

The meeting was cochaired by Dr. Vivian Pinn (NIH Office of Research on Women's Health [ORWH]) and Dr. Wulf Utian (founding president, North American Menopause Society). Program cochairs were Drs. Gloria Bachmann and Raymond Rosen of the Robert Wood Johnson Medical School (University of Medicine and Dentistry of New Jersey). A multidisciplinary, international faculty representing endocrinology, epidemiology, family medicine, infectious diseases, neurology, obstetrics and gynecology, pathology, pharmacology, psychiatry, psychology, sexual medicine, and urology was convened. Seven funded NIH–National Institute of Child Health and Development (NICHD) investigators presented clinical and basic science data as well as new assessment and treatment models based on their research programs. The conference also brought together representatives from the leading funding agencies (NICHD, ORWH), the National Vulvodynia Association, representatives of the pharmaceutical industry, and investigators from academic and clinical settings working in this area.

For this consensus paper, the panel reviewed the guidelines and publications from professional organizations as well as specific research findings reported at the meeting and in the recent peer-reviewed literature. Our major focus was on topics or concerns considered to be priority areas for future investigation or understanding. The paper does not specifically address clinical guidelines and scientific data that have been previously reported in the literature. Emphasis also was placed on the pressing need for professional and public education in this underrecognized area of women's health.

Section 1: Definition, Comorbid Conditions and Disease Progression

Definitions of generalized and localized vulvodynia have varied widely. Vulvodynia (derived from the Latin *vulva* and Greek *odynia,* or pain) is a descriptive term referring to chronic pain in the vulvar area of at least 3–6 months' duration. The condition was not officially recognized until 1880, was overlooked for more than 80 years and then resurfaced in gynecologic texts in the 1980s. The working definition for the consensus panel was chronic pain lasting from 3 to 6 months in the vulvar region without a definable cause.

Vulvodynia may be chronic or unremitting, inter-

mittent or episodic (often exacerbated premenstrually) or may occur only in response to a touch stimulus, including tight clothing or physical stimulation in the vulvar area (such as with coitus or pelvic examination). The sensation of pain from a touch stimulus is termed *allodynia*. Physical signs of vulvodynia are limited to variable erythema of the vestibule, although this finding has been found to lack reliability and interrater consistency.[2] The condition of vestibulodynia (vulvar vestibulitis [VVS]), considered a subtype of vulvodynia, is defined as chronic pain in the vestibule associated with allodynia of the introital margin (outer edge of hymen and inner edge of inner surface of labia minora), often extending to the openings of the Skene ducts on each side of the urethra. There was a lack of agreement as to whether vestibular allodynia without ongoing chronic vulvar pain represents a medical entity different from vulvodynia.[3] Other recognized medical disorders with a possible chronic vulvar pain component include vulvovaginal *Candida* infections, endometriosis, nonneoplastic epithelial conditions and neoplasms, contact dermatitis, hypoestrogenic and hypoandrogenic atrophy, neurologic etiologies (pudendal nerve entrapment syndrome), referred pain from myalgic muscles (levator ani), iatrogenic conditions (painful outcome after perineal surgery, such as episiorraphy and hemorroidectomy) and pelvic/perineal radiotherapy. However, these conditions do not fit the classification of vulvodynia since they have a concomitant clinical pathology

The panel had several recommendations regarding definition, comorbid conditions and disease progression.

1. Standardize the Definition

Currently, multiple terms are used to describe this condition. The terminology is ambiguous and potentially confusing for clinicians as well as patients. A diagnostic terminology needs to be developed and adopted by specialty societies, such as the American College of Obstetricians and Gynecologists, the Sexual Medicine Society of North America, the International Society for the Study of Vulvovaginal Disease (ISSVD), the North American Menopause Society and the International Association for the Study of Pain, so that clinicians who treat women with this condition can communicate reliably and accurately regarding their findings and diagnoses. Terminology developed recently by the ISSVD recommends classification into subtypes of generalized vs. localized and provoked vs. unprovoked vulvodynia.[4] This recommendation raises further questions regarding whether vulvar pain that is localized to 1 trigger point should be diagnosed as distinct from generalized vulvar pain. Another concern raised by the panel was whether women with referred pain that involves other areas of the body in addition to the vulvar-vaginal area should receive the same diagnosis as women with pain confined only to the vulva.

The panel noted that subtyping and diagnostic classification of vulvodynia have not been standardized, nor are they evidence based. Not all panelists endorsed the need for such subtyping. The panel proposed that the definition of vulvodynia, as one of the chronic urogenital pain syndromes, be limited to pain located in the vulvar area of at least 3–6 months' duration without another definable cause. Descriptors such as "generalized or localized" should be used, together with an accurate pain map, which describes the site and the intensity of pain by the woman's history and elicitation of symptoms by the woman's report during pelvic examination. The use of other terms to define and subtype underlying conditions may not be warranted.

Other urogenital pain syndromes that should be considered before the diagnosis of vulvodynia is made include urethral syndrome, interstitial cystitis and coccygodynia.[5] The terminology used to describe these other urogenital pain syndromes is currently under review by several specialty societies. In the future, it may be necessary to coordinate the diagnostic terminology used for chronic pain conditions since the etiology and pathophysiology of these syndromes may be similar. Regardless of the etiology and characterization, the panel viewed vulvodynia, similar to headache, as a legitimate medical entity, with a spectrum of etiologies and clinical presentations.

2. Characterize the Pain Precisely

Nomenclature describing the type and intensity of pain and the chronicity and impact of symptoms should be standardized. Pain modifiers, such as the degree and characterization of the pain (burning, pressure, throbbing, etc.), also should be included in the description. The panel questioned whether variations in pain severity or by location be considered different symptoms or (in the future) distinct subtypes of vulvodynia.

The issue of whether vulvodynia reflects pelvic floor dysfunction with trigger points of pain or

whether it is a form of referred pain or a result of dysfunctional nerve fibers in the pelvis also was raised. Any pain "locally" perceived in any region of the body can be: (1) elicited by any agonist factor, causing local damage and inflammation (chemical, physical, infectious, degenerative, endocrine, etc.); (2) referred (like the nondermatomic referred pain from myalgic muscles); (3) mediated via antidromic neurotransmission along sensory nerves leading to neurogenic degranulation of mast cells with further antegrade stimulation from mast cell chemicals, including histamine, tryptase and bradykinin; (4) referred from damaged afferent nerves (in the vulva, pudendal neuralgia); and (5) resulting from central sensitization of dorsal horn cells from altered descending inhibitory and/or excitatory input from the brain.

3. Encourage Universal Recognition of the Term Vulvodynia

A major effort should focus on better recognition of the term *vulvodynia*, especially by the lay public; that would ultimately translate into improved identification of the condition by health care providers. A distressing aspect of vulvodynia is that women with this condition frequently report that they have experienced the pain for many months, usually years, before a diagnosis is made. Others are told that their symptoms are "all in their head." This implies to the woman that somehow her pain is not real. Failing to make the diagnosis of vulvodynia and to explain the current understanding of this condition may contribute in some instances to interpersonal distress and lack of family support for the woman. Missing the diagnosis also may preclude access to the more specialized medical care often needed for this condition. Because the terminology is not widely recognized, many women with this condition are unaware of such terms as *vulvodynia* and *vestibulodynia* and may erroneously self-label themselves with an inaccurate diagnosis. Working with professional societies and public organizations that care for women is necessary and could serve as a means of promoting and encouraging clinical trial work and educational programs and projects.

4. Identify Comorbid Conditions and Risk Factors for Vulvodynia

Multiple pathologies may initiate or exacerbate symptoms, or may share common pathogenic factors with vulvodynia. Irritable bowel syndrome and interstitial cystitis, for example, have been suggested as comorbidities or risk factors.[6] However, it is not certain which comorbidities or contributing factors are directly related to vulvodynia, and research on the nature and importance of comorbid conditions/risk factors is needed. For example, recent data suggest that age at first use of hormonal contraception and early difficulty with tampon use (suggestive of a primary hyperactive pelvic floor) may be independent predictors of vulnerability to vulvodynia and dyspareunia.[1] Additionally, other reports suggest that the lower levels of ethinyl estradiol in some hormonal contraceptives might contribute to vaginal dryness and dyspareunia, which increase the probability of pain.[7] The condition may also be iatrogenic in some instances, such as associated with overzealous and chronic use of topical vulvar preparations.

5. Investigate the Biologic Mechanisms Involved

Many biologic mechanisms are being actively investigated, including inflammatory and infectious disease processes,[8,9] as well as the role of neurologic[10] and genetic factors.[11] Stress factors, either internal or external, may increase vulnerability, either directly, by altering the immune, neurologic and hormonal systems, or indirectly, through increased use of caffeine, nicotine or other lifestyle behaviors.[12]

6. Clarify Antecedent and Subsequent Sexual Dysfunction

The role of sexual dysfunction as a symptom or correlate of vulvodynia has been insufficiently studied.[13] It is not clear whether serious sexual or psychologic factors increase a woman's risk for vulvodynia or whether these problems more commonly are a consequence of chronic vulvar pain and the resulting disruption of sexual activity.

7. Establish the Natural Progression of Vulvodynia

Scant information is available regarding the natural history and progression of vulvodynia, with or without medical intervention. Predisposing, precipitating and maintaining factors, biologic, psychosexual and context dependent, should be carefully identified/diagnosed and addressed.[14] Furthermore, the proportion of women with vulvodynia who are diagnosed in a timely manner is unknown. How many clinicians women typically consult before accurate diagnosis and assistance and factors associated with an increased likelihood of obtaining a cor-

rect diagnosis are also unclear. An average delay of over 4 years has been reported between the onset of symptoms and the appropriate diagnosis of VVS.[15] Two studies of women nonselected for symptoms indicated that as many as half of those with probable vulvodynia by history no longer have the symptoms, suggesting transience, previously unrecognized[1,16]

Section 2. Diagnosis and Workup

Although references to genital pain appear as far back as antiquity, it was not until 1977 that Friedrich and Dodson proposed guidelines for diagnosing vulvodynia.[17] These authors stated that women with this condition typically refrain from intercourse, have emotional lability, and are reluctant to acknowledge a psychologic component to their condition. Ten years later, specific diagnostic criteria for VVS, variable vulvar erythema (as the sole physical finding), pain on vestibular touch or vaginal entry, and tenderness upon localized vestibular pressure, were proposed by Friedrich.[18] The evaluation and diagnosis of vulvodynia have minimally advanced over the ensuing 2 decades, as diagnosis of the condition remains largely one of exclusion. In addition to clarity regarding definition and comorbid risk factors, criteria for a standardized workup are needed.

Clinicians commonly suspect the diagnosis of vulvodynia after treatment for vulvovaginal inflammatory and infectious etiologies have failed. At the point of failure with treatment for other etiologies, aside from eliciting a history of pain, performing a pelvic examination, and, in some instances, a vaginal wet prep and culture, it appears that few clinicians perform a careful vulvar examination, including pain mapping of the vestibule. Moreover, a thorough "pain map" recording should include the perineal area and inner thighs in addition to the vulva. Bilateral tenderness and trigger points at the insertion of the levator ani on the spine, suggestive of a referred myalgic component of the vulvar pain and of a key contributor to the associated dyspareunia, should be elicited. This finding suggests the possibility of a referred component of vulvar pain and the importance of a routine examination of pelvic floor tone. Spontaneous or elicited pain in the lower third of the anterior vaginal wall also should be part of the pelvic examination, as it may be associated with bladder-related comorbidities (cystalgia, urethralgia, postcoital cystitis, interstitial cystitis) reported in up to one third of vulvodynia patients.[5]

The standard method of vulvar pain mapping is by the use of a cotton-tipped applicator. Systematically, pressure is applied to the various parts of the vulva to assess the extent and character of the pain and to quantify at what exertion of pressure applied by the examiner the pain is provoked.[19] The woman typically rates the sensation on a nominal pain scale, such as 1 (minimal pain) to 3 (mild pain) to 5 (maximum pain). However, this test has limited utility since the outcome depends upon both the clinician's skill and consistency and the patient's subjective rating of the pain. To help standardize the pressure evoking pain, use of an algesiometer or vulvagesiometer, which allows more precise measurement of pressure exerted on the vulva, has been proposed by several investigators.[20,21]

Aside from pain measurement on the vulva, a simple set of questions, such as, "*Where* do you feel pain?" (helping to record the most accurate pain map), "*When* do you feel pain?" (to differentiate spontaneous from provoked vulvodynia), "What are your thoughts when you feel the pain?" and "What are the associated problems or symptoms you experience?" may aid the clinician in assessing the pain and the woman's reaction to it. These questions also may help the clinician to substantiate the nature of the woman's pain complaint, as well as affirming the woman's subjective assessment of her condition. The latter objective may be especially important for both the woman herself *and* for the couple, particularly in cases in which there has been an inaccurate assessment of the vulvodynia complaint for months or years.

The panel had several recommendations regarding assessment.

1. Specific Education on the Diagnosis and Treatment of Vulvodynia Should Be Offered During Medical School and Residency Training Programs That Focus on Women's Health

The panel thought that clinicians who care for women should have directed training in assessment of vulvodynia so that diagnosis is not delayed. Many women erroneously are told that they have infectious vaginitis, which may or may not be present, and are treated for extended periods of time with unnecessary and ineffective medications.

2. Evidence-Based Guidelines for Assessment Should Be Developed

A standardized medical assessment, including past

and current medical, sexual, psychologic, psychiatric and surgical issues, as well as a detailed, structured physical examination, should be developed. Certain questions appear to be helpful in making the diagnosis, such as the ability to use tampons or wearing tight undergarments or trousers without discomfort. Vulvar burning after intercourse attempts, the presence of postcoital dysuria and vulvar burning from a male partner's ejaculate are typical symptoms that may be elicited from women with vulvodynia.

Standard pelvic examination guidelines for evaluation of women with chronic vulvar pain are not available. Protocols outlining how the genitalia and pelvic floor are optimally assessed should be developed. The need for colposcopy, vulvoscopy,[22] wet prep of vaginal secretions, vaginal culture, yeast subtyping, bacterial markers, pH evaluation and cytologic markers should be determined in diagnosing vulvodynia and following the response to treatment.[23] Clinical advantages of vulvalgesiometer assessment vs. cotton swab testing, use of graphic representation or a picture chart to map areas of allodynia and pain threshold testing should be investigated. Any role of comprehensive neurologic evaluation or immune function assessment also needs evaluating.

Some panelists thought that for study purposes a vestibular biopsy was useful in understanding the subtype of vulvodynia since an inflammatory component with up-regulation of mast cells has been histologically documented with immunotryptase staining.[8] Biopsy also has been reported to demonstrate the proliferation (up to 10 times) and more superficial location of pain fibers in vestibular specimens of VVS patients.[8,10] This proliferation, probably induced by the nerve growth factor nerve growth factor (NGF), produced by the up-regulated mast cells and superficial location of pain fibers, may be responsible for the hyperalgesia and allodynia, respectively.[11] These histologic findings support the hypothesis that VVS is an expression of hyperregulation of local immune and pain systems that may be induced in susceptible individuals by a variety of etiologies. Performing biopsies may help to differentiate women with an inflammatory (not necessarily infectious) etiology of pain from others with a different pathophysiology (such as neurogenic), although current criteria for this are lacking.

Section 3: Clinical Management of Vulvodynia

As with any medical intervention, a clear understanding of the woman's goals of management, along with those of her partner, is necessary. Treatment goals may include the wish to regain or restore a rewarding sexual life; to increase the understanding of chronic or intermittent pain, including the mind-body connection and role of various medications; to reduce self-generated stress; to deal more effectively with external stress; and to experience a reduction and eventually elimination of pain.

The panel reviewed several treatment studies and recent management guidelines. No standardized, evidence-based treatment guidelines or algorithms are available since clinical trials have not been performed to allow evidence-based guidelines. Current interventions include systemically administered drugs, such as tricyclic antidepressants[24,25]; selective seritonin reuptake inhibitors[26] and anticonvulsants[27]; venlafaxine; and duloxetine. Topical applications used by others include corticosteroids,[28] estrogen,[29] antiinflammatories (e.g., cromolyn), and anesthetics (such as lidocaine).[30] Dietary approaches include reduced oxalate,[31] and vitamin and mineral supplements. Physical therapy suggestions include pelvic floor manipulation,[32] electromyographic biofeedback,[33] local applications of ice packs and sitz baths, and electroanalgesia or antalgic block of the ganglion impar.[34] Excisional vestibular surgery is an additional modality advocated in some centers for localized vulvodynia after other treatments have failed.[35,36] All currently used interventions have limited data objectively measuring safety and efficacy. A comprehensive vulvodynia guideline with an algorithm included was published by Haefner et al in January 2005.[37]

As "best clinical practices" guidelines are developed from clinical trial data, a treatment protocol should be prepared to include state-of-the-art recommendations for clinicians as well as practice guidelines. The panel concurred on the need for evidence-based, "stepped care" guidelines for clinical management of vulvodynia. As the etiology and pathophysiology of the disorder is further elucidated (including the roles of potential genetic, endocrine, psychologic and immune aspects), future guidelines may be tailored more to the individual woman's needs.

The panel had several recommendations regarding management:

1. Commence Well-Designed, Prospective, Multicenter Trials

These trials should include comprehensive med-

ical—including genetic, immune and infectious—evaluation of all subjects along with comprehensive assessment of psychosexual and mental health. It might then be possible to investigate which subsets of women are most likely to benefit from specific and combined interventions (e.g., diet, pharmacologic therapy, self-management). Self-management interventions include diet and lifestyle changes, in addition to stress management, self pelvic floor massage and sex therapy interventions. Either single agents or a combination of 2 pharmacologic interventions or 1 pharmacologic intervention paired with self-management intervention should be systematically studied. Additionally, trials may clarify which women are likely to benefit from the various treatment options. Evidence-based guidelines to measure treatment outcomes for medical and surgical intervention need to be established. Procurement of long-term efficacy and outcome data also should be encouraged for treatment effects, especially from surgical interventions. Recommended treatments should ideally be based on results of well-controlled, randomized, clinical trials and subject subgroup analysis. In the interim, further study of the individual treatments used, reported side effects, and effects on pain and other outcomes should be conducted and published.

In addition to traditional interventions, the role of alternative therapies warrants further investigation. These include, but are not limited to, the role of wicking underwear, mineral oil products, olive oil, organic sanitary pads, physical therapy, dietary restrictions, special seats for such activities as bicycle riding, acupuncture, tai chi, aromatherapy, hypnosis, herbal medications and self-management interventions. Additionally, studies are needed to assess the role of complementary interventions when used prior to, or in conjunction with, pharmacologic or surgical interventions.

2. Standardize Dosing Requirements for Pharmacologic Interventions

Ideally, a management manual for clinicians should be developed in cooperation with 1 or several professional societies, with recommendations based on clinical trial data. When pharmacologic therapies are employed, not only should the actual chemical class of the intervention be evaluated, but also the dosage of medication, duration of treatment, use of other interventions simultaneously and adverse events/worsening of symptoms experienced by the woman should be recorded.

3. Address Sexual Issues

A frequent and often debilitating correlate of the disorder is sexual dysfunction. The impact of vulvodynia and related sexual dysfunction on the woman's relationship is an important area that needs to be addressed. In addition to management interventions, recommendations as to when the couple needs to be referred to a specialist are needed, as are criteria that characterize a specialist as appropriate for such a referral.

Section 4: Expand Vulvodynia Research

With 8–15% of women in the United States experiencing chronic vulvar pain at some point in their adult lives and only 70% of whom typically consult a clinician, there is a need to add more well-controlled, epidemiologic studies or clinical trials directed toward this medical condition.[1] Because of the scant data available, basic questions, such as incidence and etiology, are not accurately known.

Limited investigation of the disorder may be attributed to 3 factors: first, the condition was unrecognized for years; second, there has been a lack of consensus on terminology and diagnosis of the condition in the medical literature; and third, many clinicians do not recognize vulvodynia as a legitimate medical disorder in women. Therefore, funding for vulvodynia research has been virtually nonexistent until recently.

In 1998 the NIH recognized the need for research in this field and issued an invitation for grant applications to study the prevalence, pathology, diagnosis and treatment of vulvodynia Since that time, investigators at 7 academic institutions have been awarded funding to examine the epidemiologic, pathologic, and treatment aspects of vulvodynia: University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School (epidemiology, therapeutic interventions), Harvard University (epidemiologic studies), Yale University (cognitive behavior therapy), University of Rochester (lidocaine and desipramine clinical trials), University of Michigan (neuroimmunology and sensory processing), Johns Hopkins University (pathophysiologic mechanisms) and University of Iowa (bowel and bladder comorbidity).

Current ongoing basic research is suggesting that certain genetic variations are associated with specific subsets of women with VVS, with clusters of these genetic variations expressed differently among races and ethnicities. For example, data suggest that American and Swedish VVS patients have

a higher rate of carrying a variant of the mannose binding lectin (MBL) gene than do controls.[38] An increased susceptibility to candidal infection of the genital tract and a reduced capacity to inhibit proliferation of *Candida* as well as bacteria and viruses are associated with carriage of this MBL variant. Witkin's data show that women with VVS had an increased prevalence of specific polymorphisms in genes coding for the interleukin-1 receptor antagonist (IL-1ra) and interleukin-1β (IL-1β) as compared to control, and that these variations are associated with susceptibility to inflammation and prolong the proinflammatory response.[9] Both these findings imply that specific subsets of women with VVS are genetically more susceptible to vulvovaginal infection and/or inflammation and may respond with an exaggerated inflammatory reaction. Foster's data complement these findings by reporting that genetic polymorphisms of the melanocortin-1 receptor (MC1r) and IL-1ra may interact to enhance the inflammatory and pain response in VVS.[11] In 36 VVS patients and 69 pain-free controls studied, the combined presence of the allele 2 IL-1ra gene polymorphism and at least 1 of 6 MC1r polymorphisms resulted in an 8-fold additive risk of having VVS. Based on the MCIr polymorphisms, women with light skin and red hair have an increased risk of VVS. Melanocortin analogues may have potential preventive and treatment indications in the future. Reed also presented data supporting immunologic alterations in women with VVS at the proceedings. Fifty-two VVS subjects had increased levels of stimulated NGF when compared to 54 matched controls. This finding might explain the increased branching of distal nerve fibers noted in women with VVS.

Findings from these studies support the need for basic research in helping to identify genetic, immunologic and infectious variations that influence susceptibility to vulvodynia in as yet undefined subsets of women.

Several specific issues were explored by the panel. Vulvodynia's role in predisposing to sexual dysfunction was highlighted. An important question is whether dyspareunia is a core symptom that can precede, be concomitant with or be consequent to vulvodynia. Also, does the identification of primary, life-long sexual dysfunction associated with vulvodynia identify a subset of women/couples requiring specific psychosexual support?

The role of cofactors, such as a primary hyperactive pelvic floor (alerting symptom, difficulty with tampon use), and/or fear of penetration and a more general "risk adverse" attitude towards "risks" of sexual behavior (such as early use of hormonal contraception) also should be explored. Regarding hormonal contraception, do women reporting vaginal dryness during low-dose oral contraception use have increased vulnerability to vulvodynia? In this regard, do early interventions (such as teaching a woman how to relax the pelvic floor)[14] and/or use of hormonal contraception with higher ethinyl estradiol content (30 μg)[7] reduce the vulnerability to dyspareunia and vulvodynia?

Since many women may go through several treatment cycles with an antiinfectious agent, data have to be generated on the effects of repeated antibiotic and antifungal courses of treatment (especially in the subset of women reporting comorbidity with recurrent cystitis/irritative bladder symptoms). Recurrent *Candida* infection appears to be an indicator of vulvodynia (past positive swabs for *Candida* in 58.1% of vulvodynia patients versus 5–8% prevalence in the general population).[39]

Last, what are the common pathophysiologic pathways behind medical comorbidities that appear to be more prevalent in women with vulvodynia?

The panel had several recommendations regarding future research:

1. Investigate the Biologic and Genetic Basis of Vulvodynia

Investigation is needed into the biologic and genetic basis of vulvodynia. There may be genetic linkages with other well-known pain disorders in women (e.g., fibromyalgia), and further research in this area may help to elucidate the pathophysiology of the disorder.

2. Increase the Number of Clinical Trials

Multicenter, randomized clinical trials with defined outcomes, using assessment instruments with reproducible outcome measures of outcome, should be conducted. Randomized clinical trials and observational studies should address the role of nonpharmacologic or self-management approaches as well as medical and surgical interventions for vulvodynia. Multicenter trials are feasible to perform on this topic, given the presence of approximately 20 clinical sites in North America that have participated in clinical studies and have clinical and/or research expertise in this area. In addition, the immunologic, genetic or other biochemical markers in

women with vulvodynia should be further studied and correlated to treatment response. Also advocated are qualitative studies (e.g., focus groups, surveys) to obtain clinical impressions and subjective data, with an emphasis on how subjective data can be combined with objective, or laboratory-based, results.

3. Establish a Vulvodynia Registry

Outcome data from multicenter, randomized, clinical trials or long-term registry studies are needed. A registry study should be developed that includes baseline and follow-up data from multiple practice settings. Such a registry study might evaluate outcomes associated with first- and second-line interventions, long-term care and education and prevention initiatives along with the progression and natural history of the condition.

4. Establish a National Vulvodynia Referral Network

Establishment of a national vulvodynia referral network that makes referrals to individuals who are using set protocols, pooling their outcome data and working with health insurance agencies, is advocated. Many women are challenged trying to find health care providers familiar with the diagnosis and treatment of vulvodynia. A national (ideally, at some point, international) registry of health care providers interested in treating this patient population is needed who are willing to monitor response to interventions, collect outcomes and pool data, especially to follow vulvodynia longitudinally and prospectively.

Section 5: Conclusion

Vulvodynia is a poorly defined and understudied problem in women. In particular, evidence-based guidelines are needed to define, diagnose and treat this common disorder. Specific issues to be addressed include standardization of definition, requirements for diagnosis and selection of outcome measures for clinical and research use.

The number of RFAs for collaborative research projects with strict criteria for inclusion criteria should be increased. These should ideally focus on the etiology, pathophysiologic mechanisms, risk factors and comorbidities associated with vulvodynia. Treatment interventions should also be systematically evaluated in randomized, prospective clinical trials, particularly multicenter trials, when possible. Vulvodynia studies should be designed to determine the predictors of clinical course or response to treatment and answer questions of whether genetic, epidemiologic, infectious, hyperactivity of the pelvic floor and psychosocial factors are predictive of outcome.

It is anticipated that significant advances will occur in the next several years as the results of ongoing studies become available and greater clinical experience with the disorder is developed. Hopefully these studies will not only provide some immediate answers to management questions but outline the direction of future basic and clinical research in this area.

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