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Recent Advances in Understanding Provoked Vestibulodynia

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Vulvodynia is defined as pain in the vulva of at least three months duration in the absence of a verifiable underlying cause. Localized provoked vestibulodynia, superficial pain in the vulvar vestibule provoked by touch, is the most common subset of vulvodynia. This review will focus on provoked vestibulodynia with regard to proposed causative factors and will discuss the role of inflammation, vulvovaginal infection, mucosal nerve fiber proliferation, hormonal associations, central pain mechanisms, pelvic floor muscle dysfunction, and genetic factors.

Clinical observations, epidemiological studies, and data from basic research emphasize the heterogeneity of vulvar pain syndromes. There is a critical need to perform prospective longitudinal studies to establish better diagnosis and subgroup criteria, because it will lead to improved understanding and treatment of women with provoked vestibulodynia.

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Pelvic Floor Assessment in Women with Vulvodynia

By Stephanie Prendergast, M.P.T.

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There is consensus among vulvodynia specialists that each case of vulvodynia is unique and benefits most from a range of treatments based on a woman's symptoms and clinical findings. Although each case is unique, pelvic floor muscle dysfunction (PFMD) is a common feature that contributes to vulvar pain and functional limitations.

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Introduction

Vulvodynia, a diagnosis of exclusion, consists of various clinical features. Some women with this diagnosis experience continuous, diffuse vulvar pain (generalized, unprovoked vulvodynia), while others have provoked localized pain. The current nomenclature uses a symptom-based classification to characterize the pain with regard to (i) its location (localized, generalized, or mixed), (ii) the conditions that provoke it (contact, spontaneous, or mixed), (iii) its temporal pattern (intermittent or constant), and (iv) its onset (primary or secondary).

The vulvar pain syndrome known as localized provoked vestibulodynia (PVD) is the term used to describe pain confined to the vulvar vestibule that is provoked by touch or pressure. Some researchers suspect that PVD and generalized unprovoked vulvodynia may represent a continuum of the same condition. However, owing to the different clinical presentations, this article will focus only on PVD. In some women, vestibular pain can be caused by minimal touch, e.g., by sitting or wearing tight-fitting pants. In others, it is provoked only by vaginal penetration during sexual intercourse, tampon insertion, and/or gynecological examination, resulting in painful sexual intercourse or inability to engage in intercourse.

Some women have primary PVD, experiencing pain at first introital touch, while others describe a period of pain-free vaginal penetration before the onset of symptoms, termed secondary PVD. The pain is often described as a burning or cutting sensation and may be located throughout the vestibule or confined to the lower vestibule. Erythema (redness) may or may not be observed and is no longer considered a defining criterion.

No single causative factor of PVD has yet been identified and its etiology is considered multifactorial. The current accepted theory is that PVD represents a diverse group of disorders causing similar symptoms. The clinical diagnosis of PVD is made after other vulvovaginal disorders, such as infection or dermatosis, are ruled out. The main symptoms are entry dyspareunia (pain at introitus) and vestibular tenderness to gentle touch. Current treatment strategies follow a *trial-and-error* approach, guided mainly by expert opinion and strategies used in other pain disorders, rather than by an evidence-based approach based on randomized clinical trials.

Much effort has been made to find pathophysiological changes characteristic of PVD. Researchers have identified a range of abnormalities in different systems (vestibular mucosa, pelvic floor musculature, and peripheral and central pain regulation), as well as in different pathways (inflammatory, hormonal, and

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genetic). This review will focus on our current understanding of the proposed etiologies of PVD.

Peripheral Pain Mechanisms

Hypersensitivity of the vulvar vestibule is one of the defining characteristics of PVD. Quantitative sensory testing of the vestibular mucosa in PVD patients indicates peripheral sensitization to both mechanical and thermal stimuli. One hypothesis is that biochemical changes modify nerve fiber conduction, thereby lowering the threshold in nociceptors (pain receptors). Another proposed mechanism is hyperinnervation (increased nerve fiber density) of the vestibular mucosa, which was first described by Weström and Willén (1998) and confirmed by several others. Immunohistochemical methods determined that these nerve endings are nociceptors. This hyperinnervation, termed 'neuroproliferation,' corresponds to heightened mechanical allodynia (pain from light touch) and hyperalgesia (an increase in pain perception). These sensory changes can be either congenital or acquired.

Primary, Secondary, Acquired, and Congenital Neuroproliferative PVD

A study by Leclair (2011) showed that patients with primary provoked vestibulodynia have significantly greater neural hypertrophy than those with secondary vestibulodynia. This finding supports the hypothesis that primary and secondary PVD may have distinct histopathologic pathways rather than representing different stages of the same disorder.

It is possible that primary PVD may be congenital, or that hypersensitivity of the mucosa may be acquired in early life, initially being recognized in adolescence. A correlation between early life adverse events and PVD in adults has been found in case-control studies and was attributed to dysfunctional regulation of the hypothalamic–pituitary–adrenal axis. Recent studies of animal models found evidence that early life stress in mice induced increased vaginal sensitivity and that chemical vaginal irritation in newborn animals led to permanent vaginal hypersensitivity.

It has also been suggested that PVD may be congenital in some women. Embryologically, the vestibule is of endodermal origin, derived from the urogenital sinus, and neuroproliferation may represent a congenital anomaly (abnormality). In such cases, the neural hypersensitivity is primary and may also be present in other tissues derived from the urogenital sinus. This may explain the coexistence of PVD and interstitial cystitis in some women, as well as the significantly higher level of umbilical sensitivity in women with primary PVD. Acquired PVD has also been attributed to neural proliferation in response to endocrine factors or inflammatory processes. (See Inflammatory Mechanisms.)

The significance of this increase in nociceptors is controversial; some researchers consider neuroproliferation to be a non-specific reaction to previous mucosal trauma or inflammation and attribute the increased pain perception to neurogenic inflammation. In addition, and in contrast to what one might expect, it is well-accepted that reduced, and not increased, intraepidermal nerve fiber density is associated with an elevated risk of developing neuropathic pain. However, an additional observation supporting the contribution of peripheral pain mechanisms to PVD is that 80 percent of patients undergoing vestibulectomy, in which the hyperinnervated region is removed, experience symptomatic relief. However, it is important to recognize (i) the lack of randomized trials and (ii) the variation in outcome criteria in studies evaluating the efficacy of vestibulectomy.

Inflammatory Mechanisms and Infections

PVD was initially regarded as a chronic local inflammatory condition and was, therefore, called 'vulvar vestibulitis syndrome.' In vulvar biopsies obtained from PVD patients, it is common to see an increase in inflammatory cells, mainly T lymphocytes. This is often

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referred to as non-specific chronic inflammation. Later studies, however, found similar inflammation in the vestibules of non-affected women. Consequently, the initial inflammatory theory has been abandoned and PVD is mainly regarded as a pain syndrome.

Nevertheless, multiple studies propose that inflammation may play a role in the development of PVD. These researchers hypothesize that persistent inflammation in the vestibular mucosa promotes hypersensitivity of nociceptive c-fibers (secondary to the production of nerve growth factor), altered receptor expression, and persistent elevation of pro-inflammatory substances. Consequently, even light touch can result in exaggerated release of pro-inflammatory mediators by sensitized nerve fibers. This, in turn, activates neuroendocrine cells and mast cells to release additional pro-inflammatory substances. This self-perpetuating process of neurogenic inflammation is thought to play a key role in the maintenance of local inflammation in PVD.

Studies that have evaluated inflammatory characteristics in PVD have, however, found contradictory results. In some histological studies, mast-cell-predominant inflammation was demonstrated, while others reported inflammation without mast cell predominance.

Analysis of pro-inflammatory molecules in vulvovaginal samples has also shown inconsistent results. Some studies report an elevation in the pro-inflammatory cytokines, interleukin (IL)-1b and tumor necrosis factor (TNF)-α, and increased levels of the nerve growth factor, neurokine CGRP. Others found lower levels of TNF-α and similar levels of IL-1b among patients and controls. Levels of systemic interferon, IFN-α and IFN-γ, were similar in PVD patients and controls. Although some research disputes cell-mediated inflammation, Doppler perfusion imaging showed increased superficial blood flow in the mucosa, further supporting the neurogenic inflammation theory. A recent systematic review by Chalmers (2016) highlights the lack of a consistent inflammatory profile in PVD patients.

Vulvovaginal infections are often noted as an inciting inflammatory event that triggers the development of PVD. These patients often report a history of recurrent vulvovaginal Candida (RVVC) and connect the onset of their symptoms to vaginal yeast infections. Whether this represents an accurate association or is mainly a misinterpretation of patients' symptoms is unclear, as the history of RVVC has often been based on self-report and not confirmed by culture. Nevertheless, various studies described findings associated with a possible deficient immune response that results in RVVC and subsequent development of PVD. It has been proposed that an inability to clear vulvovaginal infections, and the resulting chronic inflammation, may lead to PVD development.

Interestingly, circulating natural 'killer cells,' a predominant factor in vaginal defense against Candida infection, are significantly lower in PVD patients. Other observations suggest a possible genetic variability causing a predisposition to RVVC. Additionally, an increased cutaneous hypersensitivity to *Candida albicans* organisms was reported in women with PVD. In an RVVC mouse model, chronic vulvar pain and increased vulvar innervations were also observed.

Foster (2007, 2015) reported that vulvar fibroblasts (active cells in connective tissue) produce high levels of pro-inflammatory substances IL-6 and IL-8, and prostaglandin E2, following stimulation by irritants in both women with PVD and controls. Vestibular fibroblasts released elevated levels of IL-6 and prostaglandin E2 compared to fibroblasts isolated from non-painful vulvar sites. Furthermore, pro-inflammatory mediator production was elevated in PVD fibroblasts compared with those of controls. Similar findings were reported when fibroblasts were injected with live yeast. Certain yeast strains led to particularly high IL-6 and prostaglandin E2 levels. Pain thresholds could, therefore, be predicted based on the type of yeast with which the patient was infected. The authors concluded that

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vulvar tissue of women with and without PVD can be differentiated by the degree of naturally occurring inflammation. They proposed that the vestibule of PVD patients is inherently more sensitive to yeast and that even a subclinical infection can trigger a maladaptive immune response in these fibroblasts.

In summary, our understanding of inflammation as a possible contributing factor to PVD development continues to evolve. Recent studies have revisited this potential origin, suggesting that inflammation is likely to play a role in provoked vestibulodynia.

Hormonal Factors

Epidemiological studies have investigated a possible correlation between hormonal contraception preparations (HCs) and PVD. Several researchers have reported that HCs increase the risk of developing secondary PVD. Results showed increased risk of PVD for ever-users of HCs compared to non-users, rising with increased duration of use and first use at a young age (<16 years). The relative risk was higher when the product used had low levels of estrogen, plus progesterone and androgens. The use of low-estrogen HCs was significantly more common in women with PVD than in the general population of HC users. Burrows and Goldstein (2013) described a case series of 50 women who developed PVD while on HCs and were successfully treated with topical estradiol and testosterone. This finding, however, was not confirmed in two epidemiologic studies.

The effect of HCs on vestibular mucosa is likely multifactorial. HCs modify the structural pattern of the vestibular mucosa, with the appearance of shallow and sparse dermal papillae (bumps). This effect may contribute to the decreased mechanical pain thresholds reported in non-affected women using HCs. These alterations may influence mechanical properties by thinning the epithelium and causing nerve endings to become more superficially located, thus altering the transduction of mechanical pressure to the receptors without affecting nerve fibers.

HCs can also affect the vestibular epithelium through interaction with hormone receptors or alteration of receptor expression. Results from studies investigating the expression of estrogen receptor α (ERα) in PVD patients are contradictory. Eva (2003) reported a decrease in vestibular ERα in women with PVD, while Johannesson (2008) reported an increased amount of vestibular ERα in patients who were past HC users, compared to controls.

Another possible mechanism in HC use would involve an alteration of serum hormone levels. In HC users, there is suppression of ovarian testosterone production and reduced ovarian estradiol. This combination leads to low free testosterone and low estradiol. Decreased estradiol may further contribute to vestibular atrophy found in patients with secondary PVD, causing introital pain. In HC users, it was also found that androgen receptors are significantly lowered in both vestibular tissue and cells of the minor vestibular glands. Goldstein (2014) identified a genetic variation in the androgen receptor in PVD patients and concluded that inefficient androgen receptor, combined with lower free testosterone, predisposes women to PVD. This has not yet been confirmed.

In summary, an association between HC use and the development of PVD is possible. The actual prevalence and susceptibility factors remain incompletely elucidated and, thus, it is not possible to make clinical recommendations at this time. It is also unclear whether termination of HC usage alone can reverse PVD or which additional treatments might be necessary.

Pelvic Floor Muscle Dysfunction

The muscles of the pelvic floor (PFMs) consist of three layers: superficial, intermediate, and deep, known collectively as the 'levator ani.' The PFMs participate in multiple activities, including mechanical support of the pelvic organs, trunk stability and mobility, defecation, urination, closure of the urinary and anal orifices, and

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enhancement of sexual pleasure.

Pelvic Floor Muscle Dysfunction (PFMD) generally refers to muscle laxity or overactivity. It can result from many causes, including musculoskeletal factors, inflammation, trauma, vaginal delivery, abdominal or pelvic surgery, neuropathic pain, and anxiety. Pelvic pain disorders and painful sexual intercourse are typically associated with PFM overactivity. Muscle contraction in response to pain is referred to as guarding, while persistent states of muscle overactivity are referred to as hypertonus and are more frequently associated with amplification in neurological tone rather than a response to pain.

It has long been recognized that PVD is often associated with some degree of PFMD. Compared to controls, women with PVD exhibit elevated resting tone, increased contractile responses to painful stimuli, decreased flexibility, lower relaxation capacity, lower pain thresholds, and lesser strength. In one study by Reissing (2005), 90 percent of the women diagnosed with PVD also had PFMD.

The mechanisms associating PFM hypertonus and PVD are not fully understood. Vaginal closure is assisted by the bulbospongiosus and puborectalis muscles, as well as activation of the levator ani. Reissing demonstrated that PVD patients display considerably higher PFM tone in the superficial layer, but found less remarkable findings in the deeper PFM layers. She concluded that the absence of generalized hypertonicity may indicate that PFM hypertonus results from, rather than causes, PVD. She hypothesized that muscle tension starts as a protective response to vestibular pain, and that this response later results in increased resting muscle tone. Increased PFM contraction causes enhanced pressure on the vestibule during penetration, increasing both pain and the protective guarding reaction. Hypertonicity may, consequently, act to maintain, as well as exacerbate, PVD. Recently, transperineal three-dimensional ultrasound imaging has been used to investigate the structure and function of the PFMs in PVD patients. Because this method does not involve vaginal penetration (as with intravaginal palpation), it is pain-free. Ultrasound also has the advantage of limiting examiner bias resulting from the patient's pain and anxiety during the procedure. In accordance with previous studies, ultrasound imaging showed higher PFM tone and reduced contractile capacity among PVD patients. These findings suggest that PVD patients display PFM impairment, which is not limited to a defense reaction, but is, in fact, chronic.

Alternatively, it has been suggested that PFMD may result from a chronic inflammatory process in the vestibular mucosa. According to this theory, mucosal inflammation or trauma may induce hypersensitivity and contraction of the underlying PFMs. This may contribute to sensitization of muscle pain receptors, which, in turn, reduce sensory pain thresholds. This hypothesis suggests a 'vicious cycle' of inflammation and further muscle contraction.

Another hypothesis proposes the opposite pathway, i.e., an underlying PFMD may act as an initiator of sensory changes in susceptible mucosa. According to this theory, exposure to noxious stimuli over a prolonged period of time leads to an abnormal neuropathic state. It has also been proposed that trigger points in PFMs refer pain to the vestibular region or that hypertonicity of the muscles that insert at the posterior vestibule can lead to allodynia, as well as neural and tissue hypoxia (lack of oxygen).

In summary, PFMD commonly documented in PVD patients, although clinically similar, could, in fact, be driven by distinctly different pathophysiological processes. These aforementioned theories have yet to be fully substantiated. Understanding the pathophysiological pathways will enable clinicians to target therapies to specific causes of vulvar pain (mucosal or muscular) and to recommend physical therapy regimens based on the type of pain and its contributors.

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Table 1
Common Symptoms of Hypertonic PFMs

- Urinary urgency, frequency, hesitancy, pain
- Constipation and painful bowel movements
- Dyspareunia
- Pain with sitting
- Vulvar, perineal, and/or anal itching, pain or burning
- Inability to achieve orgasm or pain with orgasm
- Clothing and exercise intolerance

When clinicians think of pelvic floor disorders, low-tone muscle dysfunction associated with stress urinary incontinence, pelvic organ prolapse and menopause come to mind. The treatment solution is often 'do your Kegel exercises.' Over the past two decades, many studies have concluded that hypertonic (high-tone) pelvic floor muscles are associated with pelvic pain disorders and dyspareunia. Although clinicians may be less likely to think of high-tone or overactive PFM disorders, they affect about 16 percent of women. While it is not routine for a gynecology examination to include an assessment of the pelvic floor muscles, tissues and nerves, a simple screening can be conducted. Identifying musculoskeletal dysfunction enables the health care provider to determine whether the patient is an appropriate candidate for pelvic floor physical therapy. This article will describe the components of a pelvic floor evaluation.

The PFMs and their fascia (thin sheath of fibrous tissue enclosing muscle) are responsible for urinary, bowel, and sexual function, as well as support of the pelvic organs. When these muscles become hypertonic, the symptoms that result can manifest in a variety of combinations. (See Table 1.) Since pelvic floor muscles and nerves can become impaired in a number of ways, the first step for the clinician is to identify what caused or triggered the pain. PFM dysfunction is often associated with vulvodynia, but its pathophysiological processes are not fully understood. It is thought that this musculoskeletal dysfunction may arise via several different mechanisms. Among the possible causes are: (i) increased PFM tension as a protective response to pain; (ii) pelvic floor guarding in response to stress and/or pain; (iii) biomechanical origins, such as labral tear or sacroiliac joint dysfunction, (iv) chronic constipation and (v) injury, e.g., during childbirth. Additional possibilities are gynecologic disease, irritable bowel syndrome, and vaginal or urinary tract infections.

Patient History

Since multiple triggers of vulvodynia have been recognized, taking a detailed patient history is critical for identifying contributing factors. Several types of questions are asked in a physical therapy evaluation. In addition to questions on mechanics, the clinician should screen for central nervous system hypersensitivity. History-taking includes questions on urination, vaginal infections, sexually transmitted diseases, pregnancies, oral contraceptive use and surgeries. All pathophysiological factors, whether a trigger of vulvodynia or a consequence of it, need to be taken into account in formulating a treatment plan. The information gathered from the patient history will help guide the examination of the PFMs and other relevant external components of a patient's pain and impairment.

Physical Examination

The external musculoskeletal system can wreak as much havoc on the vulva as the pelvic floor muscles, tissues and nerves. Connective tissue restrictions can lead to local and referred pain, decreased blood flow, underlying muscle dysfunction and tissue hypersensitivity. Myofascial trigger points can cause local and referred pain, proprioceptive dysfunction, and central sensitization. The relevance of myofascial trigger points is still being debated in the medical community, though many studies have indicated

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that they play a significant role in pain syndromes. Mechanical issues, such as connective tissue and muscle dysfunction, can cause nerve irritation. This irritation can lead to tissue and muscle dysfunction, and independently cause pain anywhere in the nerve's distribution. Nerves may also be sensitized by repetitive infections or other metabolic processes. Since research has shown an association between sacroiliac joint dysfunction or labral tears and pelvic pain, the patient should also be evaluated for these disorders.

The clinician typically assesses vulvar skin coloring and dermatologic changes, and notes any fissures, to determine whether a referral to a vulvovaginal dermatologist is necessary. The clitoris should be the size of a cotton swab tip and the hood should move easily, without causing pain. Reduction in the size of the clitoral head may indicate hormonal insufficiencies from oral contraceptive use, hormonal suppressive therapies, or simply menopause. Issues with mobility of the clitoral hood may stem from dermatologic disease, infection, or connective tissue disorders. The clinician inspects the vestibule for erythema (redness) and tissue integrity. A cotton swab test is done by lightly touching the vestibule and documenting the location and severity of pain. Since this test is usually painful for the patient, and increases sensitivity for the remainder of the examination, it should be done at the end of the assessment. If there is severe redness of the vulva and/or the patient has unprovoked pain, the provider may limit the number of areas touched or even skip the cotton swab test.

Pelvic floor muscles of normal length should shorten with attempted contraction and relax or 'let go' at a similar speed. If the muscles do not shorten, it could be that they are already in a shortened position because of a contracture or lack of motor control. Impaired muscles show little movement and may not relax after contracted or may relax slowly. For example, the PFMs of a woman with vulvodynia who has never given birth are often in a shortened state. Women who have had vaginal deliveries, suffer from chronic constipation, or are of advanced age may also have shortened muscles.

If the vestibule is erythemic and/or the cotton swab test is very painful, the gynecologist should be careful to avoid unnecessary pressure on the vulvar area while accessing the PFMs and nerves. If the patient exhibits little voluntary movement of muscles upon request, and the vestibule is very tender, it is likely that a PFMD exists and an evaluation by a physical therapist is warranted. Thus, it is reasonable for the provider to terminate the examination at this point. If the patient can tolerate further examination, the next steps will provide additional information.

Internal Examination

In addition to an external assessment, a transvaginal examination reveals essential information. A single, gloved lubricated finger is used during the digital internal examination. The amount of pressure used is enough to whiten the nail bed when pressing on a table. The examiner assesses tone and elasticity, while asking the patient to report tenderness and pain. Healthy muscles do not hurt when they are palpated. Based on prior experience, the examiner can distinguish 'tight' from 'normal' muscles by touch. Generally speaking, tight muscles are often painful and the patient's feedback guides the examiner. During the internal examination, motor control is also evaluated. Can the patient contract the pelvic floor muscles? Are they already in a contracted state and unable to be voluntarily relaxed? Is she able to move the pelvic floor into a lengthened position even though the muscles cannot be voluntarily relaxed? These are all factors that the examiner notes as she palpates the different pelvic floor muscles.

Numerous PFMs must be evaluated. The obturator internus is an external rotator of the hip. It is easy to identify by placing a finger in the vagina to a depth roughly past the second knuckle at 3 and 9 o'clock,

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respectively, using the ventral aspect of a flat finger. The external hand can be placed on the patient's appropriate outer knee, and the patient is told to lightly press the knee into your hand. When she moves in this manner, the obturator internus will contract under your finger, confirming you are on the muscle. This muscle can cause pain at the ischial tuberosities and tailbone, and contributes to generalized pelvic floor hypertonus. Importantly, the pudendal nerve travels through Alcock's canal, which is partly comprised of fibrous tissue of the obturator internus. The pudendal nerve can be examined for irritability by lightly palpating it in the canal. In 'normal' cases, the patient feels like you have touched a 'funny bone,' but if light palpation causes sharp, shooting or stabbing pain, or burning, the pudendal nerve may be involved in the patient's vulvodynia and pelvic pain.

Reissing (2005) found that the 'superficial urogenital diaphragm' displayed considerably higher resting tone in patients with provoked vestibulodynia. The urogenital diaphragm contains three muscles: the bulbospongiosus, ischiocavernosus, and superficial transverse perineum. An examination of these muscles will determine whether they are painful and/or cannot contract or relax. These muscles can be palpated with a pincer grasp, lightly using the index finger internally and the thumb of the same hand externally up and down the length of the three muscles. In women with painful or absent orgasm, these muscles are often tender and tight and can be activated by asking the patient to do a quick cough or quick flick muscle contraction.

The pubococcygeus, puborectalis and ischiococcygeus muscles are also palpated. The overall coordination of this muscle group can be tested by asking the patient to 'squeeze the muscles' or do a Kegel exercise. These muscles are considered impaired when palpation is painful, when they cannot contract, or if the muscles do not relax after a concentric contraction (a contraction that causes a muscle to shorten).

A thorough examination also includes inspection of the vulvar/peri-urethral connective tissue and palpation of all pudendal nerve branches and the coccygeus muscle. Motor control, muscle length and strength, and endurance are also assessed. Impaired motor control, hypertonus, and tight/short muscles are often the cause of pelvic pain and dysfunction.

Physical Therapy Treatment Plan

Physical therapy aims to normalize a patient's specific impairment through various treatment techniques (see Table 2, p. 10). Following the detailed history and extensive physical examination, a treatment plan is formulated. More often than not, women with vulvodynia have multiple pathophysiologic factors that led to development of their pain syndrome. It is critical for their doctors and physical therapists to make a differential diagnosis and collaborate on a multi-disciplinary treatment plan. This collaboration is best illustrated by case examples.

Case Examples

Leah is 30 years old and recently met a new sexual partner. She developed multiple urinary tract infections that were appropriately treated with antibiotics, but unfortunately led to several yeast infections. Upon evaluation, she presented with high-tone pelvic floor dysfunction and the treatment plan involved manual therapy and home exercises to loosen her tight muscles. Leah also consulted a naturopathic doctor to determine the underlying cause of her repetitive infections. She had developed Candida in her gut as a result of long-term antibiotic use, which also led to vaginal yeast infections. These infections irritated her pelvic tissue and led to persistent muscle hypertonus, which caused further pain. The musculoskeletal dysfunction and inflammation, and the systemic infections, were primary causes of Leah's chronic vulvar pain. Her symptoms were successfully

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managed with a low-dose tricyclic anti-depressant, manual physical therapy, a pelvic floor home exercise program, and a low-sugar, anti-Candida diet.

Michelle is 30 years old. Her vulvovaginal pain developed after she was in a car accident in which her knees hit the dashboard, causing sacroiliac joint dysfunction. Due to the close relationship between the sacroiliac joint ligaments and the pudendal nerve, she subsequently developed pudendal nerve irritation, which in turn, caused hypertonic pelvic floor muscles and constant vulvar burning. Because of the pudendal nerve irritation, Michelle could not initially tolerate manual physical therapy. Thus, she consulted a pain management physician who prescribed Cymbalta and performed a pudendal nerve block, which relieved the pain. She was then able to resume physical therapy. The treatment plan included manual therapy and orthopedic treatment strategies of joint mobilization and neuromuscular re-education of her sacroiliac joint, which was the driving factor in her case.

Gwen, 49, is a triathlete whose vulvar pain began two weeks after she started CrossFit, an exercise regime. She noticed the pain when she attempted to have sexual intercourse. The physical therapy examination did not find pelvic floor dysfunction or muscle tenderness, which can be associated with changes in exercise regimes and injuries. All musculoskeletal structures were completely normal. The history revealed that her periods had been irregular and she was in perimenopause. Upon inspection, her vulvar tissues were thin and fragile. The vulvar pain with intercourse started with a change in her exercise routine, but it also coincided with resuming intercourse after a period of inactivity and being perimenopausal. She did not need physical therapy and was successfully treated with topical hormone cream.

Conclusion

As the case examples demonstrate, even though women have similar vulvar symptoms, they require individualized treatment regimens. For many vulvodynia patients, a multimodal approach is the most effective way to relieve pain and related dysfunction. Physical therapists are well-positioned to serve as 'case managers,' because most of their patients have frequent sessions for an extended period of time. It is important that the physical therapy regimen is well-coordinated with treatments prescribed by all the patient's health care providers.

Table 2

Physical Therapy Treatment Options

Manual therapy techniques
- Connective tissue manipulation
- Myofascial release and myofascial trigger point release
- Neural mobilizations
- Joint mobilizations

Pelvic floor and girdle neuromuscular re-education

Peripheral and central nervous system desensitization strategies

Home exercise program to supplement in-office treatments
- Foam rolling
- Pelvic floor muscle relaxation exercises, e.g., pelvic floor drop
- Stretching and/or strengthening of muscles

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Central Pain Mechanisms

Among etiological factors proposed in PVD development, the alteration of pain perception in the central nervous system has also been suggested. Comorbidity of PVD with other pain syndromes is often reported, most notably with irritable bowel syndrome, fibromyalgia, interstitial cystitis, and orofacial pain. PVD patients often suffer from other bodily pain and have lower pain thresholds in regions remote from the vestibule. In addition, an increased number of painful tender points have been reported, suggesting central sensitization. Moreover, functional magnetic resonance imaging (fMRI) performed during painful vestibular pressure revealed similar activation in cerebral pain centers as seen in other chronic pain conditions. FMRIs also showed increased grey matter density in pain modulatory and stress-related areas of the brain compared to controls.

Taken together, these findings indicate that abnormal pain amplification may exist in PVD patients. This pain sensitivity may be attributed to either the chronicity of pain (central sensitization) or alternatively, as a reflection of an intrinsic defect in mechanisms of pain regulation. Patients with primary PVD exhibit greater sensitivity to thermal pain than women with secondary PVD, suggesting that subgroups of PVD patients are different with regard to non-genital pain thresholds. This finding suggests differences in underlying pathophysiological mechanisms in the two subgroups. Consideration of the contribution of central pain regulatory mechanisms may help to explain variations in both clinical presentation and treatment outcome in different subgroups of PVD patients.

In addition to overlap with other pain syndromes, the incidence of depression, anxiety, somatization, stress and catastrophizing is higher in PVD patients than in controls. These psychological factors may influence clinical presentation and response to therapy. It is unknown whether these conditions contribute to PVD, whether they represent a response to this chronic disabling disorder, or if they share a dysfunction in central regulatory systems and, as such, coexist.

Genetic Factors

Several studies indicate a possible genetic involvement based on the following findings in women with PVD: (i) polymorphisms (variations) in genes regulating the inflammatory response, (ii) polymorphisms in genes associated with an increased sensitivity to pain, and (iii) polymorphisms in genes involved in the effect of hormonal changes caused by HCs. In addition to these case-control studies, a recent study by Morgan (2016) evaluated whether provoked vestibulodynia is more common in female relatives of women diagnosed with PVD, using population-based genealogy-coded data. He found that the relative risk of vestibulectomy was elevated in first-, second-, and third-degree relatives, concluding that this familial clustering supports a genetic predisposition for PVD and warrants further studies to identify the specific genes involved.

Summary

Clinical observations and epidemiological studies emphasize the heterogeneity of vulvar pain syndromes. In addition, data from basic research suggest different mechanisms relevant to the division of women with PVD into subgroups. However, in clinical practice, the relative contributions of different triggering or persistent factors remain poorly understood, and current diagnostic criteria are based on highly subjective measures, while treatment proceeds on a trial-and-error approach. The result is that many types of therapeutic interventions have been used, yet the evidence remains largely inconclusive. The treatment efficacy rate ranges from 40 to 85 percent, and many women with PVD do not respond to treatment. Data on etiology, epidemiology, mucosal characteristics, and treatment outcome are inconclusive, because patients are

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given a single diagnosis, but have different underlying conditions. It is unlikely that studies will obtain significant results when a treatment intervention is only relevant to one subgroup of patients and is being tested on a heterogeneous population.

Constructing an algorithm that allocates patients into accurate PVD subgroups will advance both basic science and clinical research, and improve future medical management. Although a large research effort has been made in this area, only one such clinical algorithm has been suggested. Based on a patient's history and physical examination, this algorithm distinguishes between four subtypes of PVD: (i) hormonally mediated PVD, (ii) hypertonic pelvic floor muscle dysfunction, (iii) congenital neuroproliferative PVD, and (iv) acquired neuroproliferative PVD (secondary to inflammation). According to our personal experience, this classification provides better outcomes than the trial-and-error approach we used before, i.e., response rates are higher and patients experience significant improvement in a shorter time period. However, objective data are missing to support this algorithm.

Given the high incidence of PVD in the population and its huge impact on patients' lives, there is a critical need to perform prospective, longitudinal studies that will lead to better diagnostic criteria and subgrouping of patients. The information obtained from these studies will improve our understanding of PVD and its treatment.

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