

ACTA OVERVIEW

Medical and physical predictors of localized provoked vulvodynia

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Abstract

Vulvodynia in young women is a significant clinical challenge. This overview focuses on localized provoked vulvodynia (LPV) with regard to medical and physical predictors of the condition. Several causative factors have been proposed and one major conceptual issue is the role of inflammation. Trauma to the vestibular mucosa causes an initial inflammatory response which may result in peripheral and central pain sensitization. In women with LPV, evidence of mucosal nerve fiber proliferation and enhanced systemic pain perception has been found. A dysfunction of the pelvic floor muscles is common and many patients also suffer from other bodily pain. In general, the level of scientific quality in published studies on vulvodynia is low. Further research on epidemiology, etiology and conduction of clinical trials with high evidence grade is desired.

Key words: *Human sexuality, vulvodynia, provoked vestibulodynia, predictors, etiology*

Introduction

Vulvodynia means ‘pain in the vulva’ and includes many clinical features. Some patients have continuous pain in the major part of the vulvar area, whereas others suffer from more localized pain, usually provoked by vaginal intercourse or tampon use. The symptoms often interfere with the patients’ sexual function and psychological well-being (1). Superficial dyspareunia confined to the vaginal opening is the most common form of vulvodynia in young women. This condition was formerly called vulvar vestibulitis syndrome due to the inflammatory appearance of the vestibular mucosa. It is, however, now classified as a pain syndrome and a new nomenclature for vulvar pain has been proposed by the International Society for the Study of Vulvovaginal Disease (ISSVD) (2). When no recognized underlying cause of the pain is identified, the vulvodynia is either classified as generalized or localized and further categorized into provoked, unprovoked or mixed subgroups. The generalized form of vulvodynia is less common and only a few studies have been conducted. This overview will

therefore focus on the localized and provoked form of vulvodynia with regard to medical and physical predictors of the condition.

Method

The references included in this overview are publications found in Medline (PubMed) from any date. Primary search terms were vulvodynia (285), vestibulodynia (326), superficial dyspareunia (80) and vulvar vestibulitis syndrome (153), including both reviews and original articles. The search results showed a significant overlap for these terms. Additional search terms were predictors, etiology, inflammation and pain mechanisms. No meta-analyses or systematic reviews were found.

Localized provoked vulvodynia

Women with localized provoked vulvodynia (LPV) seek medical care due to an inability to have vaginal

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(Received 2 May 2010; accepted 25 September 2010)

ISSN 0001-6349 print/ISSN 1600-0412 online © 2010 Informa Healthcare
DOI: 10.3109/00016349.2010.528368

intercourse. Some women have a primary form of LPV, experiencing pain ever since first tampon use or intercourse. For others, various period of pain free vaginal penetration preceded the onset of symptoms (secondary LPV). The pain is often described as burning and sometimes knife-sharp at contact, typically located between 4 and 8 o'clock on the introitus, just exterior to the hymenal ring. In severe cases, the major part of the vestibular mucosa, including the openings of the paraurethral glands, might be affected. Erythema around the openings of the Bartholin's glands and in the posterior fourchette is often found. The mucosa is presented with an allodynia (sensation of pain from a light touch) and hypersensitivity to mechanical stimuli such as touch, pressure and vaginal penetration (3). In many women, a varying degree of vaginismus is also found.

The prevalence and incidence for LPV is unclear. As for vulvodynia, the prevalence shows a great variety from 3 to 18% in epidemiological studies (4,5). Initially, vulvodynia was thought to primarily affect Caucasian women (6,7). In survey of ethnically diverse women, similar lifetime prevalence rates of chronic vulvar burning or pain on contact were reported (8).

No single causative factor has yet been identified for LPV and the etiology is considered multi-factorial. Most probably a vast number of "triggers" may initiate the pain and if not properly taken care of, a more or less chronic pain condition might develop. A combination of causes might include psychosexual factors as well as more obvious physical trauma to the tissue such as recurrent infections. Much effort has been made to find pathophysiological changes characteristic for LPV.

The vestibular mucosa

The vestibular mucosa is of endodermal origin and by definition visceral tissue, but has a somatic innervation with perception for pain, temperature and tactile stimuli. It has a non-pigmented epithelium covered by a thin keratinized layer. The mucosa serves as a thin mechanical and immunological barrier susceptible to infections as well as mechanical trauma.

Inflammation

LPV or the former vulvar vestibulitis syndrome was first regarded as a chronic local inflammatory condition generating an interest among physicians for potential inflammatory mechanisms. Based on a number of small pilot studies, in addition to clinical observations, the initial inflammatory theory has been

abandoned and the condition is now regarded as a pain syndrome.

In vulvar biopsies obtained from women with LPV, an infiltration of mainly T-lymphocytes is located in the subepithelial part of the lamina propria and is often described as a nonspecific chronic inflammation by pathologists (9,10). However, in later studies with better selection of control specimens, similar infiltration of inflammatory cells is also seen in healthy women and cannot serve as a histological indicator of LPV (11,12).

Studies on the pro-inflammatory mediators interleukin I- β (IL-1 β) and tumor necrosis factor alpha (TNF- α) in vulvar tissue of patients with LPV have been published with conflicting results. Foster and Hasday found elevated tissue levels of IL-1 β and TNF- α , but these pro-inflammatory mediators were 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 (13). In contradiction, Eva et al. found no differences between patients and controls regarding these mediators (14). The two inducible enzymes nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX 2) are hardly detectable in the skin and mucosa under normal conditions. However, its expression increases in response to various mediators released at site of inflammation (15,16). COX 2 and iNOS were not upregulated in biopsies obtained from the vestibular mucosa in women with LPV as compared to healthy controls. This finding is inconsistent with an ongoing cell-mediated inflammation and may also explain why corticosteroids are not helpful for LPV (17).

Infections and antigen

Allergy has been discussed as a causative factor for LPV. The most likely antigen candidate would be from microbes commonly affecting the vulva. Human papillomavirus (HPV) was first considered, but in multiple studies the detection of HPV using PCR was as common in controls as in women with LPV (18,19). Herpes simplex virus (HSV) is also a common vulvar infection, but to date, HSV does not appear to cause LPV (20). Bacterial vaginosis (BV) with an overgrowth of anaerobic bacteria is also a common cause of vaginitis in young women. According to case-control studies, women with LPV are more likely to report a history of BV than asymptomatic controls (21,22).

Candida is frequently present in the vulva. Up to 75–80% of women develop symptomatic candidiasis during their lifetime (23). In many cases patients with

LPV have a history of recurrent candidiasis and they often relate the onset of LPV to an acute episode of yeast infection (24). However, the evidence for a correlation between LPV and genital infections is scanty. A correlation to recurrent symptomatic yeast infections has been reported in case–controls studies, but the data are often based on self-reported infections. There is a need for prospective observational studies with clinically and culture-confirmed cases before any conclusions can be drawn.

In a previous study, it was observed that women with a history of hives were 2.5 times more likely to develop vulvodynia, suggesting that environmentally induced allergic reactions could alter the immunoinflammatory response and predispose for the development of LPV (25).

Genetics

Recent work points to a possible genetic involvement with polymorphisms in genes regulating inflammatory response (26,27). In fact, as is common for inflammatory conditions, allele 2 of the IL-1 β gene was found in significantly more women with LPV (40%) than controls (25%) (28). In yet another study, an association of primary LPV and gene polymorphism of the mannose-binding lectin (MBL) gene was reported together with a reduced capacity for TNF- α production in response to microbial components in patients (29). It has also been suggested that women with fair skin are more susceptible to LPV (30). An increased risk of LPV was found in cases with polymorphism of the melanocortin-1 receptor (MC1R) gene in a retrospective case–control study (30).

The exploration of a possible genetic predisposition in LPV is a new area and further studies are needed. However, the studies referred to are case–control studies of moderate evidence grade with a large number of controls and no obvious sampling bias.

Hormonal influences

The first modern report on women suffering from LPV appeared in 1976, approximately 10–15 years after combined oral contraceptives (COC) were introduced in the USA. Since then, COCs have been modified to contain less ethinyl estradiol and various progestins. A possible etiological correlation between COCs and LPV has been investigated in different epidemiological studies. In a clinic-based study from 2002, the results showed a 6.6 relative risk of LPV (95% confidence interval 2.5–17.4) for

ever-users of COCs compared to non-users. When COCs were used before the age 16, the relative risk reached 9.3 and increased with the duration of COC use up to 2–4 years. The relative risk was higher when the pill used was highly pro-gestogenic and androgenic but low in estrogenic potency (31). These findings were not, however, confirmed by a population-based case–control study from 2008 (32).

The hormonal effect of COCs on genital mucosa has mainly been studied in the endometrium. Recently, it was observed that the vestibular mucosa of healthy women on COCs undergoes changes compared to non-users (33). The dermal papillae become shallower and sparser which might result in a more fragile and sensitive mucosa (34). It has also been reported that women without dyspareunia who use COCs have lower vestibular pain thresholds to mechanical stimuli (35). These findings are thought to be reflective of a gestagenic effect, and they support the data pointing to an increased risk of developing vestibular pain from using pills with high gestagenic potency. However, more data are needed. The current recommendation is to continue to prescribe the pill when needed, but both users and prescribers should be aware of side-effects such as dryness, soreness and pain.

Results from studies investigating the expression of the estrogen receptor alpha (ER α) in women with LPV are contradictory. Initially, decreased expression of ER α in the vestibular mucosa was reported (36). In a more recent but small study ($n = 39$), biopsies were taken in the same phase of the menstrual cycle and a significant increase in ER α was found in patients compared to controls. The clinical implication of this result suggests that topical estrogens might have a role in the treatment of LPV (37).

The pelvic floor

During the examination of women with LPV, a hypertonicity of the pelvic floor muscles is often described. Fear of pain and behavioral avoidance toward vaginal penetration are thought to be responsible for this reaction which is similar in vaginismus patients. It is difficult to objectively measure the tonus of the muscles during pelvic examination and surface electromyography has been used to monitor the electric activity of the pelvic floor muscles at rest and during contraction. Women with LPV have shown instability of the muscles, elevated resting baseline and poor muscle recovery after contraction (38). Similar results were reported in a study which confirmed an association with pelvic floor dysfunction and LPV, but there was no correlation with the severity of vulvar pain

(39). In clinical practice various treatments to restore the pelvic floor function are generally used and are considered important for the rehabilitation of the patients (40).

Pain mechanisms

Pain is a complex sensation involving sensory, affective and cognitive features. The sensory transmission mechanisms for acute pain are generally well understood, whereas chronic pain conditions, often characterized by severe pain with little discernable pathology, remain an enigma. The neuromatrix theory of pain suggests that pain is a multidimensional experience resulting from nerve impulses generated in a widely distributed neural network, rather than directly from sensory input evoked by a specific pathology. Thus, pain may occur even if an identified physical cause cannot be found (41). During the last 10 years, several researchers have studied different aspects of pain mechanisms in vulvodynia.

Peripheral pain mechanisms

In 1997, Westrom first reported a nerve fiber proliferation in the vestibular mucosa in women with vulvar vestibulitis (42). Since then, at least three independent studies have reported similar findings and currently, the nerve hyperplasia is the only histopathological marker of LPV (43–45). It is, however, not used routinely for diagnosis. It has been speculated whether the nerve proliferation is an unspecific reaction to inflammation, as also observed in colitis (46). Lately, an association between mast cell infiltration and degranulation in the mucosa and neural hyperplasia has been suggested (45).

Quantitative sensory testing of the vestibular mucosa has given evidence to indicate peripheral sensitization for both mechanical and thermal noxious stimuli (17,47). The enhanced peripheral pain perception is considered to be part of a neurogenic inflammation which might be initiated when sensory nerves are triggered by injury or trauma. A vicious circle is established when the primary afferents release vasoactive neuropeptides, bradykinin and nitric oxide causing increased blood-flow, extravasation of proteins and the release of additional mediators, which in turn sensitize the nociceptors, resulting in lower pain thresholds (48). Increased superficial local blood flow in the most sensitive part of the mucosa was observed by the use of laser Doppler perfusion imaging (49). This finding further supports the neurogenic inflammation theory.

The vanilloid receptor VR1 is expressed by nociceptors and activated by mediators released during inflammation. Increased amounts of immunostained VR1 nerve fibers have been found in LPV patients with a possible correlation to the mucosal hypersensitivity (50).

Central pain mechanisms

More recent research has also shown evidence of an alteration of central pain perception in women with LPV. According to epidemiological data, patients often suffer from other bodily pain (51). Experimental testing using quantitative sensory testing has shown lower pain thresholds for pressure and thermal stimuli on remote body sites in patients as compared to healthy women (47,52). Moreover, an increased number of painful tender points were reported and an enhanced pain response to mechanical stimulation beyond the anatomic location of the primary complaint was found in a study using capsaicin-evoked hyperalgesia (53,54). It was further observed that even though vestibular pain thresholds and bodily pain were significantly improved after completing treatments for LPV, the general pain thresholds were unaffected (55). Lately, morphological and functional studies of the brain have been performed. Pukall and colleagues reported that functional magnetic resonance imaging (fMRI), performed during painful vestibular pressure in patients, revealed similar activation in cerebral pain centers as in women with chronic pain conditions such as fibromyalgia, lower back pain and inflammatory bowels disease (56). In another study, using brain imaging techniques, the grey matter density was increased in pain modulatory and stress-related areas of the brain in patients compared to controls. These results additionally support the role of centrally mediated pain modulation in women with LPV (57).

Enhanced systemic pain perception may also be due to impairment in inhibitory and/or excitatory pain modulation. One endogenous pain inhibitory mechanism is diffuse noxious inhibitory controls (DNIC) which can be summarized as 'pain inhibits pain' (58). Johannesson et al. showed in one study that the majority of women with LPV have an intact DNIC response even though the general pain thresholds were lower in patients than in controls (59).

Discussion

Vulvodynia in young women is a significant challenge for many health providers. During the last 30 years,

the condition has gradually received more clinical and scientific attention. However, as compared to many other medical disorders, well conducted studies are few and the total number of publications in the area is approximately 500. In general, the level of evidence of the published studies on vulvodynia is low with poor scientific basis. There are often several limitations in the study design that preclude statistically relevant results. Randomized controlled studies are rare, whereas case-control studies and clinical observations are common. In this overview, the medical and physical predictors for provoked vestibulodynia have been discussed and in the different sections, the level of evidence has been elucidated when relevant.

The etiology of LPV is still not fully understood. Several causative factors have been proposed and one major conceptual issue is the role of inflammation. In the vestibular mucosa, the only pathophysiological finding unanimous for LPV, is a nerve proliferation which is considered an unspecific reaction to previous mucosal trauma (43). The trauma might have been triggered by a number of possible psychosexual and/or physical factors causing an inflammatory response in the tissue. Genetic studies also indicate an alteration of pro-inflammatory responses in women with LPV (27). However, by the time the patient is being referred for examination, the initial inflammatory response is usually resolved. Instead, a pain condition has been established with a present neurogenic inflammation with peripheral and central sensitization (3). There is physical evidence of general pain sensitivity in women with vulvodynia. However, no obvious causes for these observed changes has so far been identified and it is unclear whether repeated peripheral noxious stimuli lead to the enhanced systemic pain perception or if pathology of central pain modulation is the primary cause.

The importance of endogenous pain modulation has been discussed in several clinical studies. Impairment of the DNIC response has been investigated in other pain disorders with female predominance. Patients with rheumatoid arthritis display a preserved DNIC function in contrast to patients suffering from fibromyalgia who lack DNIC (60,61). These observed differences in the DNIC responses imply that endogenous pain modulation is a dynamic function and is related to not only whether a pain condition is regional or generalized, but also most probably whether the pain is intermittent or more continuous.

Another observed physical predictor of LPV is dysfunction of the pelvic floor muscles (38). Contracted muscles around the distal part of the vagina will most probably contribute to the maintenance of the provoked pain. Evaluation of a concomitant vaginismus in women with LPV is generally

recommended and should be addressed during treatment (62).

It is well known that psychological status influences pain perception. Psychosexual predictors of LPV have not been explored in this overview. Increased prevalence of co-morbid psychopathology has been reported in women with LPV in several studies (63). However, in an etiological context, it is not clear how these findings relate to LPV, since they might be considered as either a cause or a consequence for different women.

Currently, there is no standardized treatment for vulvodynia and very few randomized controlled trials have been carried out. Recommendations are in favor for a multi-disciplinary approach focusing on pain management and re-establishing the pelvic floor function (64). The impact of the patients' psychosexual health, personality traits and co-morbidities is also important to evaluate in the clinical setting since it may reflect the coping ability and quality of life for the individual sufferer.

In order to improve treatment and find possible preventive measures for women with vulvodynia, more knowledge is necessary. Do women with vulvodynia have a genetic predisposition to systemic pain sensitivity and are they more prone to develop other pain syndromes later in life? Research on epidemiology, etiology as well as the conduct of clinical trials with high evidence grades, is desired.

Declaration of interest: The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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