Current Concepts about Vulvar Vestibulitis Syndrome

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Key words: *vulvar vestibulitis syndrome,*

Abstract

Vulvar vestibulitis syndrome (VVS) is a subset of vulvodynia that is characterized by severe introital dyspareunia and tenderness to pressure localized within the vulvar vestibule. Increased awareness of VVS has led to exciting new research. This review will examine current concepts regarding the diagnosis, etiology, and treatment of VVS.

Bull Isr Soc Gynecol Obstet 2003;1:00–00

In the last few years, increased awareness of vulvar vestibulitis syndrome (VVS) has led to exciting new research. This research focuses on many different aspects of VVS including possible genetic, infectious or allergic etiologies, and on multiple treatment regimens. Even basic assumptions of early researchers have been questioned, leading to a greater understanding of VVS.

Traditionally, VVS is diagnosed using three criteria established by Freidrich. These are: severe pain during attempted vaginal entry, tenderness to pressure localized to the vulvar vestibule, and erythema of the vulvar vestibule. While these criteria can be quite useful, they have never been subjected to experimental scrutiny. A recent paper from Bergeron and colleagues [1] shows that the first two criteria are indeed useful in making the diagnosis of VVS, but that erythema is not.

A recent study from Sweden disputes our prior hypothesis that there is active inflammation in the vestibular mucosa in VVS. Bohm-Starke *et al*. [2] used indirect immunohistochemistry and Western dot-blot analyses to show that cyclooxygenase 2 and inducible nitric oxide synthase are not elevated in the mucosa of women with VVS. These studies imply that the common practice of using anti-inflammatory medications, such as topical corticosteroids, in the treatment of vulvar vestibulitis is unwarranted.

Two additional studies question our assumptions that VVS has an infectious etiology. Until recently, many physicians believed that VVS is a consequence of human papillomavirus (HPV) infection. Using polymerase chain reaction (PCR) amplification to detect HPV DNA, Morin and co-workers [3] showed, however, that HPV is not more common in women with VVS. Another study, by Bornstein *et al*. [4], questions the assumption that women with VVS have chronic candidal infections. They showed that prolonged treatment with the oral antifungal, fluconazole, was ineffective treatment for VVS. While both of these studies do not eliminate the possibility that VVS is caused by an initial infection, it appears that VVS is not a consequence of chronic infections of HPV or *Candida*.

Although some of our previously held beliefs about VVS have not survived scientific scrutiny, several new ideas do have strong experimental backing. Recent studies from Sweden and Israel have independently shown abnormalities in the vestibular mucosa of women with VSS. Bohm-Starke and colleagues [5] used PGP 9.5 immunohistochemistry to demonstrate that the number of intraepithelial nerve endings in the vestibular mucosa in women with VVS is significantly increased. In addition, they showed that calcitonin gene-related peptide, which is known to exist in nociceptive afferent nerves, was the only neuropeptide detected in the superficial nerves of the vestibular mucosa. Therefore, the increased free nerve endings within the vestibular mucosa of women with VVS are nociceptors. Bornstein *et al.* [6] confirmed these results and used computer-assisted histomorphometry to show that women with VVS have ten times the area of nerve fibers than women without VVS. Furthermore, they demonstrated the presence of increased mast cells in the mucosa of women with VVS [6]. If we examine these results along with data from Velangi [7] that shows that the skin of women with VVS is more sensitive to chemical irritants than asymptomatic women, we can formulate a new hypothesis about the cause of VVS. VVS may be initiated by an allergic reaction to a chemical irritant in the vulvar vestibule. This irritation – possibly to topical antifungal agents used to treat suspected candidiasis – causes mast cells to migrate to the vestibule. If the irritation persists, activation of mast cells leads to an uncontrolled proliferation of nociceptors in the mucosa. This hypoth-

esis explains why up to 80% of women with VVS complain of an acute onset of symptoms that includes burning and itching, which then progress to severe pain on touch. The pain on touch often then persists even after the initial symptoms of itching and burning disappear. Of course, further studies should be performed to assess the validity of this hypothesis.

Witkin and associates [8] are the first to examine a possible genetic link to VVS. They examined the relation between vulvar vestibulitis and polymorphisms in the gene coding for the interleukin-1 receptor antagonist, a naturally occurring down-regulator of pr-inflammatory immune responses. They demonstrated a unique distribution of interleukin-1 receptor antagonist alleles among women with vulvar vestibulitis. This suggests that polymorphism in this gene may lead to elevated levels of interleukin-1 (IL-1), thereby creating an exaggerated inflammatory or immune response. This hypothesis is further supported by data from Foster and Hasday [9], who showed that tissue levels of IL-1 were 2.3-fold greater in women with VVS than in controls.

Several articles have suggested that women with vulvar vestibulitis have increased pain perception that is not limited to their genitalia. Pukall and colleagues [10] used modified von Frey stimuli to measure tactile and pain thresholds around the vulvar vestibule and in five non-vestibular areas. Their data show that women with VVS had significantly lower tactile and pain thresholds than controls in the vulvar vestibule in non-vestibular regions such as the deltoid. This may imply that VVS is part of a systemic pain syndrome (such as fibromyalgia) and not just a genital condition.

Over the past few years many studies have examined treatment options for VVS. Several different treatment modalities have proven to be very successful in treating VVS. To date at least 10 papers were published examining the treatment of VVS with vestibulectomy (surgical removal of the mucosa of the vestibule). Bornstein *et al.* [11] performed a meta-analysis of all the published literature regarding vestibulectomy between 1981 and 1998 and concluded that 89% of women who had a vestibulectomy experienced a significant reduction in pain, and 72% of women had a complete resolution of their symptoms. Schneider and co-workers [12] report similar success and also present data showing that 83% of women who underwent vestibulectomy would recommend it to others.

Several papers have examined electromyographic (EMG) biofeedback for the treatment of VVS. McKay and colleagues [13] report that 52% of women demonstrated markedly decreased vestibular pain after EMG and 69% of the women resumed sexual activity. Sarig *et al*. [14] reported that 43% of women could have intercourse without pain after an average of 6 months of EMG treatment. Lastly, Bergeron et al. [15] performed the first randomized trial to compare EMG, group cognitive-behavior therapy, and vestibulectomy. They reported that all three treatment modalities offered significant improvement in the symptoms of VVS, but that women had a better outcome after vestibulectomy than with either EMG or cognitive-behavioral therapy.

Several studies have also examined interferon injections for the treatment of VVS. While this treatment strategy was initially started to treat HPV infection (which we now believe is *not* the cause of VVS), new data by Schernthaner *et al*. [16] show that interferon inhibits mast cells. If our new hypothesis about the cause of VVS is correct, this may explain why interferon has been successful. Further evidence to support this theory is provided by Gerber and team [17] , who show that women with VVS are less likely to produce interferon-alpha when they were exposed to a lipopolysaccharide stimulus than a control group of women. Marinoff *et al.* [18] report that 49% of women experienced reduction in their pain after a course of interferon injections.

Conclusion

In the last few years, scientists have made great progress in the understanding and treatment of VVS. A new hypothesis of mast cell-induced proliferation of nociceptors has emerged, data have shown a probable genetic link to VVS, and multiple treatment modalities have proven successful. There remains, however, much investigation to be performed to substantiate these hypotheses and to develop treatment regimens that help all women with VVS.

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