THE JOURNAL OF
SEXUAL MEDICINE

REVIEW

The Relationship Between Vulvovaginal Candidiasis and Provoked Vulvodynia: A Systematic Review

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ABSTRACT

Background: Provoked vulvodynia (PVD) is a chronic vulvar pain condition affecting up to 8.3% of the female population. Despite many years of research, no clear cause for PVD has been identified. Several risk factors have been studied, including vulvovaginal candidiasis (VVC). However, to date, the role of *Candida* infections in PVD has remained unclear. VVC and PVD have an overlap of symptoms that may contribute to diagnostic inaccuracy and mistreatment.

Aim: To systematically review the literature on the relationship between VVC and PVD.

Methods: Cohort and case-control studies were included that compared women with PVD with healthy controls with respect to the presence of a history of *Candida* vulvovaginitis. PVD had to be diagnosed by Friedrich's criteria or the International Society for the Study of Vulvovaginal Disease criteria. The inclusion process as well as the quality appraisal of the studies, using the Newcastle-Ottawa Quality Assessment Scale, were performed independently by 2 authors.

Main Outcome Measure: Outcomes of the population-based case-control studies were listed as odds ratio. Outcomes of the pathophysiological studies were based on local pro-inflammatory responses on Candida in vitro.

Results: We included a total of 14 studies, both population and clinic-based case-control, and pathophysiological research. 7 studies were of low methodological quality, and 7 studies were of medium methodological quality. The population-based case-control studies showed a significantly increased odds ratio for self-reported VVC in PVD cases compared with controls. The pathophysiological studies revealed a tendency for an increased local proinflammatory response on *Candida* in vitro in patients with PVD. Owing to the substantial heterogeneity of the studies, meta-analysis was not performed.

Clinical Implications: Health care providers may consider a diagnosis of PVD in women with self-reported VVC, and to act on this properly. Reiteration of antifungal prescriptions by physicians without a decent diagnosis, will lead to mistreatment. Women should be informed by their health care provider that intercourse during (or shortly after) the treatment of VVC might worsen the vulnerability of the vulvar skin.

Strength and Limitations: This is the first systematic review performed to describe the relation between VVC and PVD. An independently performed in- and exclusion process and quality appraisal, ensured optimal internal validity. However, there were important methodological limitations and the size of heterogeneity prevented establishing a meta-analysis.

Conclusion: This systematic review is unable to draw conclusions regarding a relationship between actual VVC and PVD because studies were based on self-reported VVC. Until new evidence becomes available, we advocate that PVD should be considered as an unexplained chronic pain condition. In women with recurrent or persistent VVC-like complaints, physicians should consider a diagnosis of PVD. **Leusink P, van de Pasch S, Teunissen D, et al. The Relationship Between Vulvovaginal Candidiasis and Provoked Vulvodynia: A Systematic Review. J Sex Med 2018;XX:XXX–XXX.**

Received April 27, 2018. Accepted July 13, 2018.

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https://doi.org/10.1016/j.jsxm.2018.07.011

Key Words: Vulvodynia; Vulvovaginal Candidiasis; Review; Dyspareunia; Sexual Dysfunction; Female; Women; Chronic Pain; Provoked Vulvodynia; Systematic Review

INTRODUCTION

The International Society for the Study of Vulvovaginal Disease (ISSVD) defines *vulvodynia* as "vulvar pain of at least 3 months duration without a clear identifiable cause which may have potential associated factors."[1] Provoked vulvodynia (PVD) comprises a subgroup of vulvodynia characterized by a localized vulvar pain, provoked by, for example, sexual penetration, tampon insertion, and tight clothing.[2] Estimated prevalence varies from 3.8% to 8.3%.[3–6] Women with PVD describe their pain as burning, itching, or stinging[7] and report lower quality of life,[3] reduced sexual satisfaction,[8–10] and higher depression rates.[8,11–13]

Remarkable is the association of PVD with medically unexplained physical symptoms such as fibromyalgia, irritable bowel disease, chronic fatigue syndrome, and tension headaches, as was found in outpatient departments and specialized clinics as well as in primary care.[2,12,14]

To date, no single cause has been identified in either the onset or the maintenance of PVD, which therefore is likely of multifactorial origin.[15,16] Over the past years, many potential risk factors have been studied, including hormonal factors,[17–24] genetic factors,[25–30] psychological factors,[31–34] human papilloma virus infections,[35–38] allergic factors,[39] pelvic muscle floor dysfunction,[40–43] and sexual and relationship factors.[44,45]

The most extensively studied risk factor is vulvovaginal candidiasis (VVC). As several studies state, inflammation, induced by a (repeated) vulvovaginal *Candida* infection, could alter the equilibrium in the peripheral vulvar vestibular skin, which may result in local allodynia and hyperesthesia.[16,46–48] Allodynia could be induced by intradermal or subcutaneous proinflammatory factors such as interleukin (IL)-6 and prostaglandin E2 (PGE2), which are produced by vulvar fibroblast strains in response to challenge with yeast components.[46] However, little is known about how human external vulvar and vestibular fibroblasts respond to yeast or yeast products.[46] An observational study in general practice has demonstrated that patients with an uncertain diagnosis of VVC, which was defined as recurrent or persistent vulvovaginal complaints despite treatment for VVC, showed an increased prevalence of factors known to be associated with PVD: dyspareunia, medically unexplained physical symptoms, and higher health care consumption.[49] Therefore, it was hypothesized that in some patients, PVD complaints are unintentionally mistaken for VVC owing to overlapping symptoms.[49] Women with PVD may thus be misdiagnosed, leading to undertreatment.

Studies show that one-third to one-half of recurrent VVC cases have no clear cause[50] and that about 20%–25% of women with vulvovaginal complaints remain without a microbiologically explained diagnosis, even after careful evaluation.[51–54] PVD also poses a diagnostic challenge for many general practitioners (GPs). Diagnostic delay is common, caused by both patients' avoidance to seek help and reluctance among their GPs to perform adequate sexual history and examination.[5,37,55] Because there is no diagnostic tool in primary care to confirm PVD, it is merely a diagnosis of exclusion. Diagnostics in specialist care such as vulvoscopy or pelvic floor muscle testing might be helpful. Improved knowledge of the exact relationship between PVD and VVC could lead to better identification of women with PVD and a more directed diagnostic approach. Improved insight, should VVC be of relevance for the onset of PVD, could contribute to new therapeutic options and rational allocation of current treatment strategies.

Only 1 systematic review on PVD is available, addressing the relationship between PVD and inflammatory biomarkers.[56] To date, no systematic review has been performed specifically aimed at the relationship between VVC and PVD. Therefore, we conducted a systematic review addressing the following research question: Do women with PVD have a greater likelihood of having had a history of VVC compared with healthy controls?

METHODS

Eligibility Criteria, Information Sources, and Search Strategy

We included all cohort and case-control studies that compared women with PVD to healthy controls with respect to the presence of a history of *Candida* vulvovaginitis. Only studies that were published over the past 15 years and with full text available in English, Dutch, German, or French were included. Conference abstracts, reviews, and editorials were excluded. Subjects had to be women with strictly defined complaints of PVD, preferably according to the ISSVD criteria.[1] Because the 2003 ISSVD revision of PVD terminology no longer includes erythema in the definition because erythema is not present in all PVD cases, it can occur in many other vulvar disorders and may even be physiological.[57] However, we took into account that it may take several years before a new definition is applied to studies. Therefore, studies using different criteria, such as Friedrich's criteria,[58] also were included.

The literature search was performed with the assistance of an information specialist from the Radboud University Library of Medical Sciences. We defined 2 search groups: PVD and VVC, each comprised of Medical Subject Headings (MeSH terms) and free text synonyms. Searches were executed in CINAHL, the Cochrane Library, EMBASE, MEDLINE, PsycINFO, PubMed, and Web of Science and took place on September 26, 2017. The search results were filtered by date, including studies after