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Review

Diagnosis and management of vulvodynia in postmenopausal women

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ABSTRACT

Vulvodynia, defined as vulvar pain or burning sensation for more than 3 months, without an identifiable cause, can occur at any age. In this paper, the authors address the classification, epidemiology, etiology, diagnosis, and treatment of this condition, focusing on postmenopausal women. In postmenopausal women, vulvar pain and dyspareunia can often be attributed to low levels of estrogen resulting in vulvovaginal atrophy. While correction of vulvovaginal atrophy is an important part of the management of these patients, it will usually be insufficient to manage vulvodynia. The treatment of vulvodynia includes general care measures, topical, oral, or injectable agents, psychological approaches, pelvic floor rehabilitation and, in some cases, surgery. No particular intervention has been shown to be superior, so a "trial and error" strategy is usually used.

1. Introduction

Vulvodynia is a common condition. Despite having been first described in the 19th century, is still not widely acknowledged [1,2]. Many providers are unaware of this condition, missing opportunities to help these women who have a substantially impaired sexual life and quality of life in general [3].

The diagnosis is one of exclusion. Before it can be assumed, other significant vulvar, vaginal, urological, and musculoskeletal pathology must be excluded. However, the diagnosis and management of vulvodynia are often neglected. Both can be more challenging in postmenopausal women, among whom vulvar dermatoses (e.g. lichen sclerosus) and estrogen deprivation are common and the symptoms of these can resemble and overlap those of vulvodynia [4,5]. Vulvodynia often is assumed to be "psychological" or "psychosomatic", or "vaginismus" in younger women, while it is often considered to be a consequence of low estrogen levels or vulvovaginal atrophy in the older population. Even though psychological factors often are involved, they do not seem to be the main explanation for the patients' symptoms [6,7]. Vulvodynia is a significant cause of dyspareunia; however the symptoms can be present even in the absence of intercourse [8].

In this paper, we review the approach to the diagnosis and management of vulvodynia, paying special attention to the particular aspects of the disease in older women.

2. Methods

A thorough literature search was performed using Pubmed to identify the most relevant papers and guidelines in the field. The terms "vulvodynia" or "vestibulodynia" were initially searched. These terms were also combined with "menopause".

3. Definition and classification of vulvodynia

The term "vulvodynia" was defined by the International Society for the Study of Vulvovaginal Disease (ISSVD) as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder" [9] – in practical terms, idiopathic vulvar pain, related or not related to sexual activity. In 2015, the definition and classification of vulvodynia were revised by the ISSVD, along with representation from the International Society for the Study of Women's Sexual Health (ISSWSH), and the International Pelvic Pain Society (IPPS). Vulvodynia is now defined as "vulvar pain of at least 3 months' duration, without a

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clear identifiable cause, which may have potential associated factors" [10]. Additionally, it was highlighted that women with specific vulvar disorders (e.g. vulvar dermatoses) are not necessarily excluded from having vulvodynia. Several descriptors can be used to classify or characterize vulvodynia, according to:

- Location: localized (e.g., vestibulodynia, clitorodynia), generalized (the majority of the vulva is affected) or mixed (presence of both localized and generalized pain or burning).
- Need for a stimulus to elicit the symptoms: provoked (the symptoms are elicited by a stimulus, such as intercourse, touch, bicycle seats or saddles, tight clothes), spontaneous (the symptoms occur in the absence of a stimulus) or mixed (provoked and spontaneous symptoms in the same woman).
- Onset: primary (the symptoms were always present − since the first attempt at intercourse, tampon use or, in generalized vulvodynia, the symptoms were always present) or secondary (symptoms were present at some point in life, but not previous to that).
- Temporal pattern: persistent (any pain that lasts for 3 or more months − which can be divided into "constant" or "intermittent"), immediate (symptoms start during the exposure to the provoking stimulus) or delayed (symptoms start after the provoking stimulus).

An addendum to the vulvodynia classification, clarifying the descriptors of vulvodynia is expected to be published during the next few months.

There is some controversy over whether vulvodynia should be classified as a "sexual dysfunction" − it may be more accurate to consider it a chronic dysfunctional (rather than neuropathic) pain [11].

According to the *Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition,* the "genitopelvic pain/penetration disorder" encompasses vaginismus and dyspareunia. In this document, vulvodynia is never referred as a main cause of dyspareunia; failure to diagnose it can lead to inadequate treatments [12,13].

4. Epidemiology

Vulvodynia has been described in every age group [14–16]. Its prevalence has been found to range between 6.1% and 20.8%, but most of the data relate to premenopausal women [2,14,17]. In an European study, the prevalence of vulvodynia dropped after the age of 60 [2]; in a study from the United States, considering only sexually active women, the prevalence was stable up to 70 years of age [16]. More recently, Mitro et al. found a prevalence of 4.0% of vulvodynia in postmenopausal women, although a significant number reported that the symptoms had started before the onset of menopause [17]. The lower prevalence found in the later study may be explained by ethnic factors, as it included a significant proportion of black women, who typically have lower incidences of vulvodynia [18]. The lower incidence in black women may be not real, but attributable to cultural factors (i.e. black women are more likely to consider pain as aching) [19].

Generalized vulvodynia seems to be more common in older women, while localized vulvodynia prevails in younger women [20]. Despite the apparently lower prevalence of vulvodynia in postmenopausal women, these are often very severe cases, and can be difficult to deal with [21].

5. Etiology, risk factors, and associations

Vulvodynia is multifactorial in origin; the precise causes are still being investigated. The etiology includes combinations of pelvic floor abnormalities, dysfunctional/neuropathic pain (including central processing disorders, peripheral neuropathy, and complex regional pain syndromes), increased numbers of cutaneous nerve fibers, low-grade inflammation, psychological factors (anxiety, depression), and genetic predisposition (Table 1) [22]. Most theories and studies have addressed the etiology and pathophysiology of localized rather than generalized vulvodynia, even though it remains unknown whether or not these are manifestations of the same entity [23].

Leclair et al. demonstrated that pre and postmenopausal women with vestibulodynia share histologic features of neurogenic inflammation, however these are much more pronounced in the latter [24].

A chronic neurogenic inflammation, possibly elicited by mast cell degranulation [25], is commonly found in biopsies and vestibulectomy specimens. The inflammatory process includes mast cell recruitment (also known to happen in other pain syndromes, such as fibromyalgia and bladder pain syndrome [BPS]), submucosal nerve growth (with superficial nerve endings), increased numbers of CD4-positive T cells, and sometimes plasma cells in the epithelium [25–28]. However, agreement in the literature is lacking. For example, a recent study by Papoutsis et al. found no association with mast cells in patients with vulvodynia [29]. The vestibule has its own localized immune system which Tommola et al. designated "vestibule-associated lymphoid tissue" (VALT) [27]. Several inflammatory or infectious processes, such as candidosis, may, in theory, trigger the inflammatory response by VALT. The immunological response to these processes may be heightened in women with vulvodynia [22,30].

Although a substantial number of vulvodynia patients recall a history of candidosis, most often it was a diagnosis based only on symptoms, without further laboratory confirmation, thus making it unreliable [31,32]. Nevertheless, Ventolini et al. have shown that there is a specific immunological response after exposure to *Candida* in patients with vulvodynia, and, accordingly, postulated that this can be the first insult that later leads to pain [33]. Foster et al. demonstrated that this response is different in women with and without vulvodynia [30]. Nevertheless, treatment with antifungals generally will not have an impact in vulvodynia patients − *Candida* can represent the initial insult, but does not have to be present in the following stages of the disease.

The role of the vaginal microbiome is still poorly known, but Ventolini found *L. crispatus* to be absent in women with vulvodynia, in contrast to *L. gasseri*, which was found only in those with past or previous vulvodynia [33]. Donders et al. correlated aerobic vaginitis (AV) with the severity of disease (more painful loci and more intense pain in patients with AV than in those without AV) [34].

A role for genetics with vulvodynia can be presumed by the increased incidence of vestibulectomy within women of the same family [26]. However, it must be taken into account that this can be biased, by, for instance, access to the same health care providers. As in other chronic pain syndromes, several genetic polymorphisms that increase the susceptibility to vulvodynia have been described [35]. These include polymorphisms in the gene coding for the interleukin 1 receptor antagonist [36], mannose binding lectin [37,38], and in the serotonin receptor gene (5HT-2A) [39]. In women taking oral contraceptives, polymorphisms of the guanosine triphosphate cyclohydrolase gene [40] and longer cytosine-adenine-guanine trinucleotide repeats in the androgen receptor coding gene were also identified [41].

Generalized vulvodynia is a form of complex regional pain syndrome, often associated with other pain syndromes (fibromyalgia, BPS) and an increased perception of systemic pain. This process is more likely due to central nervous system sensitization than to local factors [42–44].

Other factors possibly associated with vulvodynia are embryologic and/or related to early fetal development (the endodermal origin of the vestibule [45], which could explain the common association with the BPS) [46], dietary (however, the role of oxalates has been challenged recently) [47–49], sexual (sexual abuse, age of sexual debut) [50,51], and heightened pelvic muscle tone [52].

The role of hormones is controversial: several studies associate the use of oral contraceptives and a hypoestrogenic state with the development of vulvodynia [53,54], but others have not found this association [55].