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REVIEW

"Time is on my side". Disease trajectory of vulvodynia: a systematic review with a narrative synthesis

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Abstract

Purpose The aim of this systematic review was to shed light on the disease-trajectory of vulvodynia and identify potential risk factors which may affect such trajectory.

Methods We searched Pubmed to identify articles providing evidence on vulvodynia trajectory (i.e., remission, relapse or persistence rates) with a minimum follow-up of 2 years. A narrative approach was used for data synthesis.

Results Four articles were included (total participants: 741 women with vulvodynia; 634 controls). At a 2-year follow-up, 50.6% of women reported remission, remission with relapse was observed in 39.7% and persistence throughout time occurred in 9.6%. A decrease in pain was observed in 71.1% of patients at a 7-year follow-up. Mean pain scores and depressive symptoms resulted lower at 2-year follow-up, whereas sexual function and satisfaction were increased. Factors associated with remission of vulvodynia were greater couple cohesion, decreased reporting of pain after intercourse and lower levels of worst pain. Risk factors for symptom persistence included marriage, more severe pain ratings, depression, pain with partner touch, interstitial cystitis, pain with oral sex, fibromyalgia, older age and anxiety. Recurrence was associated with: longer duration of pain, more severe ratings of the worst pain ever and pain described as provoked.

Conclusions Symptoms of vulvodynia seem to improve over time, regardless of treatment. This finding contains a key message for patients and their physicians, considering the deleterious consequences of vulvodynia on women's lives.

Keywords Vulvodynia · Disease trajectory · Remission · Relapse · Persistence

What does this study add to the clinical work

The understanding of vulvodynia's persistence, remission, and relapse rates is still unsatisfactory. The aim of the paper is to shed light on disease trajectory in order to improve patient counseling and clinicians' understanding of this condition.

Introduction

Vulvodynia embraces in its etymology two health areas that are arguably neglected, i.e., external genitalia and chronic pain. It is defined as vulvar pain with a duration of at least 3 months, without a clear identifiable cause, which may have potential-associated factors. The pain may be either spontaneous or provoked and, in the latter case, can occur in sexual or non-sexual situations, during attempted or successful penetration or in situations which cause pressure on the vulva [1]. As such, it may profoundly impact on patients' sexual

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Time is on my side: In: The Rolling Stones No. 2, Decca, London, U.K, 1964.

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function and satisfaction as well as on relational wellbeing. In cases of spontaneous pain, which is not provoked by intercourse, vulvodynia may also limit daily activities [2]. The psychosocial burden of this condition is highlighted by its inclusion in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), listed in the category of sexual dysfunctions [3].

The literature regarding this condition, which is scarce and discordant, reflects the secondary importance awarded to vulvodynia, despite its not negligible incidence of 7–15% in the general population [1]. Multiple hypotheses regarding the pathophysiology of vulvodynia have been advanced. Correspondingly, a multitude of treatments has been suggested, although no single treatment has been proven to be efficacious in most patients [4]. In fact, papers on the topic mainly consist of expert opinions or small sample size studies, which lack an adequate experimental design or a comparison with placebo. This results in a still unsatisfactory understanding of the disease's persistence, remission, and relapse rates [5].

Addressing affected patients' distress holding such scarce knowledge constitutes a real challenge for physicians. The absence of clear data regarding the natural history of vulvodynia limits the efficacy of counseling and, consequently, the possibility of shared decision-making.

The aim of this review was to shed light on the disease-trajectory of vulvodynia in terms of remission, relapse or persistence or symptom intensity modification at a minimum 2-year follow-up and identify potential risk factors which may affect such trajectory. We deem that more comprehensive knowledge regarding spontaneous resolution of this condition is fundamental for patients to better understand the implications of such diagnosis, and thus cope with its consequences on quality of life. In addition, clearer data on disease trajectory are badly needed for the definition of the magnitude of the effect of treatments, compared with what would have happened anyway.

Methods

This systematic review (not registered in PROSPERO) was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [6]. The complete PRISMA checklist is provided (Supplemental Table 1). It should be noted that not every item of the checklist could be applied in our review, considering the qualitative approach used to summarize the data. A systematic literature search was conducted between March 2022 and January 2023 using the electronic databases PubMed and MEDLINE (last search conducted on January 7th 2023). The search strategy included terms combined with the Boolean operators "OR" and "NOT"; the final search string was the following: "vulvodynia OR vestibulodynia NOT menopausal NOT cancer NOT menopause NOT lichen". Due to the heterogeneity of terms used in the literature to describe disease trajectory, we chose to use a broad string and to subsequently select the most pertinent articles. No time restrictions were applied. Non-original articles, abstracts and papers not written in English were excluded.

Two authors (G.E.C. and C.E.M.M.) assessed the papers and independently selected the articles considered eligible for the review. Studies were included if they met the following criteria: reporting of original data, adoption of a clear definition of vulvodynia in accordance with the intersocieties document agreement [1], analysis of disease trajectory with a minimum follow-up time of 2 years. Reference lists were analyzed to identify additional studies meeting inclusion criteria. All articles analyzing the efficacy of specific treatments for vulvodynia were excluded. Discrepancies were resolved by discussion. Data extraction was performed independently by G.E.C. and C.E.M.M., who retrieved information regarding authors, date and country of publication, study design and methods, number of patients enrolled, modality of diagnosis of vulvodynia, outcome measures, treatment and follow-up time. Extracted information was organized in an Excel spreadsheet. No attempt was made to retrieve unpublished material.

Due to the exiguous number of retrieved studies and the heterogeneity in diagnosis modality and outcome measures, the data extracted from the included articles was summarized using a narrative approach, rather than a quantitative methodology. The analytic process involved line-by-line reading and coding of all articles for the identification of recurrent issues, ordering of issues for the definition of prominent themes, and creation of a narrative synthesis of the findings [7]. The quality of the articles included in the review was evaluated using the Newcastle–Ottawa quality assessment scale [8].

Results

Of the 991 articles initially identified, nine were considered eligible for in-depth reading [5, 9–16]. A total of 982 articles were excluded after screening titles and abstracts. Reasons for exclusion were not being relevant, i.e., articles not regarding disease trajectory (980 articles); not being written in English (two articles). Among the nine articles eligible for in-depth reading, five were excluded: four did not evaluate proper outcomes [5, 9, 10, 15], one did not include a minimum follow-up time of 2 years [16]. Only four articles were chosen for the review. The flowchart of the selection process of studies is represented in Fig. 1.

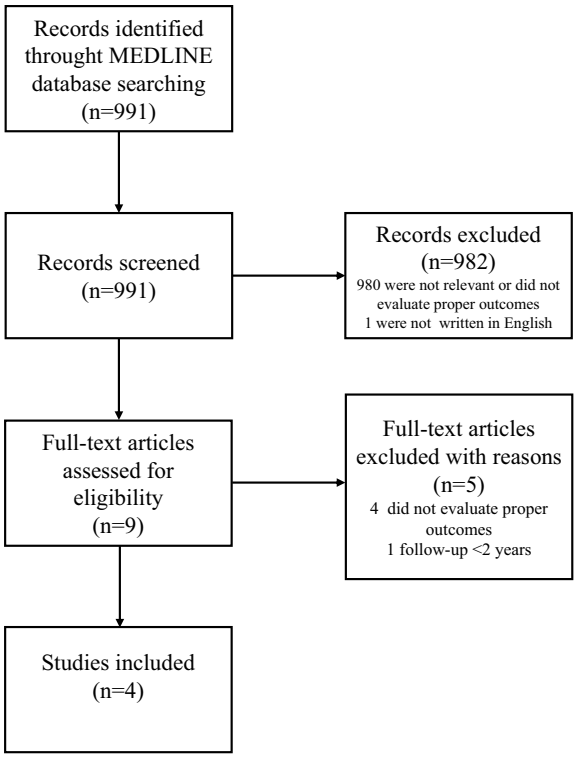

Fig. 1 Flowchart of the selection process of the studies included in the review

A total of 741 women with vulvodynia and 634 controls were included. Women's mean age was 42.3 years (SD ± 6.3). Mean follow-up time was 39 months (range 24–84 months). Two studies included women with a generic diagnosis of vulvodynia [13, 14], while the remaining two considered specifically women with provoked vestibulodynia (PVD) [11, 12]. Three studies were case series [11, 12, 14], while one study included both cases and controls [13]. Two articles were written by the same author but included different study populations [13, 14]. Details regarding the included studies are reported in Table 1.

Recruitment methods

Recruitment methods varied among studies. In Reed et al. articles [13, 14], patients were recruited by means of a research participant database. In only one of the two articles [13], eligibility was confirmed on a subset of enrolled women by means of telephone screening or through clinical evaluation. In two studies [11, 12], women were recruited both by gynecologists and through newspaper and website advertisements. Eligibility was confirmed by telephone enquiry (Harlow's criteria) [2] or by clinical examination.

Inclusion criteria

In Reed et al. studies, eligible women completed a baseline questionnaire for vulvodynia as well as an additional 2-year follow-up survey in one article [13] and four follow-up surveys every 6 months in the second article [14]. Women who resulted negative for vulvodynia at baseline were included in the control group. Both Pâquet et al. [12] and Davis et al. [11] required women to have been in a relationship at the time of inclusion and to have vulvodynia-like symptoms. In Davis et al. study [11] a further inclusion criterion was represented by age as all women were aged 18–45.

Diagnostic criteria

The criteria used to diagnose vulvodynia also differed between articles. Reed et al. [13, 14] considered women to be affected if they reported pain at the vaginal introitus for at least 3 months. The presence of infections or dermatoses was excluded in one study, only in a subset of patients [13]. More extensively, Pâquet et al. [12] included all women with distressful pain occurring in ≥ 75% of intercourse attempts or other activities that lead to pressure on the vulvar vestibule that had lasted for ≥ 6 months. Likewise, Davis et al. [11] described provoked vestibulodynia as a subjectively distressing pain lasting more than 1 year and occurring on at least 80% of attempts of intercourse or other activities that cause pressure on the vulvar vestibule. In the cohort of women recruited by physicians, diagnosis was confirmed with a cotton swab test. The presence of vulvovaginal infections, deep dyspareunia, vaginismus, dermatoses, and pregnancy were exclusion criteria.

Follow-up

In Reed et al. articles [13, 14], a validated questionnaire used for the diagnosis of vulvodynia was sent to patients 2 years following enrollment in one study [13] and every 6 months for 2 years in the second study [14]. Pâquet et al. asked participants to complete three questionnaires: one at time of enrollment, 1–2 years later and 1–7 years after enrollment [12]. The questionnaires evaluated pain intensity with a Numerical Rating Scale (NRS) and anxiety and depressive symptoms by the means of the State–Trait Anxiety Inventory and the Depression Inventory-II (BDI-II) [17]. Qualitative data regarding treatment, pain duration and localization, age at pain onset, duration of relationship, marital status and relationship quality were also retrieved. Davis et al. measured pain intensity using a visual analog scale (VAS), sexual satisfaction by the means of the Global Measure of Sexual Satisfaction (GMSEX) [18], sexual function with the Female Sexual Function Index (FSFI) [19], depressive symptoms using the Beck Depression Inventory (BDI) [17] and

Table 1 Characteristics of the studies included in the review

Author, year	Country	Study design	*N*. Patients	Modality of VD diagnosis	Outcome measures	Mean age (years)	Treatment	Follow-up (months)
Reed et al. (2008) [13]	Michigan	Prospective	724 (90 cases, 634 controls)	Online questionnaire	Remission rate of VD Identification of factors associated with remission	47	Not specified	24
Davis et al. (2013) [11]	Canada	Prospective	239 (239 cases, 0 controls)	49% diagnosed by Ob/Gyn; 51% diagnosed using phone screening	Changes in pain intensity (VAS) and in depressive symptoms (BDI) Changes in sexual outcomes (GMSEX, FSFI, DAS, sexual intercourse attempts over the past month), accorging to treatment type	30.9	Physical therapy Sex therapy, psychotherapy Medical treatment Surgery Acupuncture Other	24
Reed et al. (2016) [14]	Michigan	Prospective	239 (239 cases, 0 controls)	Validated screening test	Rates of remission, relapse and persistence Relationship between remision, relapse, persistence and treatment type	47.6	Estrogen ± progesterone Antifungals Topical steroids Moisturizing creams	24
Pâquet et al. (2019) [12]	Quebec	Prospective	173 (173 cases, 0 controls)	49% diagnosed by Ob/Gyn; 51% diagnosed using phone screening	Changes in pain intensity (NRS) Relationship between pain reduction, persistence and: treatment type, pain characteristics, anxiety, depression and relationship variables	31.2	Not specified	84

VD vulvodynia, *VAS* Visual Analog scale, *BDI* beck Depression Inventory, *GMSEX* global measure of sexual satisfaction, *FSFI* female sexual function inventory, *DAS* dyadic adjustment scale, *NRS* numeric rating scale

relationship satisfaction by the means of the revised Dyadic Adjustment Scale (DAS) [20]. Patients were also asked how many times they had attempted to have sexual intercourse with vaginal penetration over the past month [11]. The survey was given at time of enrollment and 2 years later.

Disease trajectory

Rates of remission and persistence of vulvodynia were the main outcomes of one article [13]. Reed et al. also analyzed relapse rates [14]. The rate of pain reduction in women with vulvodynia was the main outcome of the remaining two studies [11, 12].

There is no accepted standard definition of remission of vulvodynia. In both articles Reed et al. defined remission as no longer meeting criteria for vulvodynia following a positive screen. Relapse was defined as being newly positive following remission, and persistence was defined as continuing to screen positive for vulvodynia at every follow-up [13, 14].

Reed et al. found that 22% of women with vulvodynia reported remission at a 2-year follow-up [13]. Eight years later, the same authors observed remission in 50.6% of

patients, remission with relapse in 39.7% and persistence throughout time in 9.6% [14]. When analyzing pain trajectory at a 7-year follow-up, Pâquet et al. observed a decrease in pain in 71.1% of patients and a persistence of pain in 28.9% [12]. Finally, Davis et al. analyzed changes in symptoms at a 2-year follow-up in a cohort of 239 patients with vulvodynia. Mean pain NRS scores resulted lower (− 2.8 points), as were depressive symptoms (− 2.4 BDI points), whereas sexual function (+ 1.4 FSFI points) and sexual satisfaction (+ 1.8 GMSEX points) were increased. The number of attempts at intercourse over the past month and dyadic adjustment did not change significantly [11].

Risk factors and protective factors

In Reed et al. first study, remission was associated with decreased reporting of pain after intercourse at time of enrollment (50% compared with 82%, OR 0.2; 95% CI 0.0–0.9) and with a lower level of worst pain in the past 6 months (2.8 ± 1.9 compared with 4 ± 1.2 points on a 0–5 pain scale, OR 0.6; 95% CI 0.4–0.9) [14]. In Reed et al. subsequent article, the factors significantly associated with persistence of symptoms were: marriage, more severe ratings of the worst pain ever (OR 1.26; 95% CI 1.06–1.49), depression (OR 2.9; 95% CI 1.1–8.17), pain with partner touch (OR 3.2; 95% CI 1.24–8.35), interstitial cystitis (OR 3.6; 95% CI 1.17–11.04), pain with intercourse (OR 3.9; 95% CI 1.02–15.66 in patients with mild pain, OR 7.9; 95% CI 1.74–35.47 in patients with moderate pain, OR 6.9; 95% CI 1.19–40.44 in patients with severe pain), pain with oral sex (OR 5.9; 95% CI 1.78–20.11), severe pain after intercourse (OR 8.3; 95% CI 1.01–67.58) and presence of fibromyalgia (OR 9.21; 95% CI 3.29–25.80). Factors associated with recurrence were longer duration of pain (OR 1.03; 95% CI 1.01–1.05), more severe ratings of the worst pain ever (OR 1.2; 95% CI 1.06–1.30), moderate pain with intercourse (OR 2.3; 95% CI 1.03–5.24), moderate pain after intercourse (OR 3.1; 95% CI 1.20–8.56), pain described as provoked (OR 3.3; 95% CI 1.43–7.82) [14]. Pâquet et al. found marriage (34.2% vs. 19.1%), older age at first pain onset (46 years vs. 25 years), pain at another vulvar localization in addition to the vestibule (40.8% vs. 22.1%) and anxiety (45.9% vs. 42.7%), to be risk factors for persistence of the pain. Conversely, a greater couple cohesion was found to be a protective factor (11.6% vs. 12.7%) [12]. Davis et al. reported no correlations between demographic variables or pain characteristics and outcome variables [11]. Table 2 summarizes risk factors and protective factors reported in the included studies.

Influence of treatment on disease trajectory

Three out of four authors analyzed treatment types [11, 12, 14]. In Reed et al. study, only 12.5% of patients with a diagnosis of vulvodynia reported taking medications at the time of their positive screen. Among these, 50% were on estrogen ± progesterone, 13% on antifungals, 20% on topical steroids, 23% on topical creams or moisturizers, and 13% reported taking miscellaneous treatments. None were on pain medication, on antidepressants or anticonvulsants. Clinical outcome was not associated with treatment [14]. In Pâquet et al. analysis, 71.1% of patients received treatment for vulvodynia, although treatment type was not specified. Having undergone a treatment was not significantly associated with a specific disease trajectory [12]. A total of 59% of women with vulvodynia had undergone treatment in Davis et al. study. Overall, 41% of these had undergone physical therapy, 19.2% sex therapy/psychotherapy, 18.8% medical treatment, 7.1% surgery, 2.5% acupuncture, 8.4% other treatments and 25.5% multiple treatments. The authors observed a statistically significant reduction in pain for all treatments except for acupuncture, with a significant reduction also in those not receiving treatment. None of the treatment types were associated with significant changes in the number of attempts at intercourse or in relationship satisfaction. Regarding sexual function, all groups were in a dysfunctional range at time of enrollment and only the "other treatment" group was in a functional range at time of follow-up. As to what concerns depressive symptoms, an improvement was observed only in patients receiving treatment [11].

Discussion

Vulvodynia is a distressing condition caused by multiple and interdependent biopsychosocial factors that poses a considerable burden on women's health. It has long been considered a chronic pain disorder in which remission of symptoms is rare [13]. However, data regarding disease trajectory of this condition are scarce. The majority of the evidence regarding natural history of vulvodynia is limited by methodological drawbacks. In particular, retrospective studies may be biased by the fact that women often fail to recall pain documented at an earlier stage.

The aim of our review was to shed light on the disease trajectory of vulvodynia with the objective of trying to improve the quality of patient counseling. In fact, we deem that gaining this knowledge is crucial for understanding and accepting the diagnosis, as well as representing a starting point for a more adequate evaluation of the efficacy of treatments.

When analyzing women with vulvodynia at a 2-year follow-up, Reed et al. observed remission of the disease in more than 20% of patients [13]. The same authors monitored

Table 2 Risk factors and protective factors associated with disease trajectory

	Protective factors for remission of vulvodynia	Risk factors for persistence of vulvodynia	Factors associated with recurrence of vulvodynia
Reed et al. (2008) [13]	Decreased reporting of pain after intercourse at time of enrollment (OR 0.2) Lower levels of worst pain in the past 6 months OR 0.6)	NA	NA
Reed et al. (2016) [14]	NA	Marriage More severe ratings of the worst pain ever (OR 1.3) Depression (OR 2.9) Pain with partner touch (OR 3.2) Interstitial cystitis (OR 3.6) Pain with intercourse (OR 3.9) Pain with oral sex (OR 5.9) Severe pain after intercourse (OR 8.3) Fibromyalgia (OR 9.2)	Longer duration of pain (OR 1) More severe ratings of the worst pain ever (OR 1.2) Moderate pain with intercourse (OR 2.3) Moderate pain after intercourse (OR 3.1) Pain described as provoked (OR 3.3)
Pâquet et al. (2019) [12]	Greater couple cohesion (13% vs. 12%)	Marriage (34% vs. 19%) Older age at first pain onset (46 years vs. 25 years) Pain at another vulvar localization in addition to the vestibule (40.8% vs. 22.1%) Anxiety (46% vs. 42%)	NA

OR odds ratio, *NA* not applicable

a similar cohort of patients every 6 months for a minimum of 2 years and found remission in more than two thirds of patients. However, in nearly half of these, remission was followed by relapse. Persistence of symptoms was observed in less than 10% of women [14]. Although results differ between articles, a non-negligible rate of remission or of remission with relapse was observed. These data do not appear to be coherent with the definition of chronic disease.

Analyzing pain trajectory at a 7-year follow-up, Pâquet et al. found a decrease in pain in approximately two thirds of patients [12], while at a 2-year follow-up Davis et al. reported lower mean pain scores and depressive symptoms, together with increased sexual function and satisfaction [11]. The evidence of an improvement of symptoms over time is an important clinical data which, however, does not exclude the definition of chronic disease.

Interestingly, improvement of pain was reported both in patients who had received treatment and in those who had not. The same cannot be said for psychosexual outcomes, which were significantly improved only in treated patients [11]. This is probably due to the fact that reduction of pain itself is not sufficient to improve reduced sexual desire, arousal and satisfaction, feeling of shame and inadequacy as a sexual partner, reduced body appreciation and lower self-esteem [1]. It must also be noted that statistical change is important but does not necessarily imply clinical relevance.

The percentage of women seeking treatment for vulvodynia was heterogeneous between studies and ranged between 12.5% and 71.1% [11, 12, 14]. According to Reed et al. [14] and Pâquet et al. [12], treatment type was not associated with a specifics disease or pain trajectory, whereas in Davis et al. study a significant reduction in pain was observed in all treatment groups except for acupuncture and no single modality of treatment appeared superior to any other [11].

It is important to note that in Reed et al. study women reported the use of estrogens, antifungals, topical steroids and moisturizers, while none were on pain medications [14]. These data raise the question of a correct diagnosis of vulvodynia: were enrolled patients really suffering from vulvodynia or were women with infections, dermatoses and vulvovaginal atrophy erroneously included? In this study diagnosis was performed by the means of a questionnaire and only a subset of patients was called for a clinical in-person evaluation. Moreover, women enrolled in the study had a mean age of 47.6 years and as such may have been suffering

from other diseases causing vulvar pain, namely, vulvovaginal atrophy and vulvar dermatoses. A similar limitation, which is common to all studies included in the review, is the absence of a differential diagnosis with neurological conditions leading to vulvar pain, such as pudendal neuralgia.

Many sociodemographic and clinical characteristics have been found to be protective or risk factors for the persistence of pain. Older age at pain onset seems to be a risk factor for persistence of vulvodynia [12], although Reed and co-workers found no difference in disease trajectory according to age [14]. Marital status was associated with a reduced probability of remission [14] and the presence of comorbidities such as fibromyalgia, interstitial cystitis, anxiety and depression has been described as a risk factor for persistence and of relapse, as has the presence of provoked vulvodynia [12, 14]. Conversely, greater couple cohesion and lower levels of pain have been found to be protective for remission [12, 13].

Conclusions

The main outcomes of the studies included in the present review are difficult to compare due to the heterogeneity of data. However, it appears that symptoms of vulvodynia generally improve over time in as many as two thirds of women, also in those not receiving treatment. Considering the possible deleterious consequences of vulvodynia on women's lives, evidence regarding an improvement of symptoms over time is fundamental.

However, future studies should be conducted adopting reliable and standardized diagnostic and follow-up modalities. The adoption of a common set of core outcomes, as those defined by Foster et al. would be useful to compare data from different centers [21]. Only then could women with vulvodynia be empowered to understand more clearly what they should expect in the forthcoming years, both with and without treatment. Finally, uncontrolled studies should no longer be conducted as, considering the not negligible spontaneous remission of symptoms, it would be difficult if not impossible to quantify the specific effect of treatments.

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Declarations

Conflict of interest The authors declare no financial or non-financial conflicts of interest.

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