Journal of Gynecology and Obstetrics
2024, Vol. 12, No. 6, pp. 118-131
https://doi.org/10.11648/j.jgo.20241206.11

Research Article

Comorbidity Pattern and Autonomic Nervous System Dysfunction in Patients with Chronic Vulvar Discomfort

Vesna Harni[1, *], Damir Babic[2], Suzana Ljubojevic Hadzavdic[3], Dubravko Barisic[4], Magdalena Karadza[5]

[1]Department of Obstetrics and Gynaecology, Polyclinic Harni, Zagreb, Croatia
[2]Department of Pathology and Cytology, University Hospital Centre, Zagreb, Croatia
[3]Department of Dermatovenereology, University Hospital Centre, Zagreb, Croatia
[4]Department of Obstetrics and Gynaecology, Kardinal Schwarzenberg Klinikum GmbH, Schwarzach im Pongau, Austria
[5]Department of Obstetrics and Gynaecology, University Hospital Centre, Zagreb, Croatia

Abstract

This study examines novel concepts of comorbidity in patients with chronic vulvar discomfort using data from the DATRIV (Diagnostic Accuracy of Three Rings Vulvoscopy) study, which involved 328 participants categorized into four groups: asymptomatic individuals with normal or impaired vulvar skin and patients with chronic vulvar discomfort, classified as either vulvodynia or vulvar dermatosis. Clinical data were collected through a structured questionnaire and analyzed using statistical software, including StatSoft (Dell, Austin, TX, USA), Statistica 12 (TIBCO®, Palo Alto, CA, USA), and SPSS 20 (IBM, Armonk, NY, USA). The study received approval from the Institutional Review Board of Polyclinic Harni, and all participants provided written informed consent. The findings reveal significantly higher comorbidity rates in patients with chronic vulvar discomfort compared to other groups ($p = 0.0000$). A substantial percentage of asymptomatic participants with both normal (63.4%) and impaired (70.7%) vulvar skin also reported comorbid conditions. Analysis of comorbidity curves revealed distinct patterns of symptom progression, with a gradual increase in frequency from asymptomatic individuals to patients with vulvodynia, followed by a decline in vulvar dermatosis cases. These patterns highlight the central role of autonomic nervous system (ANS) dysfunction, where sympathetic hyperactivity and parasympathetic depression contribute to separate comorbidity chains. These dysfunctions may act independently or concurrently, leading to various health issues. The elevated comorbidity rates and overlapping symptomatology suggest complex pathophysiology driven by ANS dysregulation. Further research on comorbidity clusters may unveil new therapeutic targets and guide the development of multifaceted treatment strategies.

Keywords

Chronic Vulvar Discomfort, Vulvodynia, Vulvar Dermatosis, Comorbidity, Comorbidity Network, Comorbidity Cluster, Comorbidity Chain, Autonomous Nervous System, ANS Dysfunction

[*]Corresponding author: vesnaharni@gmail.com (Vesna Harni)

Received: 20 September 2024; **Accepted:** 10 October 2024; **Published:** 12 November 2024

1. Introduction

Chronic discomfort in the vulva represents a multifaceted challenge in a perplexing scenario. It persists for more than three months despite extensive investigations that reveal no or minimal organic abnormalities, with a significant impact on the physical and psychological well-being of women [1-3].

It encompasses persistent vulvar discomfort, often referred to as vulvar pain, categorized into primary idiopathic pain with no apparent cause and secondary vulvar pain arising from specific conditions such as vulvar dermatoses [4, 5]. Vulvodynia is classified as primary idiopathic pain lasting at least three months, presenting without a clear cause and potentially coinciding with other conditions [6-13].

Comorbidity refers to the simultaneous presence of two or more medical conditions in an individual over their lifetime [14]. Comorbidity patterns describe the occurrence and relationships between multiple medical conditions within individuals or populations. Key concepts within a comorbidity network include comorbidity clusters and chains [15, 16].

Comorbidity clusters are groups of diseases or conditions that tend to occur together more frequently than would be expected by chance. These clusters can reveal patterns and relationships between health conditions [17, 18].

Comorbidity chains refer to causal sequences or pathways through which one condition leads to another over time. This concept focuses on the temporal progression and causal relationships between conditions [17, 18].

Recognizing comorbidity clusters and chains allows healthcare providers to offer more personalized and effective treatment plans. Healthcare systems can allocate resources more efficiently by understanding which comorbidities commonly occur together and prioritizing interventions for these clusters. Identifying these patterns can inform public health policies and research priorities, leading to better-targeted health initiatives and funding.

The interactions between multiple comorbid conditions can be highly complex, requiring sophisticated analytical methods and interdisciplinary approaches to understand fully. Comorbidity patterns vary widely among different populations, influenced by age, gender, ethnicity, and socioeconomic status. Understanding comorbidity patterns is crucial for improving patient outcomes, optimizing healthcare delivery, and enhancing the quality of life for individuals with multiple health conditions [17, 18].

Research indicates a significant prevalence of comorbidities among patients experiencing chronic vulvar discomfort [19-22].

Chronic vulvar discomfort often intertwines or coexists with other forms of functional pain, such as fibromyalgia, irritable bowel syndrome (IBS), urinary dysfunction, and temporomandibular joint disorder (TMJD), suggesting common underlying mechanisms [23-28]. Psychological disorders, particularly anxiety and depression, are common, mainly stemming from the distress associated with chronic pain [29-31]. Sexual dysfunction, encompassing reduced desire, arousal difficulties, and dyspareunia, is also widespread [32, 33].

Additionally, autoimmune disorders such as systemic lupus erythematosus (SLE) and Sjögren's syndrome may correlate with chronic vulvar discomfort, indicating potential involvement of the immune system [34, 35]. Other gynecological issues, including endometriosis and pelvic floor dysfunction, can also coincide with chronic vulvar pain, emphasizing the contribution of multiple overlapping factors to vulvar discomfort and highlighting its complex nature [36, 37].

Pathophysiological parallels between chronic vulvar pain and other forms of chronic functional pain indicate shared similarities in etiology, encompassing infectious, autoimmune, and sympathetic dysregulation mechanisms [3]. The cascade of changes resulting in chronic vulvar pain begins with an initial nociceptive factor that induces local secretion of algogenic substances, activates afferent nociceptive fibers, and triggers neurogenic inflammation. The outcome is intense spinal cord stimulation, leading to a lowered pain threshold, increased neuronal excitability, and expansion of receptor fields beyond the affected organ, characteristic of sensitization [3].

The nuanced interplay between the autonomic nervous system (ANS) and comorbidities underscores the complex aspects of vulvar discomfort endurance. Imbalances in any section of the ANS - sympathetic (SNS), parasympathetic (PNS), and enteric nervous system (ENS), can contribute to the development of coexisting conditions or be influenced by them [38-41]. Generally, the SNS and PNS have opposing effects, with the SNS defined by "fight or flight" responses and associated with stress. At the same time, the PNS regulates rest, digestion, diuresis, and excretion, which are linked to "peace" [40]. The ENS works with the PNS and SNS to control digestion. The ability to adapt to environmental stressors is severely compromised by autonomic failure [40].

Key considerations include recognizing a complex relationship, identifying common underlying mechanisms, understanding the burden of additional symptoms, and addressing treatment challenges [41]. The ANS plays a significant role in regulating physiological functions and maintaining homeostasis [42, 43]. Imbalances within its components can contribute to specific health conditions, while comorbidities can also affect ANS function, indicating a reciprocal relationship [44]. Specific health conditions and autonomic imbalances may share common mechanisms or risk factors, making ANS imbalance a common pathway linking these comorbidities [45, 46].

Consequently, ANS dysregulation may be involved in the onset or exacerbation of chronic vulvar discomfort and related conditions [42, 43]. Understanding the interactions and impacts of the ANS on the spectrum of comorbidities and vice versa is crucial [44]. Comorbidities involving autonomic dysfunction can exacerbate symptom burden. Furthermore, comorbidities and ANS imbalances can complicate treatment,

as managing one condition may directly or indirectly affect ANS function, impacting other conditions (*Figure 1*). Therefore, personalized, coordinated treatment plans are often necessary to address specific health issues and ANS imbalances [46, 47].

Understanding the connections between ANS dysfunction, termed "autonomic dysfunction" or "dysautonomia," and comorbidities offers insights into disease development, symptomatology, and potential treatments [41]. Prolonged sympathetic hyperactivity can contribute to hypertension, cardiovascular diseases, metabolic disorders, and immune system dysregulation, influenced by the release of stress hormones, increased heart rate, vasoconstriction, and altered immune responses [46-48]. Reduced parasympathetic control of the gastrointestinal tract can lead to digestive disorders such as gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), or functional dyspepsia [49, 50].

In gynecology, ANS dysfunction and imbalance can have specific implications. Dysautonomia or ANS neuropathy may manifest as irregular menstrual cycles, abnormal uterine bleeding, or dyspareunia [51]. Autonomic imbalance may also contribute to conditions such as polycystic ovary syndrome (PCOS), endometriosis, or pelvic pain disorders, affecting hormonal regulation, blood flow, and pain perception in the pelvic area [52, 53].

The primary goal of this study was to identify the comorbidity network and examine the causal connection between the autonomic nervous system (ANS) and its components (SNS/PNS) with the emergence of comorbid clusters and chains in patients with vulvar discomfort and a control group without such complaints. This investigation involved participants in the DATRIV study [54, 55].

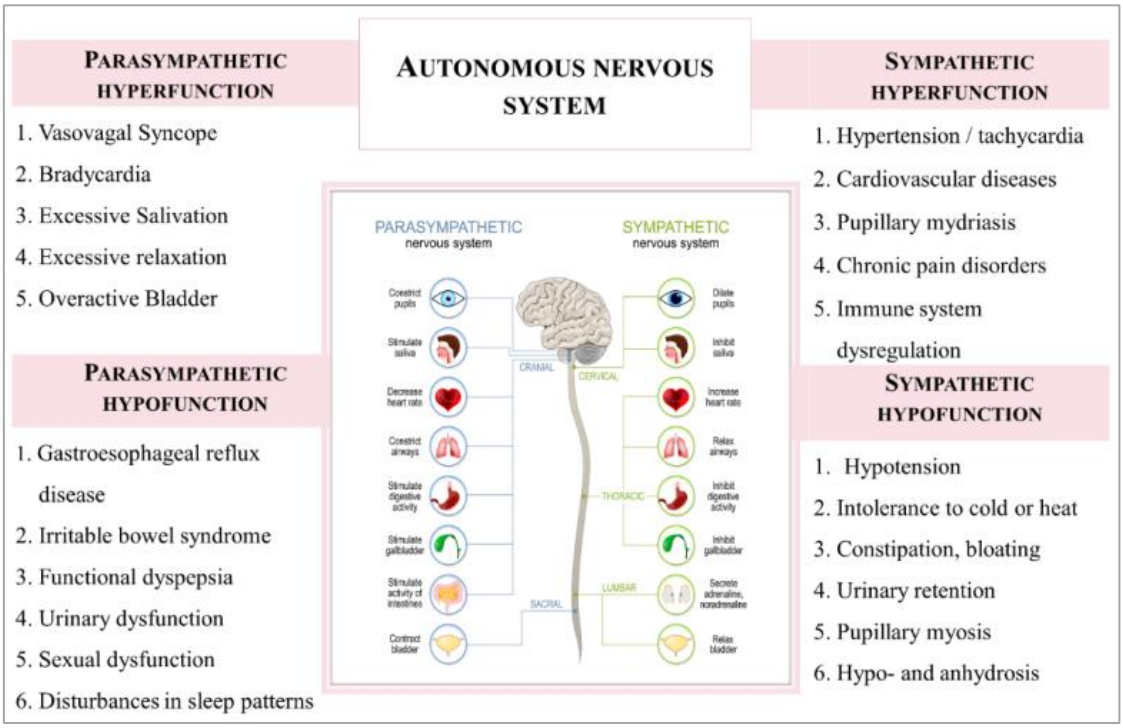

Figure 1. *Overview of hyper- and hypofunction symptoms of the parasympathetic (PNS) and sympathetic division (SNS) of the autonomic nervous system (ANS).*

2. Methods

2.1. Study Design

The DATRIV study (Diagnostic Accuracy of Three Rings Vulvoscopy) was initiated to refine the diagnosis and treatment of vulvar discomfort [54, 55], focusing on utilizing Three Rings Vulvoscopy (TRIV). The study also aimed to establish standardized outcome measures for vulvoscopy.

Lesions observed during the study were categorized based on established principles [56, 57]. Dermatological lesions displaying secondary morphological characteristics were termed "specific lesions." Their locations were meticulously documented concerning the three vulvar rings.

The study participants were divided into four groups using patient history, ISSVD Vulvodynia Pattern Questionnaire responses, and clinical assessments. Asymptomatic individuals were further classified into those with a "normal vulva" and those with "impaired vulvar skin," while patients experiencing chronic vulvar discomfort were subdivided into primary vulvar pain/vulvodynia and secondary discomfort attributed to vulvar dermatosis.

Regardless of observed vulvar lesions, vulvodynia was diagnosed following Friedrich's criteria and recent recommendations [6-13]. Diagnosing vulvar dermatosis involved identifying specific dermatological lesions with secondary morphological manifestations and assessing the presence and distribution of nonspecific lesions across the three vulvar rings.

Conducted at the Polyclinic Harni in Zagreb, Croatia, between December 1, 2011, and December 31, 2016, the study encompassed both symptomatic and asymptomatic patients. Certain vulvar conditions, incomplete medical records, and protocol deviations were exclusion criteria.

All participant groups underwent TRIV and vulvar biopsy with histopathology, with biopsies being routine for symptomatic patients and asymptomatic individuals selected from those scheduled for labiaplasty.

2.2. Data Analysis

The data analysis methodology in this study was tailored to the characteristics and distribution of the variables under investigation.

For qualitative variables, such as different categories or groups, we utilized the chi-squared test with Yates correction or Fisher's exact test with smaller sample sizes. When comparing two percentages, the t-test for proportions was employed.

Quantitative variables exhibiting a normal distribution were analyzed by calculating the arithmetic mean and standard deviation. Variance analysis (ANOVA) was conducted to compare means across multiple groups. Post hoc Tukey HSD tests were performed in instances of significant differences to identify specific group variations. The t-test was applied to compare the two groups.

In cases where quantitative variables did not follow a normal distribution, nonparametric tests were used. The Kruskal-Wallis ANOVA assessed differences among several groups, while the Mann-Whitney U test compared differences between two groups.

All statistical analyses were conducted using the Statistical Package 12.0 on a personal computer (PC).

2.3. Ethical Approval

Participants were explicitly informed about the voluntary nature of their study participation and allowed to decline the questionnaire if they wished. Written informed consent was obtained for patients undergoing vulvoscopy and vulvar biopsy. That ensured they thoroughly understood the procedures, potential risks, benefits, and voluntary participation agreement.

Ethical clearance was obtained from the Institutional Review Board of Polyclinic Harni, indicated by the Ethical Approval Number (20111201001). That demonstrates compliance with ethical standards and directives from the review board.

The DATRIV study was registered on ClinicalTrials.gov under the identifier NCT02732145. This registration enhances transparency by disseminating the study's objectives, design, and outcomes to the research community and the public.

These ethical measures underscore the study's dedication to ethical protocols and protecting participant rights. Adherence to informed consent and voluntary participation is essential in research, while ethical approval and study registration uphold these principles and enhance research transparency.

3. Results

3.1. General Distribution of Comorbidities According to Groups of Patients from the DATRIV Study

The research findings indicate that patients with chronic vulvar discomfort, including vulvodynia (96.3%) and vulvar dermatosis (91.5%), exhibit significantly higher rates of comorbidities and additional symptoms compared to other groups, with p-values of 0.0000. Notably, a substantial portion of patients with both normal (63.4%) and impaired (70.7%) vulvar skin also experience these conditions (*Tables 1 and 2*).

Lumbar pain (17.1%) and recurrent headache (15.8%) were observed in a significant percentage of asymptomatic women, with an increased prevalence in those with impaired vulvar skin (29.3% and 20.7%, respectively). The highest prevalence was noted in women with vulvodynia (48.8% and 25.6%, respectively), followed by a slight decrease, though lumbar pain remains significantly prevalent in women with vulvar dermatosis (41.5% and 17.1%, respectively).

Table 1. *The frequency of specific comorbidities/symptoms and associated diseases in four groups of patients in the DATRIV study was determined according to the ISSVD questionnaire.*

Comorbidities Age (years/mean)	Normal vulva N=82 (34.2)	Impaired vulvar skin N=82 (34.4)	Vulvodynia N=82 (34.2)	Vulvar dermatosis N=82 (51.0)
Additional symptoms or diseases	52 (63.4%)	58 (70.7%)	79 (96.3%)**	75 (91.5%)**
Hypertension	2 (2.4%)	0 (0.0%)	2 (2.4%)	22 (26.8%)**
Angina pectoris	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)

Comorbidities Age (years/mean)	Normal vulva N=82 (34.2)	Impaired vulvar skin N=82 (34.4)	Vulvodynia N=82 (34.2)	Vulvar dermatosis N=82 (51.0)
Weight loss /unintended	7 (8.5%)	1 (1.2%)	6 (7.3%)	4 (4.9%)
Recurrent headache	13 (15.8%)	17 (20.7%)	21 (25.6%)	14 (17.1%)
Lumbar pain	14 (17.1%)	24 (29.3%)	40 (48.8%)**	34 (41.5%)**
Endometriosis	1 (1.2%)	4 (4.9%)	6 (7.3%)	4 (4.9%)
Dysmenorrhea/Dysuria /Dyspareunia	0 (0.0%)	1 (1.2%)	7 (8.5%)*	1 (1.2%)

*=p<0.05; **=p<0.001; DATRIV=Diagnostic Accuracy of Three Rings Vulvoscopy; ISSVD= International Society for Study of Vulvovaginal Diseases

In the absence of apparent patterns, other pelvic pain syndromes and conditions such as endometriosis (7.3%) and a significantly more frequent triad of dysmenorrhea, dyspareunia, and dysuria (8.5%; p<.05) were reported far more frequently in patients with vulvodynia. Additionally, patients with vulvar dermatosis exhibited significantly higher rates of hypertension (26.8%).

The study revealed that patients with chronic vulvar discomfort showed a significantly higher prevalence of chronic fatigue, fibromyalgia, energy loss, and pelvic pain compared to asymptomatic groups (*Table 2*).

In a manner analogous to lumbar pain and headache, chronic fatigue, fibromyalgia, energy loss, and pelvic pain exhibited a consistent pattern of increased prevalence, which was observed to begin in the cohort of women with normal vulva, progress through those with impaired vulvar skin, and reach its peak among women diagnosed with vulvodynia. Patients presenting with vulvar dermatosis demonstrated a lower prevalence of these symptoms compared to those with vulvodynia; however, their prevalence remained significantly elevated compared to asymptomatic individuals (p<.001).

Pelvic pain as a self-limiting symptom was notably more prevalent in women with vulvodynia, affecting 34.1% of this group, compared to those with vulvar dermatosis. Conversely, sleep disturbances were more commonly reported among patients with vulvar dermatosis, with a prevalence of 42.7%.

Table 2. *The frequency of specific comorbidities/symptoms and associated diseases in four groups of patients in the DATRIV study was determined according to the ISSVD questionnaire.*

Comorbidities	Normal vulva (N=82)	Impaired vulvar skin (N=82)	Vulvodynia (N=82)	Vulvar dermatosis (N=82)
Chronic fatigue	4 (4.9%)	10 (12.2%)	28 (34.1%)**	25 (30.5%)**
Fibromyalgia	3 (3.7%)	13 (15.8%)	31 (37.8%)**	23 (28.0%)**
Energy loss	11 (13.4%)	22 (26.8%)	50 (61.0%)**	43 (52.4%)**
Pelvic pain	2 (2.4%)	7 (8.5%)	28 (34.1%)**	17 (20.7%)**
Sleep disturbances	9 (11.0%)	14 (17.1%)	23 (28.1%)	35 (42.7%)**
		Hi-square test		
Sleep disturbances		p = 0.05	23 (28.0%)	35 (42.7%)*
Pelvic pain		p = 0.05	28 (34.1%)*	17 (20.7%)

*=p<0.05; **=p<0.001; DATRIV=Diagnostic Accuracy of Three Rings Vulvoscopy; ISSVD= International Society for Study of Vulvovaginal Diseases

Conditions associated with immune system dysregulation, such as recurrent sinusitis and abnormal PAP smears (*Table 3*), were more frequently observed in patients with impaired vulvar skin (31.7% and 23.2%, respectively) and vulvodynia (28.1% and 30.5%, respectively).

The incidence of abnormal PAP tests and genital warts exhibited a pattern of increasing prevalence in the following sequence: normal vulva, impaired vulvar skin, and vulvodynia. In contrast, recurrent sinusitis and conization were more prevalent among patients with impaired vulvar skin.

Table 3. *The frequency of specific comorbidities/symptoms and diseases related to immune system dysregulation in four groups of patients in the DATRIV study was determined according to the ISSVD questionnaire.*

Immune system dysregulation	Normal vulva (N=82)	Impaired vulvar skin (N=82)	Vulvodynia (N=82)	Vulvar dermatosis (N=82)
Genital herpes	2 (2.4%)	1 (1.2%)	2 (2.4%)	2 (2.4%)
Drug allergy	9 (11.0%)	8 (9.8%)	15 (18.3%)	8 (9.8%)
Recurrent sinusitis	10 (12.2%)	26 (31.7%)*	23 (28.1%)*	15 (18.3%)
Abnormal PAP smear	8 (9.8%)	19 (23.2%)*	25 (30.5%)*	10 (12.2%)
Genital warts	1 (1.2%)	3 (3.7%)	6 (7.3%)	3 (3.7%)
Conization/LETZ	4 (4.9%)	11 (13.4%)	10 (12.2%)	7 (8.5%)
Genital herpes	2 (2.4%)	1 (1.2%)	2 (2.4%)	2 (2.4%)
Drug allergy	9 (11.0%)	8 (9.8%)	15 (18.3%)	8 (9.8%)

*=p<0.05; **=p<0.001; DATRIV=Diagnostic Accuracy of Three Rings Vulvoscopy; ISSVD= International Society for Study of Vulvovaginal Diseases

Urinary tract issues were prevalent across all patient groups, with a notably higher incidence among those experiencing chronic vulvar discomfort (*Table 4*).

36.6% of patients with a normal vulva reported urinary tract symptoms. The most frequent complaints, in descending order, included nocturia (30.5%), urinary incontinence (19.5%), urgency (13.4%), dysuria (8.5%), and difficulties initiating urination (2.4%).

Among asymptomatic individuals with nonspecific vulvoscopic lesions, periodic urinary complaints were also common. Nocturia affected 24.4%, urgency 13.4%, urinary incontinence 12.2%, dysuria 8.5%, and difficulties initiating urination 1.2%.

In the vulvodynia group, 48.8% reported periodic or frequent urinary problems. Nocturia affected 48.8% (with 11.0% experiencing it often), dysuria 43.9% (12.2% frequently), urgency 29.3% (2.1% usually), incontinence 23.2% (2.4% often), recurrent cystitis 18.3%, and difficulties initiating urination 14.6%.

In 68.3% of cases, patients with vulvar dermatosis reported periodic or frequent urinary problems. Nocturia affected 68.3% (36.6% often), dysuria 40.2% (8.5% frequently), urgency 29.3% (11.0% usually), incontinence 39.0% (13.4% often), recurrent cystitis 12.2%, and difficulties initiating urination 11.0%.

Table 4. *The frequency of specific comorbidities/symptoms and diseases related to urinary tract dysfunction in four groups of patients in the DATRIV study was determined according to the ISSVD questionnaire.*

Comorbidities	Normal vulva (N=82)	Impaired vulvar skin (N=82)	Vulvodynia (N=82)	Vulvar dermatosis (N=82)
Urinary or bowel dysfunction	54 (65.9%)	47 (57.3%)	74 (90.2%)**	72 (87.8%)**
Urinary disorders	30 (36.6%)	22 (26.8%)	40 (48.8%)	56 (68.3%)**
Dysuria	7 (8.5%)	7 (8.5%)	36 (43.9%)**	33 (40.2%)**
Periodical (SNS)	7 (8.5%)	7 (8.5%)	26 (31.7%)	26 (31.7%)
Frequent (PNS)	0 (0.0%)	0 (0.0%)	10 (12.2%)	7 (8.5%)
Urinary incontinence	16 (19.5%)	11 (13.4%)	19 (23.2%)	32 (39.0%)**
Periodical (SNS)	16 (19.5%)	10 (12.2%)	17 (20.7%)	21 (25.6%)
Frequent (PNS)	0 (0.0%)	1 (1.2%)	2 (2.4%)	11 (13.4%)**
Difficulties at starting voiding	2 (2.4%)	1 (1.2%)	12 (14.6%)*	9 (11.0%)*
Periodical (SNS)	2 (2.4%)	0 (0.0%)	11 (13.4%)*	7 (8.5%)*
Frequent (PNS)	0 (0.0%)	1 (1.2%)	1 (1.2%)	2 (2.4%)

Comorbidities	Normal vulva (N=82)	Impaired vulvar skin (N=82)	Vulvodynia (N=82)	Vulvar dermatosis (N=82)
Urgency	11 (13.4%)	11 (13.4%)	24 (29.3%)*	24 (29.3%)*
Periodical (SNS)	11 (13.4%)	11 (13.4%)	22 (26.8%)	15 (18.3%)
Frequent (PNS)	0 (0.0%)	0 (0.0%)	2 (2.1%)	9 (11.0%)**
Nocturia	30 (36.6%)	22 (26.8%)	40 (48.8%)	56 (68.3%)**
Periodical (SNS)	25 (30.5%)	20 (24.4%)	31 (37.8%)	30 (36.6%)
Frequent (PNS)	5 (6.1%)	2 (2.4%)	9 (11.0%)	26 (31.7%)**
Recurrent cystitis	8 (9.8%)	4 (4.9%)	15 (18.3%)	10 (12.2%)

*=p<0.05; **=p<0.001; DATRIV=Diagnostic Accuracy of Three Rings Vulvoscopy; ISSVD= International Society for Study of Vulvovaginal Diseases

Bowel dysfunction was notably prevalent among patients with chronic vulvar discomfort, with incidences of 32.8% in those with vulvodynia and 24.4% in those with vulvar dermatosis, following the previously described pattern (*Table 5*).

Constipation was significantly more prevalent in symptomatic patients, with no significant differences in periodicity among the different groups. The frequency of constipation followed the previously described pattern of increasing incidence: normal vulva (14.6%), impaired vulvar skin (19.5%), and vulvodynia (32.9%). There was a slight decrease in the incidence of constipation in the vulvar dermatosis group (24.4%) compared to those with vulvodynia.

The only two exceptions to the comorbidity incidence pattern were observed in the cases of diarrhea and irritable colon. The incidence of these conditions increased across all four examined groups, with the highest incidence occurring in the group of women with vulvar dermatosis. This elevated incidence was evident in periodic and frequent disease forms.

Table 5. *The frequency of specific comorbidities/symptoms and diseases related to bowel dysfunction in four groups of patients in the DATRIV study was determined according to the ISSVD questionnaire.*

Comorbidities	Normal vulva (N=82)	Impaired vulvar skin (N=82)	Vulvodynia (N=82)	Vulvar dermatosis (N=82)
Bowel dysfunction	12 (14.6%)	16 (19.5%)	27 (32.9%)*	20 (24.4%)*
Constipation	12 (14.6%)	16 (19.5%)	27 (32.9%)*	20 (24.4%)*
Periodical	9 (11.0%)	13 (15.8%)	20 (24.4%)	14 (17.1%)
Frequent	3 (3.7%)	3 (3.7%)	7 (8.5%)	6 (7.3%)
Diarrhea	3 (3.7%)	2 (2.4%)	9 (11.0%)*	12 (14.6%)*
Periodical (SNS)	3 (3.7%)	1 (1.2%)	7 (8.5%)*	10 (12.2%)*
Frequent (PNS)	0 (0.0%)	1 (1.2%)	2 (2.1%)	2 (2.4%)
Irritable colon	0 (0.0%)	2 (2.1%)	7 (8.5%)*	9 (11.0%)*

*=p<0.05; **=p<0.001; DATRIV=Diagnostic Accuracy of Three Rings Vulvoscopy; ISSVD= International Society for Study of Vulvovaginal Diseases

3.2. Distribution of Comorbidities According to ANS Dysfunction

Figures 2 to 5 illustrate the prevalence of comorbid symptoms and conditions in distinct groups of subjects, categorized based on dysautonomia affecting the sympathetic, parasympathetic, or both divisions of the autonomic nervous system.

3.2.1. Sympathetic Nervous System Hyperactivity

An analysis of the current literature identified symptoms and conditions caused by SNS hyperactivity, the frequency of which is depicted for the examined groups in *Figure 2*. The common feature of almost all these comorbidities was a

continuous increase in their frequency from the group with normal vulva through to those with impaired vulvar skin, reaching a peak in patients with vulvodynia and, most often, a sudden drop in incidence in the group of patients with vulvar dermatosis. Exceptions to this pattern were hypertension and sleep disturbances, which showed maximum frequency in patients with vulvar dermatosis.

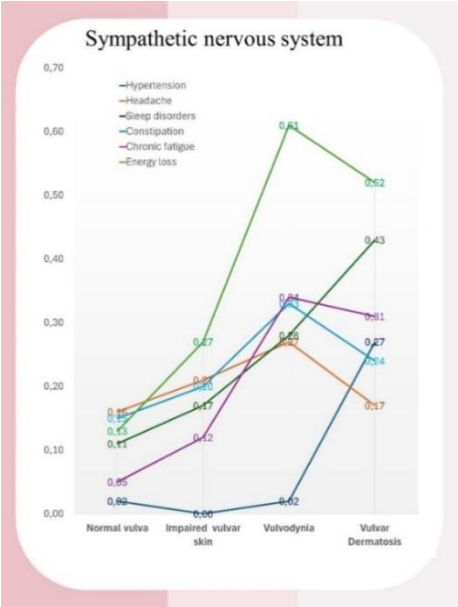

Figure 2. *Comorbidities driven by hyperactivity of the sympathetic nervous system.*

3.2.2. Parasympathetic Nervous System Depression

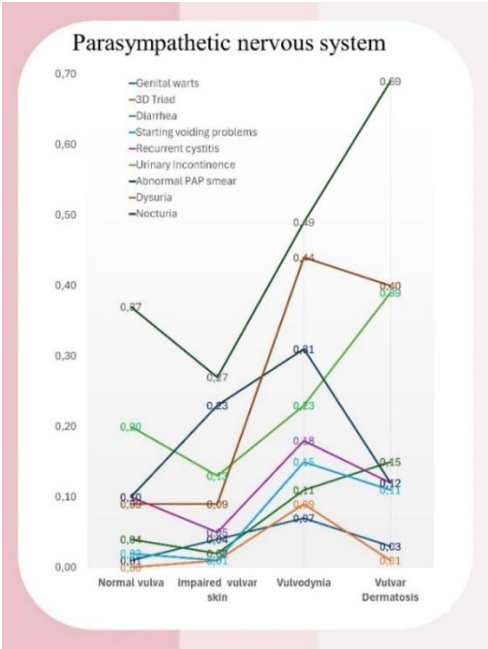

Figure 3. *Comorbidities connected with depression of the parasympathetic nervous system.*

According to recent literature, *Figure 3* displays the incidence of comorbidities caused by PNS depression in the examined groups. The shared characteristic of most of these comorbidities (seven out of nine) was a successive increase in their frequency from the group with normal vulva to those with impaired vulvar skin, peaking in patients with vulvodynia, and then often showing a sharp decline in incidence in the group of patients with vulvar dermatosis. Exceptions to this pattern were hypertension and sleep disturbances, which exhibited maximum frequency in patients with vulvar dermatosis.

3.2.3. Combined SNS Hyperactivity and PNS Depression

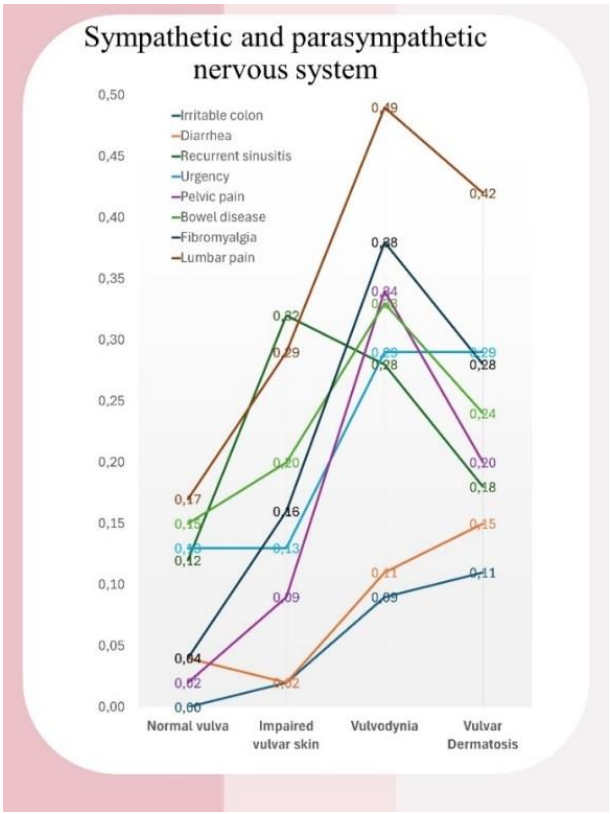

Figure 4. *Comorbidities linked to the combined effects of hyperactive sympathetic nervous system and depressed parasympathetic nervous system.*

Figure 4 shows comorbidities associated with the combined action of a hyperactive SNS and a depressed PNS. The most common shape of the comorbidity curves observed (in four out of eight) was represented by a gradual increase in incidence among the examined groups, reaching a peak in patients with vulvodynia, followed by a decrease in subjects with vulvar dermatosis. This pattern was observed in lumbar pain (49%), fibromyalgia (38%), pelvic pain (34%), and bowel disease (33%), with the percentages indicating the occurrence of these conditions in women with vulvodynia.

A second type of curve was noted for urgency, which occurred with equal frequency in both subgroups of asymptomatic women (13%) and again with equal frequency of 29% in both groups of patients with chronic vulvar discomfort. Two comorbid conditions (diarrhea and irritable colon) exhibited maximum frequency in patients with vulvar dermatosis (15% and 11%, respectively). In the case of recurrent sinusitis, the pattern deviated entirely from those described above, showing an increase in frequency among asymptomatic women, a decrease in patients with vulvodynia, and a further reduction in those with vulvar dermatosis.

3.2.4. Vulvar Dermatosis Group

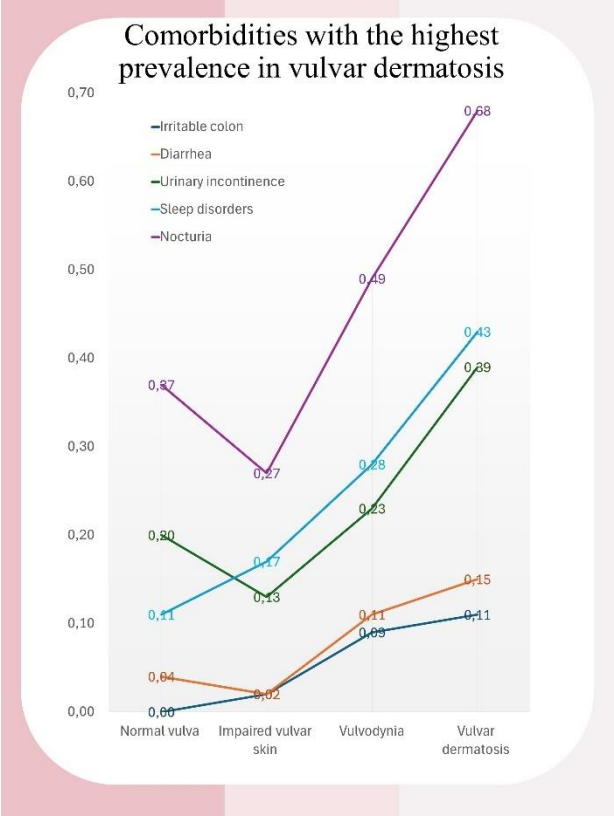

Figure 5. *Comorbidities with the highest prevalence in the group of vulvar dermatosis.*

In the vulvar dermatosis group, the comorbidity network with the highest prevalence encompasses several conditions (*Figure 5*). The most notable feature of all curves is the continuous increase in the frequency of comorbidities between patients with vulvodynia and vulvar dermatosis. Nocturia was reported by 68% of respondents, while sleep disorders and urinary incontinence were present in 43% and 39% of patients with vulvar dermatosis, respectively.

A critical characteristic of the prevalence curves for diarrhea, urinary incontinence, and nocturia (three out of five) is the disruption of the otherwise continuous increase and decrease in the frequency of these conditions among asymptomatic patients with nonspecific changes on the vulva.

4. Discussion

The high prevalence of comorbidities, defined as the coexistence of two or more medical conditions in a patient, highlights the complexity of chronic vulvar discomfort. Understanding the patterns and distribution of these comorbidities is crucial for clinicians to tailor comprehensive treatment plans. Traditional approaches to comorbidity analysis often focus on two-dimensional models, overlooking the body's third dimension—its volumetric fluid composition. Human body fluids, which vary by age, gender, and body composition, serve as the medium for all biochemical processes. This volumetric dimension, particularly its role in facilitating intracellular and intercellular exchanges, adds a critical layer to the analysis of comorbidity networks.

This study expands the analysis of comorbidities by incorporating concepts of comorbidity clusters and networks [15, 16], focusing on the interplay between the autonomic nervous system (ANS) and various health conditions. The findings confirm previous research by identifying key comorbidities such as chronic fatigue, fibromyalgia, pelvic pain, dyspareunia, urinary incontinence, and nocturia [14-37]. The results show significantly higher rates of comorbidities in patients with chronic vulvar discomfort ($p = 0.0000$). Additionally, a high percentage of asymptomatic patients reported comorbid conditions, underscoring the importance of preventive measures like proper vulvar hygiene for all women, irrespective of symptoms [9, 58].

The results reveal significantly higher rates of comorbidities in patients with chronic vulvar discomfort, such as vulvodynia and vulvar dermatosis, compared to other groups, with p-values of 0.0000. A large proportion of patients with both normal (63.4%) and impaired (70.7%) vulvar skin also experience these conditions. The high prevalence of comorbidities in asymptomatic patients, including those with no visible vulvar changes, underscores the importance of preventive measures, particularly proper vulvar hygiene, for all women, regardless of the presence of nonspecific changes. Vulvar care guidelines emphasize "gentle care of the vulva," recommending avoiding irritants and using adequate lubrication [9]. Previous research has shown that adherence to these guidelines can reduce the severity of symptoms such as dyspareunia, postcoital burning, vulvar burning, itching, and pain [58].

Recommended vulvar care measures include wearing cotton underwear during the day and none at night, avoiding vulvar irritants such as perfumes, dyed toiletries, shampoos, detergents, and vaginal douches, and using mild soap, ensuring none is applied directly to the vulva. The vulva should be cleaned gently with water and patted dry. After cleansing, an emollient free of preservatives, such as vegetable oil or plain petrolatum, can help retain moisture and improve barrier

function. If menstrual pads cause irritation, cotton pads may be beneficial. Adequate lubrication during intercourse is also advised. Additionally, rinsing and patting the vulva dry after urination may be helpful, while the use of hair dryers should be avoided [9, 59].

This observed arrangement and pattern of comorbidities suggest that these conditions constitute a distinct comorbidity cluster associated with chronic vulvar discomfort. In this study, asymptomatic patients with normal vulva served as the control group. A comorbidity cluster refers to the co-occurrence of multiple chronic conditions in a single patient, with interrelated or interconnected pathways that reflect shared risk factors, pathophysiological mechanisms, or genetic predispositions.

Identifying comorbidity clusters can reveal common biological, environmental, or lifestyle factors contributing to multiple conditions' development and progression. This insight is crucial for understanding the underlying mechanisms linking different diseases and advancing targeted therapies' development.

Initial comorbidities from this cluster appear at a high frequency in asymptomatic patients with a normal vulva. These include sleep disturbances (11%), drug allergies (11%), recurrent sinusitis (12.2%), urgency (13.4%), energy loss (13.4%), constipation (14.6%), headache (15.8%), lumbar pain (17.1%), urinary incontinence (19.5%), and nocturia (36.6%) (*Tables 1-5*). While these symptoms may seem minor and not indicative of a specific disease, they could represent the initial manifestations of chronic vulvar discomfort. This hypothesis is further supported by the behavior of the comorbidity curves (*Figures 1-5*).

Notably, specific conditions, such as immune dysregulation manifesting in abnormal PAP smear results and genital warts (*Table 3*), were more common in vulvodynia patients. In contrast, conditions like recurrent sinusitis and conization were more prevalent among those with impaired vulvar skin. Identifying comorbidity clusters provides valuable insight into shared pathophysiological mechanisms, offering potential avenues for targeted interventions.

Pelvic pain was notably more common in women with vulvodynia, affecting 34.1% of this group, compared to those with vulvar dermatosis. Other pelvic pain syndromes, including endometriosis (7.3%) and the triad of dysmenorrhea, dyspareunia, and dysuria (8.5%; $p<.05$), were significantly more frequent in patients with vulvodynia. The 20-year age difference between patient cohorts with chronic vulvar discomfort may explain the significantly higher rate of hypertension (26.8%) observed in the vulvar dermatosis group.

Urinary and bowel dysfunctions were prevalent in patients with chronic vulvar discomfort (*Table 4*), particularly nocturia and constipation, suggesting a potential link with ANS dysfunction. Sympathetic hyperactivity and parasympathetic depression, as observed in these patients, may underpin the development of these comorbidity networks [35-36]. The analysis of comorbidity curves further emphasizes the distinct patterns of symptom escalation across patient groups, particularly in those with vulvodynia and vulvar dermatosis.

A substantial number of patients with a normal vulva (36.6%) reported urinary symptoms, with nocturia (30.5%), urinary incontinence (19.5%), and urgency (13.4%) being the most frequent complaints. Among asymptomatic patients with impaired vulvar skin, urinary symptoms were also common but occurred at a lower rate compared to the normal vulva group. This trend, unique to these urinary complaints, appears across both groups.

The deviation in urinary symptoms may be attributed to deeper physiological mechanisms, particularly the complex interaction between the autonomic nervous system (ANS) and various health conditions [35, 36]. These mechanisms could involve increased parasympathetic depression or decreased sympathetic hyperactivity between the time the vulva is normal and the appearance of nonspecific lesions.

A second deviation was noted in the prevalence of urinary incontinence (39.0%) and irritable bowel syndrome (11.0%), which were significantly higher in patients with vulvar dermatosis than in those with vulvodynia (23.2% and 8.5%, respectively). Urgency symptoms (29.3%) remained consistent across both groups.

Bowel dysfunction was prevalent among patients with chronic vulvar discomfort, affecting 32.8% of those with vulvodynia and 24.4% of those with vulvar dermatosis. Exceptions to the comorbidity pattern included diarrhea and irritable bowel syndrome, whose incidence increased across all four patient groups, with the highest rates observed in women with vulvar dermatosis (*Table 5*). These findings align with current research highlighting the intricate relationship between ANS dysfunction and various health conditions [38-42]. Sympathetic hyperactivity has been linked to hypertension, cardiovascular diseases, and immune system dysregulation [43, 46-48].

Analysis of comorbidity curves in study participants underscores the critical role of ANS dysfunction in forming this comorbidity network. Although both the sympathetic and parasympathetic branches of the ANS are independent, dominant dysfunctions – sympathetic hyperactivity and parasympathetic depression – trigger symptoms and conditions associated with their respective comorbidity chains. These comorbidities may occur independently or simultaneously, leading to various health issues.

Hypertension was a distinguishing symptom linked to sympathetic hyperactivity, observed in 26.8% of patients with vulvar dermatosis and showing a statistically significant association ($p<0.001$). In contrast, the "3D triad", another indicator of sympathetic hyperactivity, was more prevalent among patients with vulvodynia ($p<0.05$). However, symptoms such as lumbar pain and dysuria, while more common in patients with vulvodynia and vulvar dermatosis ($p<0.001$), were also frequent in asymptomatic patients, limiting their diagnostic utility. Headaches were prevalent across all groups without significant differences.

Comorbidities linked to parasympathetic depression followed distinct patterns. Nocturia was notably more common in the vulvar dermatosis group (68.3%) and affected nearly half of the patients with vulvodynia. Although constipation was more frequent in symptomatic patients, its high prevalence among women with a normal vulva reduces its usefulness as a differential symptom.

In summary, the initial symptoms of ANS dysfunction – dysuria (8.5%), nocturia (36.6%), lumbar pain (17.1%), and constipation (14.6%) – were rare in healthy women but increased significantly in patients with vulvar discomfort. These findings highlight the potential of using symptom profiles to detect underlying ANS dysregulation in this patient population. The most common pattern, especially in women with vulvodynia, showed a gradual increase in symptom frequency from patients with a normal vulva to those with impaired vulvar skin, peaking in vulvodynia patients, followed by a drop in incidence among patients with vulvar dermatosis. A second pattern, seen most frequently in women with vulvar dermatosis, characterized by a continued rise in comorbidity frequency between vulvodynia and vulvar dermatosis patients.

These results underscore the intricate relationship between sympathetic and parasympathetic nervous system functions in the manifestation and progression of various health conditions, particularly those affecting the vulvar region. The high rates of comorbidity and overlapping symptomatology across different conditions suggest a complex pathophysiology involving ANS dysregulation.

Further research into comorbidity clusters may identify new therapeutic targets and support the development of treatments addressing multiple conditions. Advanced statistical methods and analytical techniques, such as factor analysis, cluster analysis, and network analysis, are essential for identifying these clusters and enhancing the use of large patient datasets. Understanding comorbidity clusters is critical for advancing our knowledge of disease mechanisms, improving clinical management, developing effective preventive strategies, and driving innovation in medical science.

5. Conclusion

The DATRIV study confirms previous findings by identifying a distinct comorbidity network among patients with chronic vulvar discomfort. This network, characterized by chronic conditions such as chronic fatigue, fibromyalgia, pelvic pain, dyspareunia, and urinary incontinence, reveals interconnected pathways, particularly in vulvodynia and vulvar dermatosis patients. The significantly higher rates of comorbidities in these patients, combined with the prevalence of comorbid conditions even among asymptomatic individuals, highlight the importance of preventive strategies, including proper vulvar care.

The findings suggest a potential underlying connection between chronic vulvar discomfort and broader systemic conditions, particularly those linked to ANS dysfunction. The role of sympathetic hyperactivity and parasympathetic depression in forming these comorbidity chains underscores the complexity of the condition and the need for comprehensive management strategies. Urinary and bowel dysfunctions, along with other symptoms of ANS dysregulation, offer valuable clues for early detection and intervention.

Certain conditions, such as chronic fatigue, fibromyalgia, and abnormal Pap smear results, follow a consistent pattern of increased prevalence in women with impaired vulvar skin, peaking among those diagnosed with vulvodynia. This pattern suggests a possible underlying connection between these conditions, possibly representing different phases or manifestations of the same disease. Future studies should investigate this relationship further.

Urinary tract issues and bowel dysfunction were prevalent across all patient groups, especially among those with chronic vulvar discomfort. These findings resonate with current research, emphasizing the complex interplay between the autonomic nervous system (ANS) and various health conditions. Sympathetic hyperactivity and parasympathetic depression play critical roles in the development of this comorbidity network.

The initial symptoms of sympathetic and parasympathetic nervous system dysfunction, including dysuria, nocturia, lumbar pain, and constipation, were rare in healthy women but significantly increased in patients with vulvar discomfort. These findings highlight the potential value of using symptom profiles to detect underlying autonomic nervous system dysregulation in this patient population.

Future research should focus on further exploring these comorbidity clusters, using advanced statistical techniques to identify common biological and pathophysiological mechanisms. Understanding these networks may facilitate the development of therapies that address multiple conditions simultaneously, advancing our knowledge of disease mechanisms and improving patient outcomes.

Abbreviations

DATRIV	Diagnostic Accuracy of Three Rings Vulvoscopy
ANS	Autonomic Nervous System
IBS	Irritable Bowel Syndrome
TMJD	Temporomandibular Joint Disorder
SLE	Systemic Lupus Erythematosus
GERD	Gastroesophageal Reflux Disease
PCOS	Polycystic Ovary Syndrome
SNS	Sympathetic Nervous System
PNS	Parasympathetic Nervous System
TRIV	Three Rings Vulvoscopy
ISSVD	The International Society for Study of Vulvovaginal Disease

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] International Association for the Study of Pain, Subcommittee on Taxonomy. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. *Pain Supplement* 1986; 3: S1-S226.

[2] Engeler D, Baranowski AP, Dinis-Oliveira P, Elneil S, Hughes J, Messelink EJ et al. The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. Eur Urol. 2013 Sep; 64(3): 431-9. https://doi.org/10.1016/j.eururo.2013.04.035

[3] Ploteau S, Labat JJ, Riant T, Levesque A, Robert R and Nizzard J. New Concepts and Functional Chronic Pelvic and Perineal Pain: Pathophysiology and Multidisciplinary Management. Discov Med 2015; 19(104): 185-92.

[4] Teigen, Per Kristen, Hagemann, Cecilie Therese, Fors, Egil Andreas, Stauri, Elisabeth, Hoffmann, Risa Lonn é and Schei, Berit. Chronic vulvar pain in gynecological outpatients. *Scand J Pain*, 2023; 23(1): 97-103. https://doi.org/10.1515/sjpain-2021-0223

[5] Harlow BL, Stewart EG. A population-based assessment of chronic unexplained vulvar pain: have we underestimated the prevalence of vulvodynia? *Journal of the American Medical Women's Association* 1972; 58(2): 82-8.

[6] Friedrich EG Jr. Vulvar vestibulitis syndrome. *J Reprod Med* 1987; 32: 110-4. PMID: 3560069.

[7] Julian T. Vulvar Pain: Diagnoses, Evaluation, and Management. *J Lower Genit Tract Dis* 1997; 1(3): 185-94.

[8] Moyal-Barracco M, Lynch P. 2003 ISSVD terminology and classification vulvodynia: a historical perspective. *J Reprod Med* 2004; 49: 772-7.

[9] Haefner H, Collins M, Davis GD, Edwards L, Foster D, Hartmann E, et al. The Vulvodynia Guideline. *J Lower Genit Tract Dis* 2005; 9: 40-51. https://doi.org/10.1097/00128360-200501000-00009

[10] Bornstein J, Sideri M, Tatti S, Walker P, Prendiwille W, Haefner HK. 2011 Terminology of the Vulva of the International Federation for Cervical Pathology and Colposcopy. *J Lower Genit Tract Dis* 2012; 16: 290-5. https://doi.org/10.1097/LGT.0b013e31825934c7

[11] Stockdale CK, Lawson HW. 2013 Vulvodynia Guideline update. *J Low Genit Tract Dis* 2014; 18: 93–100. https://doi.org/10.1097/LGT.0000000000000021

[12] Bornstein J, Goldstein AT, Stockdale CK, Bergeron S, Pukall C, Zolnoun D and Coady D. 2015 ISSVD, ISSWSH, and IPPS Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia. *J Lower Genit Tract Dis* 2016; 20(2): 126-30. https://doi.org/10.1097/LGT.0000000000000190

[13] Pukall CF, Goldstein AT, Bergeron S, Foster D, Stein A, Kellogg-Spadt S, Bachmann G. Vulvodynia: Definition, Prevalence, Impact, and Pathophysiological Factors, The Journal of Sexual Medicine 2016; (13)3: 291–304. https://doi.org/10.1016/j.jsxm.2015.12.021

[14] Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining Comorbidity: Implications for Understanding Health and Health Services. The Annals of Family Medicine 2009; 7(4): 357-63. https://doi.org/10.1370/afm.983

[15] Cramer AOJ, Waldrop LJ, van der Maas HL, Borsboom D. Comorbidity: a network perspective. Behav Brain Sci, 2010; 33 (2-3): 137-50. https://doi.org/10.1017/S014025X09991567

[16] Brown R, Thorstensson E. Models od comorbidity. Chapter in Brown R. Comorbidity, Springer International Publishing, 2020, pp 23-41.

[17] Brown R., Thorsteinsson E. Comorbidity: What Is It and Why Is It Important? In: Brown R, Thorsteinsson E. (eds) comorbidity. Palgrave Macmillan, Cham. 2020. pp 1–22.

[18] Brown, R., Thorsteinsson E. Models of Comorbidity. In: Brown R, Thorsteinsson E. (eds) comorbidity. Palgrave Macmillan, Cham. 2020. pp 23–41.

[19] Graziottin A, Murina F, Gambini D, Taraborrelli S, Gardella B, Campo M. Vulvar pain: The revealing scenario of leading comorbidities in 1183 cases. *Eur J Obstet Gynecol Reprod Biol* 2020; 252: 50-55. https://doi.org/10.1016/j.ejogrb.2020.05.052

[20] Doyen J, Demoulin S, Delbecque K, Goffin F, Kridelka F, Delvenne P. Vulvar Skin Disorders throughout Lifetime: About Some Representative Dermatoses. *BioMed Research International* 2014: 2014: 595286, https://doi.org/10.1155/2014/595286

[21] Arnold LD, Bachmann GA, Kelly S, Rosen R and Rhoads GG. Vulvodynia: Characteristics and Quality of Life and Associations with Comorbidities. *Obstet Gynecol* 2006; 107(3): 617–24. https://doi.org/10.1097/01.AOG.0000199951.26822.27

[22] Patla G, Mazur-Bialy AI, Humaj-Grysztar M, Bonior J. Chronic Vulvar Pain and Health-Related Quality of Life in Women with Vulvodynia. *Life (Basel)* 2023; 13(2): 328. https://doi.org/10.3390/life13020328

[23] Biasi G, Di Sabatino V, Ghizzani A, Galeazzi M. Chronic pelvic pain: comorbidity between chronic musculoskeletal pain and vulvodynia. *Reumatismo* 2014; 66(1): 87-91. https://doi.org/10.4081/reumatismo.2014.768

[24] Wesselmann U, Burnett AL, Heinberg LJ. The urogenital and rectal pain syndromes. *Pain* 1997; 73(3): 269-94. https://doi.org/10.1016/S0304-3959(97)00076-6

[25] Berger MB, Damico NJ, Menees SB, Fenner DE, Haefner HK. Rates of Self-Reported Urinary, Gastrointestinal, and Pain Comorbidities in Women With Vulvar Lichen Sclerosus. *J Lower Genit Tract Dis* 2012; 16(3): 285-9. https://doi.org/10.1097/LGT.0b013e3182562f1e

[26] S öderlund JM, Hieta NK, Kurki SH, Orte KJ, Polo-Kantola P, Hietanen SH et al. Comorbidity of Urogynecological and Gastrointestinal Disorders in Female Patients With Lichen Sclerosus. *J Low Genit Tract Dis* 2023; 27: 156–160.

[27] Sun Y, Harlow BL. The association of vulvar pain and urological urgency and frequency: Findings from a community-based case-control study. *Int Urogynecol J* 2019; 30(11): 1871-8. https://doi.org/10.1007/s00192-019-04052-2

[28] Lim PF, Maixner W, Khan AA. Temporomandibular disorder and comorbid pain conditions. *J Am Dent Assoc* 2011; 142(12): 1365–1367. https://doi.org/10.14219/jada.archive.2011.0137

[29] Reed BD, Haefner HK, Punch MR, Roth RS, Gorenflo DW, Gillespie BW. Psychosocial and sexual functioning in women with vulvodynia and chronic pelvic pain. A comparative evaluation. *J Reprod Med* 2000; 45(8): 624-32.

[30] Chisari C, Monajemi MB, Scott W, Moss-Morris R, McCracken LM. Psychosocial factors associated with pain and sexual function in women with Vulvodynia: A systematic review. *European Journal of Pain* 2020; (25)1: 39-50. https://doi.org/10.1002/ejp.1668

[31] Ferraz SD, Rodrigues Candido AC, Rodrigues Uggioni ML, Colonetti T, Dagostin VS, Rosa MI. Assessment of anxiety, depression and somatization in women with vulvodynia: A systematic review and META-analysis, *Journal of Affective Disorders* 2024; 344: 122-31. https://doi.org/10.1016/j.jad.2023.10.025

[32] Gordon D, Gardella C, Eschenbach D, Mitchell CM. High Prevalence of Sexual Dysfunction in a Vulvovaginal Specialty Clinic. *J Lower Gen Tract Dis* 2016; 20: 80–84. https://doi.org/10.1097/LGT.0000000000000085

[33] Haefner HK, Aldrich NZ, Marcus SB, Dalton VK, Patel DA, Berger MB. The Impact of Vulvar Lichen Sclerosus on Sexual Dysfunction. *J Womens Health (Larchmt)* 2014; 23(9): 765–770. https://doi.org/10.1089/jwh.2014.4805

[34] Cooper SM, Baldo AM, Wojnarowska F. The association of lichen sclerosus and erosive lichen planus of the vulva with autoimmune disease: a case-control study. *Arch Dermatol.* 2008; 144 (11): 1432-1435.

[35] Driul L, Bertozzi S, Londero AP, Fruscalzo A, Rusalen A, Marchesoni D, Di Benedetto P. Risk factors for chronic pelvic pain in a cohort of primipara and secondipara at one year after delivery: association of chronic pelvic pain with autoimmune pathologies. *Minerva Ginecol* 2011; 63(2): 181-7.

[36] Stanford EJ, Koziol J, Feng A. The prevalence of interstitial cystitis, endometriosis, adhesions, and vulvar pain in women with chronic pelvic pain. *J Minim Invasive Gynecol* 2005; 12(1): 43-9. https://doi.org/10.1016/j.jmig.2004.12.016

[37] Bachmann GA, Rosen R, Arnold LD, Burd I, Rhoads GG, Leiblum SR, Avis N. Chronic vulvar and other gynecologic pain: prevalence and characteristics in a self-reported survey. *J Reprod Med* 2006; 51(1): 3-9.

[38] R Bankenahally R, Krovvidi H. Autonomic nervous system: anatomy, physiology, and relevance in anaesthesia and critical care medicine. BJA Education 2016; 16 (11): 381-7. https://doi.org/10.1093/bjaed/mkw011

[39] Arslan D, Ünal Çevik I. Interactions between the painful disorders and the autonomic nervous system. Agri 2022; 34(3): 155–165. https://doi.org/10.14744/agri.2021.43078.

[40] Novak P. Autonomic disorders. Am J Med 2019; 132: 420–36. https://doi.org/10.1016/j.amjmed.2018.09.027

[41] Furness JB. The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol 2012; 9: 286–94. https://doi.org/10.1038/nrgastro.2012.32

[42] Bellocchi C, Carandina A, Montinaro B, Targetti E, Furlan L, Rodrigues GD, Tobaldini E, Montano N. The Interplay between Autonomic Nervous System and Inflammation across Systemic Autoimmune Diseases. Int. J. Mol. Sci. 2022, 23(5): 2449. https://doi.org/10.3390/ijms23052449

[43] Chen X, Xu L, Li Z. Autonomic Neural Circuit and Intervention for Comorbidity Anxiety and Cardiovascular Disease. Front Physiol. 2022; (27): 13: 852891. https://doi.org/10.3389/fphys.2022.852891

[44] Haugen FP. The autonomic nervous system and pain**.** *Anesthesiology* 1968; 29(4): 785-92. https://doi.org/10.1097/00000542-196807000-00022

[45] Cortelli P, Pierangeli G. Chronic pain-autonomic interactions. *Neurol Sci* 2003; 24 Suppl 2: S68-70. https://doi.org/10.1007/s100720300045

[46] Iriki M, Simon E. Differential control of efferent sympathetic activity revisited. *J Physiol Sci* 2012; 62(4): 275-98. https://doi.org/10.1007/s12576-012-0208-9

[47] Sohn R, Jenei-Lanzl Z. Role of the Sympathetic Nervous System in Mild Chronic Inflammatory Diseases: Focus on Osteoarthritis. *Neuroimmunomodulation* 2023; 30(1): 143-166. https://doi.org/10.1159/000531798

[48] Kuntz A. The autonomic nervous system in relation to etiology and management of allergic disease. *Int Arch Allergy Appl Immunol* 1950; 1(2): 77-92. https://doi.org/10.1159/000227850

[49] Vingerhoets AJ. The role of the parasympathetic division of the autonomic nervous system in stress and the emotions. *Int J Psychosom* 1985; 32(3): 28-34.

[50] Naser PV, Kuner R. Molecular, Cellular and Circuit Basis of Cholinergic Modulation of Pain. *Neuroscience* 2018; 387: 135-148. https://doi.org/10.1016/j.neuroscience.2017.08.049

[51] Yun AJ, Lee PY, Bazar KA. Temporal variation of autonomic balance and diseases during circadian, seasonal, reproductive, and lifespan cycles. *Med Hypotheses* 2004; 63(1): 155-62. https://doi.org/10.1016/j.mehy.2004.02.030

[52] Wei Y, Liang Y, Lin H, Dai Y, Yao S. Autonomic nervous system and inflammation interaction in endometriosis-associated pain. *J Neuroinflammation* 2020; 17(1): 80. https://doi.org/10.1186/s12974-020-01752-1

[53] Coxon L, Horne AW, Vincent K. Pathophysiology of endometriosis-associated pain: A review of pelvic and central nervous system mechanisms. *Best Pract Res Clin Obstet Gynaecol* 2018; 51: 53-67. https://doi.org/10.1016/j.bpobgyn.2018.01.014

[54] Harni V, Babic D, Hadzavdic S, Barisic D. Diagnostic Accuracy of the Vulvoscopy Index for Detection of Vulvar Dermatosis (DATRIV Study, Part 1). *Journal of Gynecology and Obstetrics* 2022; Vol. 10, No. 1, 39-47. https://doi.org/10.11648.j.jgo.20221001.16

[55] Harni V, Babic D, Hadzavdic S, Barisic D. Clinical Value of the N-S-P Scheme for Detection of Vulvar Dermatosis (DATRIV Study, Part 2). *Journal of Gynecology and Obstetrics* 2022; Vol. 10, No. 3, 159-166. https://doi.org/10.11648.j.jgo.20221003.11

[56] Byrne MA, Walker MM, Leonard J, Pryce D, Taylor-Robinson D. Recognising covert disease in women with chronic vulval symptoms attending an STD clinic: value of detailed examination including colposcopy. *Genitourin Med* 1989; 65: 46-9. https://doi.org/10.1136/sti.65.1.46

[57] Audisio T, Zarazaga J, Vainer O. A Classification of Vulvoscopic Findings for Clinical Diagnosis. *J Lower Genit Tract Dis* 1999; 3: 7-18. https://doi.org/10.1046/j.1526-0976.1999.08079.x

[58] Lifits-Podorozhansky YM, Podorozhansky Y, Hofstetter S, Gavard JA. Role of Vulvar Care Guidelines in the Initial Management of Vulvar Complaints. J Low Genit Tract Dis 2012; 16 (2): 88-91. https://doi.org/10.1097/LGT.0b013e318232fd9a

[59] Majerovich JA, Canty A, Miedema B. Chronic vulvar irritation: could toilet paper be th culprit? Can Fam Physician 2010; 56: 350-2.