



The Association Between Urological Conditions Across the Life Course and Provoked Vulvodynia

Bernard L. Harlow, PhD,¹ Hanna Mührlad, PhD,^{2,3} Jane Yan, BS,⁴ Donghao Lu, PhD,⁴
and Nina Bohm-Starke, MD, PhD²

Abstract

Objective: Vulvodynia is a condition characterized by chronic pain and discomfort in the vulvar region often accompanied with physical and psychological comorbidities. Interstitial cystitis (IC)/bladder pain syndrome (BPS), a chronic condition characterized by bladder pain and urinary urgency, has repeatedly been shown to comorbidly be present in a large proportion of women with vulvodynia. However, recent studies have shown that women with vulvodynia experienced additional bladder-related symptoms beyond that of just IC/BPS.

Materials and Methods: Using Swedish National Registry data, we assessed the association between urological symptoms in the presence and absence of IC/BPS in women with vulvodynia/vaginismus relative to women with no vulvar pain history.

Results: After adjustment for birth year, parity, education, and residential location, women with vulvar pain had a 2.2-fold greater risk of cystitis or urethritis as expected (95% confidence interval [CI] 1.9–2.6). However, when women with cystitis codes were excluded, those with urethra disorders or other urinary symptoms codes were 1.9 times more likely to be vulvar pain cases (95% CI 1.7–2.1).

Conclusions: These findings support the belief that vulvodynia is not limited to being comorbid with IC/BPS but may also likely be associated with a wide range of urological disorders.

Keywords: vulvodynia, urinary disorders, risk factors, interstitial cystitis, urinary incontinence, lower urinary tract symptoms (LUTS), life course

Introduction

Vulvodynia is a complex and often misunderstood condition characterized by chronic pain and discomfort in the vulvar region. Symptoms can manifest as burning, stinging, irritation, or rawness and may significantly impact a person's quality of life, such as daily activities, sexual function, and emotional well-being.^{1,2} Despite its prevalence, vulvodynia remains underdiagnosed and under-researched, leading to challenges in understanding its causes and effective treatments.^{3,4}

Comorbidities associated with vulvodynia can vary widely and include both physical and psychological conditions.⁵ One

such example is the significant overlap between vulvodynia and interstitial cystitis (IC)/bladder pain syndrome (BPS), a chronic condition characterized by bladder pain and urinary urgency.⁶ A small study of women with and without clinically confirmed vulvodynia found that in the absence of IC/BPS, women with vulvodynia continued to experience greater urinary symptoms.⁷ A more recent nationally based study showed that women with “genital pain” experienced additional bladder-related symptoms beyond that of just IC/BPS. However, the investigators could not distinguish diagnosed vulvodynia from other genital pain disorders.⁸

¹Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts, USA.

²Department of Clinical Sciences, Division of Obstetrics and Gynecology, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden.

³Department of Global Public Health, Karolinska Institute, Stockholm, Sweden.

⁴Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

We sought to assess the prevalence of all urinary related health issues across the life course among women with diagnostic codes for vulvodynia and vaginismus relative to women with no history of vulvar pain using Swedish National Registry data. We further assessed the association between urological symptoms in the absence of IC/BPS in women with vulvodynia/vaginismus relative to women with no vulvar pain history.

Materials and Methods

Data sources, sampling frame, and study design

Swedish Health Registers are repositories of medical diagnoses, treatments, prescriptions, and outcomes for nearly all individuals receiving care in Sweden that are maintained by the Swedish National Board of Health and Welfare. All Swedish residents receive a unique personal identification number at birth, or upon arrival to Sweden, which enables investigators to cross-link data from multiple administrative registers. Swedish Registry data have been shown to be highly valid.^{9–11} After approval by the Swedish Ethical Review Authority (reference number: 2018/1475–32/3), we included as our sampling frame all women included in the Swedish administrative data for the period 1981–2018.

We obtained from the National Patient Register all inpatient visits between 1987 and 2018 (1987 is when the register became nationwide) and >80% of outpatient visits to hospital-based specialized health care physicians between 2001 and 2018 (this register became active in 2001). The National Patient Register contains information on diagnoses, date of admission and discharge, procedures, and treatments. Deaths were identified *via* the National Cause of Death Register. We excluded women who died at 15 years of age or younger or who were not alive in 2001.

Study design

We chose to conduct a case-control study within this sampling frame of all women born in Sweden between 1981 and 1996, virtually all of whom are registered in the Medical Birth Register ($N = 832,276$). We included only women still living and residing in Sweden as of 2018 ($N = 745,291$). Our cases were all women diagnosed with localized provoked vulvodynia ($n = 4,787$), vaginismus ($n = 2,063$), or both ($n = 867$) based on International Classification of Diseases (ICD) codes recorded in the National Patient Register between 2001 and 2018 (see below). Each case was matched on the

birth year to two randomly selected controls without a diagnosis of either vulvodynia or vaginismus ($n = 15,434$).

Classification of outcomes—vulvodynia and vaginismus

In Sweden, the ICD-10 code of N76.3 is used for provoked vulvodynia and N94.2 or F52.5 for vaginismus. Since vulvodynia is often accompanied with or misclassified as vaginismus, we therefore considered both conditions for this analysis.^{12,13} By including both vulvodynia and vaginismus, we increase the sensitivity of our outcome and the likelihood of capturing most women who met the diagnostic criteria for provoked vulvodynia. In consultation with our clinical colleagues, we learned that an ICD Code of N90.8 refers to unprovoked or generalized vulvodynia. However, the consensus is that this code is not valid for the assessment of localized provoked vulvodynia. Therefore, we conservatively chose to exclude 372 women with vulvodynia only, 126 with vaginismus only, and 118 with vulvodynia and vaginismus due to the presence of the N90.8 code. Thus, our final sample of cases included 4,415 women with vulvodynia only, 1,937 with vaginismus only, and 749 with both (total N of cases = 7,101). We also excluded 102 women with N90.8 codes from our sample of controls leaving a total of 15,332 for our analyses.

Classification of urological conditions and other covariates

We used the National Patient Register to identify urological conditions from birth through 2018. As shown in Table 1, we stratified these conditions into those classified as cystitis or urethritis (ICD9 codes 595 or 597; ICD10 codes N30 or N34), urethral disorders (ICD9 codes 598 or 599; ICD10 codes N35 through N39), and general symptoms and signs of urinary system issues (ICD9 codes 788; ICD10 codes of R30 through R39).

Information on education was obtained from Statistics Sweden's Longitudinal Integration Database for Health Insurance and Labor Market Studies. These data contain annual information on education for all individuals older than 16 years, between 1990 and 2018. For everyone, we collected information on the highest level of education attained by the end of 2018. The Medical Birth Register provided data on year of birth and number of prior pregnancies as of the end of 2018 as well.

Statistical analyses

We assessed the distributions of demographic characteristics including birth year, history of live births, region of

TABLE 1. ICD-9 AND ICD-10 CODES FOR UROLOGICAL CONDITIONS AMONG WOMEN BORN IN SWEDEN BETWEEN 1973 AND 1996

	No vulvar pain ($N = 15,332$)	Vulvodynia ($N = 4,415$)	Vaginismus ($N = 1,937$)	Both vulvodynia and vaginismus ($N = 749$)
ICD9/ICD10 codes	n (%)	n (%)	n (%)	n (%)
Cystitis or urethritis 595, 597/N30, N34	641 (4.2)	463 (10.5)	156 (8.1)	98 (13.1)
Urethral disorders 598–599/N35–N39	1,065 (6.9)	539 (12.2)	250 (12.9)	88 (11.7)
Symptoms and signs of urinary system 788/R30–R39	411 (2.7)	294 (6.7)	120 (6.2)	71 (9.5)

residency, and education among those with vulvodynia only, vaginismus only, both vulvodynia and vaginismus, and those with no vulvar pain history. After comparing the distributions between the three vulvar pain categories we found them to be similar across the demographics, birth-related events, and immune conditions and thus combined all vulvar pain categories in our analyses. We further assessed these demographic characteristics in relation to those with and without urological disorders across the lifespan.

We assessed the proportion of women with ICD codes in each of the three categories of urological disorders by those with vulvodynia only, vaginismus only, or both, relative to those with no vulvar pain. We further assessed those distributions among females with codes in only one of the three urological categories, in two of the three categories, and then in all three of the urological disorder categories. Multivariable conditional logistic regression methods were used to calculate odds ratios and 95% confidence intervals (CIs) that estimated associations of the various urological conditions across the life course with vulvar pain. We adjusted for birth year, parity, education, and region of residence at birth in all analyses. Additionally, we assessed the associations in those who had various combinations of urological conditions in relation to those with and without vulvar pain.

Results

Women with vulvodynia, vaginismus, or both had a median age of 23 at their first vulvar pain code in the registry. Fewer than 10% were entered at age 18 or younger, or 30 years of age or older. The distribution of women with no urological versus any urological conditions was similar by birth year and region of residence (Table 2). Parous women were more likely to experience urological conditions relative to nulliparous

women, and more highly educated women were less likely to experience urological conditions. The distribution of women with no vulvar pain versus either vulvodynia only, vaginismus only, or both was similar by birth year and region of residence. Women with vulvodynia, vaginismus, or both were less likely to be multiparous and more highly educated relative to women with no vulvar pain.

Table 3 shows the distribution of urological conditions among women with no vulvar pain, versus women with vulvodynia only, vaginismus only, or both. Across each of the three urological categories, women with vulvar pain had higher rates of ICD-classified urological conditions compared to women with no vulvar pain history. The prevalence of those with combinations of the three urological condition categories was substantially lower among women with no vulvar pain than that observed in women with vulvodynia only, vaginismus only, or both.

After adjustment for birthyear, parity, education, and residential location, women with vulvar pain had a 2.2-fold greater risk of cystitis or urethritis as expected (Table 4). However, when women with cystitis codes were excluded, those with urethra disorders only, or other urinary symptoms codes only, were 1.8 and 2.4 times more likely to be vulvar pain cases, respectively. Women with both urethral disorders or other urinary symptoms, and not IC/BPS, were 2.6 times more likely to be vulvar pain cases relative to controls (95% CI 2.0–3.5).

Lastly, when we separated women who only experienced any cystitis diagnoses, from those who experienced other urethral disorders or diagnosed symptoms or signs of urinary system issues, we see that both are strongly associated with vulvodynia, vaginismus or both after both adjustment for demographic covariates, as well as immune disorders experiences across the life course (Table 5).

TABLE 2. DISTRIBUTION OF BIRTH YEAR, PARITY, REGIONAL OF RESIDENCE, AND HIGHEST EDUCATION AMONG WOMEN WITH AND WITHOUT UROLOGICAL DISORDERS, AND WOMEN WITH AND WITHOUT VULVODYNIA, VAGINISMUS, OR BOTH

	<i>No urological disorders</i> (N = 19,079)	<i>Any urological disorders</i> (N = 3,354)	<i>No vulvar pain</i> (N = 15,332)	<i>Vulvodynia, vaginismus, or both (N = 7,101)</i>
	n (%)	n (%)	n (%)	n (%)
Birth year				
1981–1984	4,605 (24.1)	867 (25.8)	3,742 (24.4)	1,730 (24.4)
1985–1989	6,809 (35.7)	1,319 (39.3)	5,571 (36.3)	2,557 (36.0)
1990–1994	6,334 (33.2)	977 (29.1)	4,989 (32.5)	2,322 (32.7)
1995–1999	1,331 (7.0)	191 (5.7)	1,030 (6.7)	492 (6.9)
Parity				
0	11,442 (60.0)	1,805 (53.8)	8,770 (57.2)	4,477 (63.0)
1	3,149 (16.5)	683 (20.4)	2,613 (17.0)	1,219 (17.2)
2 or more	4,488 (23.5)	866 (25.8)	3,949 (25.8)	1,405 (19.8)
Region of residence at birth				
South	4,124 (21.6)	709 (21.1)	3,491 (22.8)	1,342 (18.9)
Middle	10,783 (56.5)	2,028 (60.5)	8,694 (56.7)	4,117 (58.0)
North	4,171 (21.9)	617 (18.4)	3,146 (20.5)	1,642 (23.1)
Missing	1 (<0.1)	0 (0)	1 (<0.1)	0 (0)
Highest education				
<High school (<9 years)	1,100 (5.8)	307 (9.2)	1,119 (7.3)	288 (4.1)
High school (9 years)	7,375 (38.7)	1,491 (44.5)	6,436 (42.0)	2,430 (34.2)
>High school (>9 years)	10,602 (55.6)	1,556 (46.4)	7,775 (50.7)	4,383 (61.7)
Missing	2 (<0.1)	0 (0)	2 (<0.1)	0 (0)

TABLE 3. UROLOGICAL CONDITIONS ALONE OR IN COMBINATION WITH OTHERS

	No vulvar pain (N = 15,332)	Vulvodynia (N = 4,415)	Vaginismus (N = 1,937)	Vulvodynia and vaginismus (N = 749)	Vulvodynia or vaginismus (N = 7,101)
<i>Urological disorders</i>	n (%)	n (%)	n (%)	n (%)	n (%)
None of the disorders below	13,540 (88.3)	3,433 (77.8)	1,538 (79.4)	568 (75.8)	5,539 (78.0)
1. Cystitis or Urethritis <i>only</i>	446 (2.9)	262 (5.9)	76 (3.9)	48 (6.4)	386 (5.4)
2. Urethral disorders <i>only</i>	815 (5.3)	319 (7.2)	168 (8.7)	47 (6.3)	534 (7.5)
3. Symptoms/signs of urinary system <i>only</i>	242 (1.6)	140 (3.2)	57 (2.9)	24 (3.2)	221 (3.1)
1 and 2 above <i>but not</i> 3	120 (0.8)	107 (2.4)	35 (1.8)	15 (2.0)	157 (2.2)
1 and 3 above <i>but not</i> 2	39 (0.3)	41 (0.9)	16 (0.8)	21 (2.8)	78 (1.1)
2 and 3 above <i>but not</i> 1	94 (0.6)	60 (1.4)	18 (0.9)	12 (1.6)	90 (1.3)
1 and 2 and 3 above	36 (0.2)	53 (1.2)	29 (1.5)	14 (1.9)	96 (1.4)

Discussion

Our findings suggest that women with vulvodynia, vaginismus, or both experience a wide spectrum of urological conditions at a substantially greater rate than women with no vulvar pain history. This excess risk is not merely confined to those with IC or BPS but is present for a wide spectrum of urological symptoms in the absence of IC or BPS as well.

Sun et al. report that women with vulvodynia were 19 times more likely to report severe urgency after urination and 4 times more likely to be usually or always bothered by bladder pain or urgency.⁷ In their analyses, the authors excluded questions from the Pelvic Pain, Urgency, and Frequency Questionnaire related to bladder or vulvovaginal pain (factors known to be highly correlated with vulvodynia) and adjusted for a history of urinary tract infections (UTIs). Thus, these findings support ours that women with vulvodynia are more likely to be bothered by a wide spectrum of lower urinary tract symptoms and not just bladder pain or UTIs.

A recent study from the National Institutes of Health PLUS research consortium reported that women with any genital pain experienced worse bladder health and function scores based on a validated instrument¹⁴ across all domains compared with women with nongenital pain only and more so in comparison to women with no genital pain as classified in their analyses.⁸ Although their findings support our conclusions as well, they were limited in their ability to categorized

genital pain specifically as vulvodynia or vaginismus. Nevertheless, the authors concluded that genital pain is not just comorbidly observed in those with IC/BPS but across a wide spectrum of urological disorders.

There is a biological rationale as to why women with vulvodynia, vaginismus, or both might be more likely to experience a wide spectrum of urological conditions. Pelvic floor myofascial pain is commonly observed in women with a wide variety of pelvic pain disorders.^{15–17} This heightened pain sensitivity in the genital area can lead to a compensatory reaction through muscular changes as a way of responding to the pain. The pelvic floor muscles can become overactive or hypertonic. Thus, these muscles are in a constant state of tension or contraction, often as a protective mechanism or perhaps to pain-related muscle guarding. In addition, we recently showed that women with clinically confirmed vulvodynia may exhibit signs of chronic inflammation or a compromised immune system.¹⁸ The interplay between chronic inflammation and a heightened myofascial response may contribute to a range of overlapping symptoms. These can include increased pain, discomfort, and other urogenital symptoms such as urinary urgency, frequency, and pain.

Our study has several strengths including the use of a data source that represents the entire population of women in Sweden. The Swedish registers are known to be highly accurate and because of universal health care, most outpatient and inpatient diagnoses are captured and not self-reported. However, we recognize that our study is not without limitations. First, since the exact date of onset of vulvar pain symptoms cannot be reliably documented using the Swedish register system, a prospective analysis with time-to-event data was not feasible and we therefore chose a case-control study design. Thus, the temporal sequence of urological conditions relative to the onset of vulvar pain could not be established. We also recognize that a true diagnosis of IC/BPS may not always be captured within the broad category of ICD coding for “cystitis.” However, given that our findings show strong associations across all urological ICD coding, this potential misclassification should have little impact on our findings. Another limitation is the lack of potential confounding covariates such as smoking habits, diet, physical activity, or obesity within the Swedish registers. Thus, we cannot determine the extent to which these factors might influence both the onset of urological conditions and vulvar

TABLE 4. ASSOCIATION BETWEEN UROLOGICAL CONDITIONS AND VULVODYNIA, VAGINISMUS, OR BOTH

<i>Urological conditions</i>	<i>Crude OR (95% CI)</i>	<i>Adjusted* OR (95% CI)</i>
None of the disorders below	1.0	1.0
1. Cystitis or urethritis <i>only</i>	2.1 (1.8–2.4)	2.2 (1.9–2.6)
2. Urethral disorders <i>only</i>	1.6 (1.4–1.8)	1.8 (1.6–2.0)
3. Symptoms/signs of urinary system <i>only</i>	2.2 (1.9–2.7)	2.4 (2.0–2.9)
1 and 2 above <i>but not</i> 3	3.2 (2.5–4.1)	3.6 (2.8–4.6)
1 and 3 above <i>but not</i> 2	4.9 (3.3–7.2)	4.7 (3.2–7.0)
2 and 3 above <i>but not</i> 1	2.3 (1.7–3.1)	2.6 (2.0–3.5)
1 and 2 and 3 above	6.5 (4.4–9.6)	7.8 (5.3–11.5)

*Adjusted for birth year, parity, education, and residential location. CI, confidence interval; OR, odds ratio.

TABLE 5. CYSTITIS VERSUS OTHER UROLOGICAL CONDITIONS

Urological conditions	No vulvar pain (N = 15,332)	Vulvodynia or vaginismus (N = 7,101)	Crude OR (95% CI)	Adjusted* OR (95% CI)	Adjusted** OR (95% CI)
	n (%)	n (%)			
None of the disorders below	13,540 (88.3)	5,539 (78.0)	1.0	1.0	1.0
Any cystitis	641 (4.2)	717 (10.1)	2.7 (2.4–3.1)	2.9 (2.6–3.3)	2.8 (2.5–3.1)
Urethral disorders or symptoms/ signs of urinary system only	1,151 (7.5)	845 (11.9)	1.8 (1.6–2.0)	2.0 (1.8–2.2)	1.9 (1.7–2.1)

*Adjusted for birth year, parity, education, and residential location.

**Additionally adjusted for immune-related disorders across the life course (none, 1 code only, 2 different codes, 3 or more different codes), cesarean section, preterm birth, or low birth weight at delivery.

CI, confidence interval; OR, odds ratio.

pain. We also recognized that a large proportion of women fail to seek care for their vulvar pain and perhaps even urological conditions. Thus, there is the potential for underreporting of both urological and vulvar pain codes within the Swedish registries. However, this type of underreporting is more likely to be independent of urological and vulvar pain conditions and would likely lead to an attenuation of the true associations.

Despite these limitations, understanding the associations between urological comorbidities and vulvar pain can help guide clinical practice. Carefully distinguishing symptoms related to pain during sexual activity and pain related to micturition will impact the clinical approach to care since treatment may differ depending upon the symptoms. For example, if clinical interventions are directed only toward vulvodynia, then true improvement may not be observed due to the continuous symptoms emanating from the urinary tract, particularly the urethra. This same scenario holds true if treatment is focused only on urinary symptoms. Cases with both vulvodynia and urological disorders are considered more complicated, and treatment is often optimized by collaboration between gynecologists and urologists when possible.

In conclusion, our findings support the belief that vulvodynia, is not limited to being comorbid with IC/BPS but may also likely be associated with a wide range of urological disorders. These findings suggest that clinicians treating women for vulvar pain should consider a more comprehensive evaluation of urological symptoms, not just a focus on urological pain conditions such as IC/BPS.

Authors' Contribution

B.L.H.: carried out conceptualization, methodology, and writing, review and editing. H.M.: provided editorial assistance and interpretation of the findings. D.L.: assisted with methods, interpretation of analyses and editing manuscript. J.Y.: carried out all statistical analyses. N.B.S.: contributed to clinically relevant findings, interpretation of data, and manuscript editing.

Author Disclosure Statement

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Address correspondence to:

Bernard L. Harlow, PhD

Department of Epidemiology

Boston University School of Public Health

Boston, MA 02118

USA

E-mail: harlow@bu.edu