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Remission of Vulvar Pain among Women with Primary Vulvodynia

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Abstract

Objective—To determine whether rates of remission differed among women with primary versus secondary vulvodynia.

Methods—Using a community-based observational study based in Minneapolis/St. Paul, 138 clinically-confirmed cases of vulvodynia between 18 – 40 years old were classified as primary (vulvar pain starting at the time of sexual debut or first tampon insertion) or secondary (vulvar pain starting after a time period of pain-free intercourse), and queried regarding their pain history to determine whether they had ever experienced any vulvar pain-free time (remission), or pain-free time lasting ≥3 months.

Results—Remission prevalence was 26% (9/34) for women in the shortest quartile of duration of vulvar pain (<3.8 yrs), and 38% (13/34) for the longest quartile of duration (≥13 yrs). After adjusting for vulvar pain duration, generalized vestibular pain, medical treatment, body mass index (BMI), and history of pregnancy, women who had primary vulvodynia were 43% less likely to report remission (95% CI: 0.33 – 0.99) than women with later onset (secondary cases). The association was strengthened when restricting to only remissions lasting ≥3 months (adj. RR=0.43, 95% CI: 0.22 – 0.84). Generalized vestibulodynia and obesity also reduced the likelihood of remission.

Conclusion—Our study underscores the heterogeneity of vulvodynia and provides evidence that primary vulvodynia may have a less wavering course, and as such, a potentially different underlying mechanism than that of secondary vulvodynia.

Keywords

vulvodynia; remission; pain; primary; secondary

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INTRODUCTION

Approximately 10% – 18% of American women have had chronic vulvar pain symptoms consistent with vulvodynia [1,2]. In addition to effects on women's physical, sexual, emotional health, and relationships, the economic burden of vulvodynia is estimated to be substantial at up to $72 billion per year in the U.S. [3]

Each year approximately 10% of women with vulvodynia may experience remission from their vulvar pain [4], with some experiencing remission in the absence of medical therapy [5]. The probability of remission may be related to women's vulvodynia characteristics, such as the timing of vulvar pain onset. Specifically, women who have had pain since first provocation (primary) [6] may represent a different underlying mechanism [6–8] than women who develop vulvar pain later (secondary) [8]. For example, women with primary vulvodynia differ from those with secondary with respect to how pain is processed and modulated by the central nervous system [9], thus suggesting different biological mechanisms that could be considered when evaluating etiology or treatment strategies.

Treatment studies have in fact noted reduced effectiveness between the two subtypes of women [8,10,11]. However, this literature is based upon samples of healthcare-seeking women, who represent only half of those with chronic vulvar pain[1], thus potentially not generalizable to all women.

We assessed whether remission from vulvar pain differed by primary compared to secondary onset. We studied women sampled from the community, who after initial screening were clinically-confirmed as having vulvodynia.

METHODS

Source of Participants

This study protocol was approved by the University of Minnesota Institutional Review Board prior to its initiation. Between 2010 and 2013, women 18–40 years of age in the metropolitan area of Minneapolis/St. Paul, Minnesota were screened for the presence of vulvar pain. Participants were randomly selected from those who had been seen for any reason at any of the Twin Cities Metro Area Fairview Health Services Clinics within the previous two years and who listed a home address within a 70-mile radius of the University of Minnesota Twin Cities campus.

For this study, a total of 25,754 women were identified as initially eligible for vulvar pain screening. These women were mailed a self-administered survey regarding their history of chronic vulvar pain. In addition, basic demographics, reproductive history, and other histories regarding pain were assessed. Women were given the option of completing the survey in one of three ways: via the enclosed hard copy survey with a prepaid return envelope, a secure online site, or over the telephone with trained interviewers. After 3 mailed attempts, we received 13,740 (53.4%) screener surveys.

The 1,039 women who reported a history consistent with a vulvodynia diagnosis using validated screening questions[12] were invited to participate in a clinic visit to have their

vulvar pain confirmed as vulvodynia by trained clinicians, consisting of physicians and a certified nurse midwife instructed on the clinical protocol for examination that implemented the International Society for the Study of Vulvovaginal Disease consensus guideline [2]. Briefly, clinicians began with assessing a pain history, followed by evaluation of the vulvar architecture and noting presence of erythema. The diagnosis of vulvodynia excluded women with other causes of vulvar pain including signs of an infection by using a vaginal wet prep microscopic examination and noting presence of abnormal vaginal discharge, as well as inspection for underlying dermatologic conditions such as lichen planus or lichen sclerosus. Vulvar pain mapping was conducted using a dry cotton-tip applicator using the 'clock face' method by systematically applying pressure (exerting only enough force to indent the mucosa) at different clock positions of the vulva to assess the extent of the pain. Of the women identified from the community-based screener at the time of this study, 203 completed the clinical visit and 138 (68%) were clinically-confirmed to have vulvodynia. These clinically confirmed cases comprise those included in this analysis.

Assessment of Remission, Type of Vulvodynia, and Other Key Covariates

Following clinical confirmation of vulvodynia and willingness to participate, women responded to a telephone-administered interview regarding their medical history. During this interview, women were asked whether there was a period of time in which they were free of vulvar pain. Those who endorsed this question were considered to have had a history of remission. If a remission was reported, women were queried to provide additional details including: dates, duration, frequency, factors associated with the remission, and pain patterns coming into and out of the remission.

Many women had difficulty reporting the details of a remission, particularly if there were multiple pain-free periods. Due to this level of uncertainty, we first classified remission into any pain-free period. As there is no accepted standard for the definition of a remission, for sensitivity analyses, we later restricted the definition to include only women who were certain that at least one of their pain-free periods lasted 3 months or more, a definition previously reported by Reed et al[4].

During the interview, women were also asked, "Have you always had discomfort during intercourse or did it appear after a period of painless intercourse?". If a woman endorsed that she, "Always had pain on contact" she was defined as having primary vulvodynia [6,8]. If she endorsed, "Pain on contact started later" she was defined as having secondary vulvodynia. There were 12 women with missing responses. For those individuals, primary or secondary status was assigned after answering the question, "[What] was the difficulty that you experienced the first few times you tried (even if you tried only once) to insert a tampon?". If they reported no difficulty or pain (n=4) they were classified as secondary; and if they reported some (n=6) or great (n=2) pain, they were classified as primary.

The following variables were considered as covariates in our multivariate analyses. Duration of vulvodynia was calculated as the difference in time between vulvar pain symptom onset and the time of the interview; the duration did not account for periods of remission. Body mass index (BMI) was calculated from self-reported height and weight at the time of the survey, as was the demographic data. Cut-points for BMI followed published categories for

underweight, normal, overweight and obese. History of pregnancy was dichotomized into previously pregnant or not. Women also self-reported having ever sought care for their vulvar pain or ever having received treatment for their vulvar pain. To attempt to account for severity of vulvar pain in our analyses, we used the clinician assessment of generalized vestibulodynia made during the clinic exam; a woman was determined to have generalized vestibulodynia if she experienced pain at each point on the clock face upon provocation with a cotton swab.

Statistical Analyses

Descriptive statistics were used to assess univariate differences between women who reported any remission and those who experienced no remission. P-values were determined by chi-square statistics for categorical variables, Student's t-test for continuous variables, and a test for trend for variables with potential dose-response with remission (such as duration of vulvodynia and BMI).

A history of remission was not rare in our sample and therefore we could not use a logistic regression model, but instead chose to use a binomial regression model to estimate risk of remission and to adjust for confounding variables. Generalized linear models with a log link and binomial family allowed estimation of the adjusted risk ratios. Duration of vulvar pain was categorized into quartiles and placed into the model as a dummy variable. Duration and age were correlated (correlation coefficient = 0.54), and therefore both could not be included in the final model. We chose duration because onset of pain differed between women and therefore, duration would better capture the women's risk period. For the multivariable model, normal BMI was considered the referent and BMI placed into the model as a dummy variable. The final model selection procedure included assessing statistical significance and previous literature, including variables that have been found to be significantly associated with an increase or decrease in chronic pain for some women (i.e., treatment, extent of vulvar pain, BMI), and reports that indicated pregnancy was associated with remission in some. Statistical analyses were conducted using STATA v. 12 (College Station, TX).

RESULTS

Our study included 138 clinically-confirmed cases of vulvodynia. Table 1 provides the prevalence of having a history of remission; the prevalence was 26% for those in the quartile representing the shortest duration group, and 38% in those representing the longest duration group. (Table 1)

Table 2 lists the demographic variables by history of remission. Thirty-three percent of women (46/138) reported having experienced at least one pain-free episode (remission), and 80% of these remitters had at least one remission lasting ≥ 3 months.

Twenty-eight percent of the remitters and 38% of the non-remitters had primary vulvodynia (Table 3). We also observed that normal BMI was associated with the greatest likelihood of remission, with the most dramatic difference in prevalence observed with the obese category.

Table 4 describes the multivariable binary regression models and reports the adjusted risk ratios (adj. RR) for remission. Women who were missing health-seeking behavior variables (n=3) were excluded from these analyses. After adjustment, women with primary vulvodynia were 43% less likely to have a remission compared to those with later vulvar pain onset (adj. RR = 0.57, 95% CI: 0.33 – 0.99). Women with generalized vestibulodynia were also significantly less likely than those with localized area(s) to report a remission (adj. RR = 0.61, 95% CI: 0.39 – 0.97). Relative to women with normal BMI, those who were underweight or obese were significantly less likely to have had a remission, with obese women being 76% less likely.

Sensitivity analyses were used to examine if the associations remained after restricting remission to only those that lasted ≥3 months. After excluding the women who reported a remission of <3 months, we found an even greater reduction in the likelihood of remission among women with primary versus secondary vulvodynia (adj. RR = 0.43, 95% CI: 0.22, 0.84). (Table 4)

DISCUSSION

We provide novel data from a community-based study indicating that remission from vulvar pain is quite common, and that women with primary vulvodynia are less likely to have a remission than women with secondary vulvodynia. This finding was further strengthened when restricting the definition of remission to at least 3 months. Originally considered to be a confounder to our primary research question, we also found that women with generalized vestibular pain were significantly and independently less likely to remit than those with more isolated vestibular pain.

Overall, we did not find a significant association between remission and health behaviors, such as seeking care for vulvar pain and receiving therapy for pain, though our study may not have been adequately powered to examine such questions. Instead, we included these behaviors as broad indicators of the women's overall attempts to relieve vulvar pain. It remains unclear to what extent medical care influences resolution of symptoms, and to what extent remission occurs in untreated women. Greater understanding of both spontaneous remission, and improvement due to therapy, will ultimately provide guidance in developing more effective interventions.

Our findings on the differences between women with primary and secondary vulvodynia are mechanistically plausible based on recent clinical studies. Using brain imaging techniques to assess central pain processing of evoked pain stimuli, Hampson et al found that women with primary vulvodynia were more likely than secondary cases to possess characteristics of augmented centralized pain processing [9]. The authors also found that primary cases differed from secondary cases in their clinical presentation, and were more consistent with pain states indicative of aberrant underlying centralized pain mechanisms than those of a purely neuropathic or musculoskeletal origin. Evidence also suggests differences in peripheral pain assessments between primary and secondary pain sufferers. Using biopsies of painful vulvar tissue, Goetsch et al found that women with primary vulvodynia had increased nerve density compared to secondary cases [13]. Also through biopsy tissue analyses, women with primary

vulvodynia have been found to have increased hyperplasia and hypertrophy [14]. Taken together, women with primary vulvodynia have been shown to have involvement of both peripheral and central pain factors, all of which may explain our finding that primary vulvar pain sufferers are significantly less likely to experience a remission, especially one lasting at least 3 months.

Our study has several unique strengths. Approximately half of women with chronic vulvar pain consistent with vulvodynia do not seek care for their pain [1], which we have also found to be true in this study as well [15]. The differences in phenotype between those who do and do not seek care for vulvar pain are largely unknown. However, literature from other chronic pain conditions support that individuals who have higher pain or greater functional disability are more likely to seek care [16,17] thus potentially biasing clinic-based populations toward more women with severe pain profiles who may be less likely to achieve pain relief. This study, however, sampled women from the community and therefore was not subject to the potential for selection bias of clinic-based studies. In addition, methodology for vulvodynia diagnoses are diverse and use of different clinical criteria can increase heterogeneity in the cases. Our study employed one standardized protocol for diagnosis of vulvodynia, and the generalized vestibulodynia phenotype, therefore generating improved homogeneity in our cases.

In addition, the previous study of remission was not able to examine other covariates that may influence remission[4]. For example, we describe that increasing weight was associated with decreased likelihood of remission. The dose-response nature and level of reduction in the likelihood of remission associated with overweight and obese categories was striking. However, due to our methodology, we are unable to determine the temporal association between excess weight, particularly weight gain, and the continuance of vulvar pain.

However, our study is not free of limitations. The design of the parent study employed prevalence-based assessment of cases from which we assessed the history of remission, therefore only capturing women who relapsed back to vulvar pain. The result of this study limitation therefore is that we are unable to capture women who once had vulvar pain that later remitted and never returned. Therefore, an alternative conclusion to our findings is that women with primary vulvodynia are more likely to have remissions that relapsed back into pain than women with secondary vulvodynia. However, at this time, there are no prospective studies that could enumerate how frequent it is to have vulvar pain that resolves permanently.

Several other limitations should be considered when interpreting our results. First, our study was limited in its recalled ascertainment of the details of a woman’s history of remission. We were therefore limited in our ability to investigate time-varying factors that could have led to a remission, such as extent of vulvar pain, BMI, and health seeking behaviors around the times of remission. Due to this lack of detailed information, we were unable to examine the temporal relationship between these factors and remission. This lack in temporality, however, would not have affected our primary exposure of interest (primary and secondary) because these classifications are static and thus do not vary over the course of vulvodynia pain.

In conclusion, our investigation using this community-based sample suggests that women with primary vulvodynia may experience a different clinical course than women with secondary onset with respect to remission. These findings suggest a critical need for future community-based studies that prospectively assess changes in vulvar pain and any potential factors that may influence women's likelihood to achieve relief from her vulvar pain, whether as a consequence of treatment or otherwise.

Acknowledgments

DISCLOSURES

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TABLE 1

Prevalence of any remission by quartile of duration with vulvar pain among 138 women with clinically confirmed vulvodynia in the Minneapolis/St. Paul metropolitan area, 2010 – 2013.

Quartiles of Duration of Vulvar Pain (y)	Any Remission (%)	95% CI
0.9 – 3.79	26	11 – 41
3.8 – 7.44	34	18 – 50
7.45 – 12.9	34	18 – 50
13.0 – 25.8	38	22 – 54

TABLE 2

Distribution of demographic variable for women with 138 clinically-confirmed vulvodynia cases stratified by history of remission from vulvar pain.

Demographic variable	Women reporting remission (n = 46)		Women not reporting remission (n = 92)		
	No.	%	No.	%	p-value
Mean age, *y* (SD)	28.8 (5.7)		29.0 (4.8)		0.16
Age categories, *y*					0.21
18–19	1	2.2	2	2.2	
20–24	11	23.9	10	10.9	
25–29	14	30.4	42	45.7	
30–34	11	23.9	25	27.2	
35–40	9	19.6	13	14.1	
Race					0.55
White	40	87.0	81	88.0	
Black	1	2.2	1	1.1	
Biracial	5	10.9	7	7.6	
Other	0	0	3	3.3	
Current Marital Status					0.99
Single, never married	19	41.3	37	40.2	
Married/partnered	25	54.3	51	55.4	
Separated/divorced	2	4.4	4	4.4	
Highest Level of Education					0.92
High School	2	4.4	2	2.2	
Some college	6	13.0	16	17.4	
Associate’s degree	5	10.9	11	11.9	
Bachelor’s degree	23	50.0	44	47.8	
Graduate degree	10	21.7	19	20.7	

TABLE 3

Selected pain and medical history characteristics by remission status among 138 women with clinically-confirmed vulvodynia sampled from a population-based study in the Minneapolis/St. Paul metropolitan area, 2010 – 2013.

Characteristic	Women reporting any remission (n = 46)		Women not reporting remission (n = 92)		
	No.	%	No.	%	p-value
Type					0.26
Primary	13	28.3	35	38.0	
Secondary	33	71.7	57	62.0	
Mean Duration, *y* (range)	9.2 (2.0 – 24.4)		7.0 (0.9 – 25.8)		0.59
Duration in Quartiles, *y*					0.77
< 3.8	9	19.6	25	27.2	
3.8 – 7.49	12	26.1	23	25.0	
7.5 – 12.9	12	26.1	23	25.0	
≥ 13.0	13	28.3	21	22.8	
Body Mass Index (BMI)					0.08
Underweight (< 18.5)	3	6.5	3	3.3	
Normal weight (18.5–24.9)	29	63.0	45	48.9	
Overweight (25.0–29.9)	12	26.1	26	28.3	
Obese (≥30.0)	2	4.4	18	19.5	
History of pregnancy					
Yes	19	41.3	42	45.7	0.63
No	27	58.7	50	54.3	
Location of pain on the vestibule					
Generalized	19	41.3	40	43.5	0.09
Localized	27	58.7	52	56.5	
Sought treatment for pain					
Yes	21	45.6	48	52.2	0.82
No	20	43.5	42	45.7	
Missing	5	10.9	2	2.1	

Characteristic	Women reporting any remission (n = 46)		Women not reporting remission (n = 92)			
Received treatment for pain						0.78
Yes	8	17.4	20	21.7		
No	32	76.1	70	76.1		
Missing	6	13.0	2	2.2		

TABLE 4

The associations of vulvar pain phenotype, medical history, and health behaviors with likelihood of remission among women clinically-confirmed vulvodynia from a population-based study from the Minneapolis/St. Paul metropolitan area, 2010 – 2013, among (a) all cases (n=135), and (b) the sensitivity analyses excluding women who with a remission lasting less than 3 months (n=127).

	(a) All cases			(b) Excluding women who had remission lasting <3 months		
	Adj. RR	**95% CI**	**p-value**	**Adj. RR**	**95% CI**	**p-value**
Primary	0.57	0.33 – 0.99	0.05	0.43	0.22 – 0.84	0.01
Generalized	0.61	0.39 – 0.97	0.04	0.61	0.37 – 0.99	0.05
Duration quartiles, *y*						
< 3.8	1.0 (ref)	--	--	1.0 (ref)	--	--
3.8 – 7.49	1.36	0.66 – 2.78	0.40	1.95	0.75 – 5.08	0.17
7.5 – 12.9	1.98	1.0 – 3.94	0.05	3.19	1.29 – 7.89	0.01
≥ 13.0	2.31	1.22 – 4.38	0.01	3.62	1.49 – 8.79	<0.01
Body Mass Index						
Underweight (< 18.5)	0.97	0.96 – 0.98	<0.01	0.94	0.94 – 0.95	<0.01
Normal weight (18.5 – 24.9)	1.0 (ref)	--	--	1.0 (ref)	--	--
Overweight (25.0 – 29.9)	0.71	0.43 – 1.18	0.18	0.64	0.36 – 1.14	0.13
Obese (≥ 30.0)	0.24	0.06 – 0.91	0.04	0.14	0.02 – 1.01	0.05
History of Pregnancy	0.97	0.61 – 1.55	0.89	0.96	0.59 – 1.55	0.86
Sought treatment for pain	0.70	0.43 – 1.13	0.14	0.62	0.35 – 1.09	0.10
Ever received treatment	1.01	0.54 – 1.91	0.97	1.40	0.75 – 2.61	0.28

*Risk ratios are adjusted for all other variables in the model.