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Multimodal vulvar and peripheral sensitivity among women with vulvodynia: A Case-Control Study

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Abstract

Objective—To assess differences in vulvar and peripheral sensitivity between women with and without vulvodynia.

Methods—Women with vulvodynia (N=41) and age-matched controls (N=43) seen in the outpatient setting were evaluated via surveys, clinical examination, and multimodal sensory testing (pressure, heat, cold, vibration, and electrical stimulation). The relationship between sensitivity to various sensory modalities and case/control status, as well as by vulvodynia subgroups, were assessed using logistic regression.

Results—Women with vulvodynia were more sensitive to pressure and to electrical stimuli than were control women at the vulva (Median 22 vs 230 grams and 0.495 vs 0.769 mA, respectively, $p < 0.001$ for each) and at the thumb (Median 2500 vs 4250 grams and 0.578 vs 0764 mA, respectively, $p = 0.006$ for pressure, $p < 0.001$ for electrical stimulation). Heat, cold, and vibration detection thresholds did not differ significantly between these groups ($p > 0.025$). Those reporting spontaneous pain versus provoked pain had greater pressure sensitivity to the thumb (Median 1850 vs 2690 grams, $p = 0.020$) and greater electrical sensitivity at the introitus (0.450 vs 0.608 mA, $p = 0.011$), and those with primary versus secondary vulvodynia, had substantially greater pressure sensitivity to the thumb (Median 2438 vs 3125 grams, $p = 0.004$). However, having localized versus generalized vulvodynia was not associated with differences in pressure or electrical sensitivity.

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Declaration of Interests

The authors have no conflicts of interest to declare.

Conclusions—Sensitivity to pressure and electrical stimuli is greater among vulvodynia cases than among controls, and supports two previously defined subgroups -- those reporting spontaneous pain versus those whose pain only occurred when provoked, and those with primary versus secondary vulvodynia.

Graphical Abstract

Precis: Sensitivities to pressure and electrical stimuli are greater among vulvodynia cases than among controls, and support two previously defined subgroups.

Keywords

Sensory testing; Vulvodynia; electricity; subgroups; pressure; central sensitization

Introduction

Vulvodynia is a vulvar pain syndrome occurring in approximately 8% of women at any one time [1, 2]. It is characterized by increased discomfort in the vulvar region, most commonly at the vestibule – the area between Hart's line in the introitus and the hymenal remnants. Although the mechanisms responsible for this pain are not completely understood, data indicating increased mechanical sensitivity at the introitus [3-7], enhanced systemic sensitivity [4, 6], altered fMRI findings in the brain when vulvar pressure is applied [7-9], and the presence of pain after intercourse [7, 10, 11] suggest that central sensitization plays a role in the pathophysiology of this morbid disorder. This central sensitization (an increase in the excitability of neurons within the central nervous system, such that normal inputs produce abnormal responses) [12], in conjunction with increased branching of distal nerves in vulvar biopsy tissue [13, 14] suggest that vulvodynia involves alterations in function of central neurologic processes that may include neuropathic components [15] with additional alterations in function of central neurologic processes. Although quantitative sensory testing (QST), is not recommended for the diagnosis of neuropathic pain, using a variety of sensory modalities (pressure, temperature, vibration, etc.) may characterize sensory attributes, help clarify pain mechanisms, and predict clinical course or treatment responses among normal persons and those with abnormal sensory presentations [16].

The term vulvodynia is applied to women who present with a broad range of vulvar pain characteristics and severities. Within this large group are subgroups with differing pain qualities, varying risk factors, and a variety of clinical course possibilities, including remission, relapsing, and persistence of symptoms [17, 18]. Many previous attempts to define clinically relevant subgroups of vulvodynia have been based on expert opinion, such as characterizing subgroups as localized vulvodynia (vestibulodynia, clitorodynia) versus generalized vulvodynia (symptoms beyond the localized site), provoked versus spontaneous versus mixed (provoked and spontaneous) pain, and primary versus secondary vulvodynia. Empirical evidence that differentiates these vulvodynia subgroups would be expected to help guide research on pathophysiology, clinical course, and treatment of this condition.

The present study was designed to assess differential responses to multimodal sensory testing among women with and without vulvodynia, and to further characterize the sensory

profiles and their relationship to pain characteristics among individuals with vulvodynia in order to further define response to various sensory modalities, and to refute or validate previously suggested subgroupings.

Methods

This case-control study compared women with vulvodynia to control women without vulvar pain. Approval was obtained from the University of Michigan Medical IRB (#2004-0296), and signed consent forms were obtained and retained. Enrollment occurred at three University of Michigan Clinics – The Center for Vulvar Diseases and the general Gynecology Clinics in Ann Arbor, MI, and the Vulva Clinic at the University of Michigan Family Practice Center in Chelsea, Michigan. All women aged 18-70 years who presented with vulvodynia on the days of enrollment, and age-matched (by decade of age) women without vulvar pain who presented to the clinic on the same days, were invited to participate. Cases with vulvodynia met the criteria of the International Society of Vulvovaginal Disease (2003), including vulvar pain/burning/irritation localized predominately to the vestibule and/or hymenal remnants that had been present for at least three months, with no other demonstrable cause for their symptoms (e.g. untreated infections, dermatologic disorders, etc.) [19]. The case definition identified cases who would also meet the more recent consensus statements of 2015 [20]. Pain could be described as either localized or generalized, and could be provoked and/or spontaneous (unprovoked) in quality, and may have been present since first intercourse or tampon use (primary) or have started after a time of no pain to these provocations (secondary). Control women had no history of prolonged vulvar pain. Exclusion criteria included currently being pregnant or breastfeeding, presence of a known diagnosis of a systemic pain syndrome such as diagnosed fibromyalgia or chronic fatigue syndrome, vulvar rash or lesions, or a history of vulvar surgery.

Each participant filled out a self-administered questionnaire to gather information on demographic characteristics, medical history, and pain history and characteristics. A general examination with a focused pelvic examination was performed to confirm case or control status and to exclude untreated infections (microscopy plus yeast culture).

Psychophysical evaluation at the vulva and periphery was performed on confirmed cases and controls via use of differing sensory modalities. Participants were familiarized with the equipment and sensations to be delivered, and were introduced to the 21-point box scale for rating pain intensity – a scale from 0 to 20 that combined a numerical score with words expressing pain intensity (very intense, very weak, etc). [21].

Sub- and suprathreshold pressure testing at the thumbnail was conducted using a testing device that delivers 5-second duration pressure stimuli to the left thumb by a 1 cm-diameter hard rubber probe [4]. The probe was attached to a pneumatic piston capable of delivering precise pressure stimulation with a near rectangular waveform within the range of 250 gm to 10 kg. A discrete ascending series of pressures, as well as a multiple random staircase series of pressures were used to determine pressures at which pain was first perceived, and pressures that evoked mild discomfort and slightly intense pain (9.5 and 14.5 on the 21-point pain scale) [22].

Temperature sensitivity (heat and cold) at the medial periungual thumb was determined using the Medoc TSA II analyzer (Medoc Ltd., Ramat Yishai, Israel). A cold-sterilized, 5 × 5 mm probe was applied to the testing site and the temperatures manipulated by software from 37°C, increasing 1°C every 10 seconds to maximum of 51°C. The temperature at which warmth was first detected (threshold), and the temperature at which a pain rating of 9.5 was reached (mild to moderate heat pain) were recorded. Sensitivity to cold was similarly determined, recording temperatures at which coolness was first detected and then the level at which cold pain (at a rating of 9.5 or greater) occurred (minimum of 5°C).

Vibratory sensitivity detection was determined using the VSA-3000 Vibratory Sensory Analyzer, (Medoc, Inc.). The VSA-3000 detects large nerve fiber dysfunction by measuring thresholds for vibratory stimuli in the range of 0-130 microns at a set frequency of 100Hz. One trial of increasing the intensity until a sensation was felt and subsequently decreasing the intensity until no sensation was felt was used.

Finally, *electrical sensitivity* was determined at the left medial periungual thumb, using constant current electrical stimuli delivered by a battery-operated stimulator developed by one of the investigators (RG). This device was capable of delivering 0-10 mA through skin impedances ranging from 50-100 kOhms, with the output isolated from ground. Three levels of current (threshold level and levels at which pain was considered moderate and slightly intense using the 21-point intensity scale) were determined.

Sensitivity testing at the vulva was similar to that used for the thumb. Pressure sensitivity (ranging from 35 to 1500 grams) was further determined using the vulvodorimeter that we developed and calibrated previously to produce levels of pressure found to be below and above those pressures typically found to be painful in women with vulvodynia [4]. Subthreshold and suprathreshold pressure testing at the vulva was measured at 21 vulvar locations (including sites of the labia majora, interlabial sulcus, and vestibule) and at the upper legs. An ascending pressure model was used for pressure testing at the vestibule to levels at which discomfort first occurred and then when discomfort was moderately severe (level 14 on the 21-point intensity scale). Heat, cold, vibration, and electrical sensitivities were determined at the vulvar vestibule, using methods similar to that described for thumb electrical sensitivities.

Frequencies of all variables were calculated, and demographic characteristics of cases and controls were assessed by logistic regression, t-tests, and chi-square analyses. Relationships between the sensory modality thresholds were determined using correlations of standardized values. T-tests and ANOVA were used to assess relationships between demographic and pain characteristics with sensitivity measures. Because the sensory measures were continuous variables with occasional censoring (level of discomfort not reached at highest level of stimulation), Cox proportional hazards analyses were used to compare the levels of pressure and of electrical current needed to reach specific degrees of discomfort between cases and controls, and, among cases, to determine the relationship between sensory threshold measures and vulvodynia subgroups. All analyses of sensitivity measures were controlled for age (the matching variable used during enrollment). Statistical significance was defined

as $p < 0.025$, in light of multiple testing. All statistics were performed using SPSS Statistics for the Mac (Version 22, IBM Corporation).

Role of the funding source

NIH had no role in the study design; collection, analysis, and interpretation of the data; in the writing of the manuscript; or in the decision to publish. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between June 2005 and October 2008, 84 women (43 with vulvodynia and 41 controls) were enrolled and completed the informed consent. Participants ranged in age from 18 to 69 years, and due to matching cases to controls by decade in age, no difference in age was noted between cases (mean = 33.7 ± 11.8 years) and controls (mean = 38.3 ± 14.4 years, OR 0.97, $p = 0.118$). Overall, 81% ($N = 68$) of participants were Caucasian, 2.4% ($N = 2$) were Hispanic, 9.5% ($N = 8$) were Black, 4.8% ($N = 4$) were southeast Asian, and 2.4% ($N = 2$) were “other” – but cases differed significantly from controls only in the percentage who were Caucasian. The relationships between demographic characteristics of participants and case status are shown in **Table 1**.

Pain characteristics of women with vulvodynia are shown in **Table 2**. It is often stated that spontaneous pain suggests generalized location, and provoked pain is localized. Although the proportions of women demonstrating localized pain was identical to the proportion whose pain was described as provoked-only, these were not the same women. These two subgroups were statistically associated (OR = 5.0, 95% CI 1.3, 19.8, $p = 0.018$). Although those with generalized pain were more likely to have spontaneous pain (9/15, or 60%) and those with localized pain were more likely to report provoked-only pain (20/26, 76.9%), 12/41 (29.3%) either reported having localized pain associated with spontaneous pain (with or without provokable pain) or generalized pain described as provoked-only ($p = 0.018$). Hence, suggesting that localized pain indicates provokable pain and that generalized pain suggests spontaneous pain is often in error.

We further stratified the spontaneous/provoked classifications into three categories: spontaneous-only (17.1%, $N = 7$), spontaneous plus provoked (19.5%, $N = 8$) and provoked-only (63.4%, $N = 26$). The association between the two categories that included those with spontaneous pain did not differ from each other in location of the pain (localized vs. generalized). Hence, the dichotomized subgrouping (spontaneous $\pm$ provoked versus provoked-only) was used in all further analyses.

Furthermore, there was substantial overlap regarding age and type of pain experienced with 28.6% of women ages 39 and less reporting the presence of spontaneous pain ($p = 0.12$), and 50% of those 50 years of age and older reporting pain that was provoked-only ($p = 0.46$). Having primary or secondary vulvodynia was not associated with either having spontaneous versus provokable-only pain ($p = 0.31$), or with having localized or generalized discomfort ($p = 0.65$).

Sensory testing

Increasing age was associated with less vulvar pressure sensitivity (higher threshold for pain, $p<0.001$) less thumb pressure sensitivity ($p<0.040$), increased vulvar and hymen vibration thresholds ($p<0.001$), but not with vulvar, hymenal, or thumb electrical sensitivity ($p>0.453$, $p>0.232$, and $p>0.491$, respectively). Furthermore, other variables associated with case status above (nulliparity, marital status, and current oral contraceptive use), although associated with vulvar sensitivity in the univariate analysis, were no longer associated with sensitivity once controlled for age.

The relationships between case/control status and sensitivity at the vulva, hymen, and thumb to pressure, electricity, vibration, heat, and cold are shown in **Table 3**. The hazard ratio is the ratio of the instantaneous probability of reporting the desired level of sensitivity at increasing stimulation levels in cases versus controls – with a positive ratio indicating the cases are more likely to report the given level of sensitivity at a lower level of stimulation than did the controls. Cases were more sensitive to mechanical pressure at the vulva as well as at the thumbnail, and were more sensitive to electrical stimulation at the vulva, hymenal remnants, and thumb. Heat, cold, and vibration sensitivity did not differ between cases and controls at the thumb, the vulva, or the hymen ($p>0.025$).

Pressure sensitivity and electrical sensitivity at specific sites (hymen, vulva, or thumb) were statistically correlated ($r>0.258$, $p=0.019$). Types of QST (pressure or electrical) across sites (vulva/hymen versus thumb) were also statistically correlated ($r>0.284$, $p=0.009$, data not shown).

Sensory characteristics among traditional subgroup classifications

We further evaluated whether pressure and electrical sensitivity differentiated women falling into traditional subgroup categories of vulvodynia patients. The level of pressure sensitivity at the thumb did differentiate those with primary vulvodynia compared to those with secondary vulvodynia, and between those with spontaneous pain and those with provoked-only pain; yet sensitivity at the vulva did *not* differentiate the two categories in each of these groups (**Table 4**). Electrical sensitivity at the vulva (but not the thumb) was greater (lower threshold) among those with spontaneous vulvar pain compared to those with provoked pain only. Neither pressure sensitivity nor electrical sensitivity (at the vulvar or thumb) differentiated those with “generalized” versus “localized” vulvodynia.

Discussion

This study provides further evidence that increased vulvar sensitivity to pressure applied at the introitus distinguishes vulvodynia cases from controls. In addition, sensitivity to electrical stimulation was markedly different between cases and controls— a finding in concordance with that of Murina et al. [23]. The enhanced local and systemic sensitivity to pressure and electrical modalities provides additional evidence of central nervous system sensitization in vulvodynia. We found little evidence to support categorization of subgroups into generalized versus localized, but did find sensory threshold differences between women

with vulvodynia with spontaneous versus provoked-only pain, and primary versus secondary vulvodynia.

Previous psychophysical testing of women with vulvodynia has demonstrated differences in pain sensitivity compared to control women [3, 5, 7, 24]. Localized [3, 4, 6, 7] as well as systemic [4, 6] tenderness to pressure among women with vestibulodynia or vulvodynia compared to controls has been demonstrated repeatedly, suggesting a central nervous system “sensitization” associated with vulvodynia. Brain imaging studies have also demonstrated increased cerebral activations in the insula and frontal cortical regions in women with vulvodynia compared to controls when stimulated with pressure at the posterior vestibule [8, 9] and at the thumb [9].

In contrast to previous reports [3, 5], sensitivity to heat and cold stimulation did not reliably discriminate between women with and without vulvodynia, and did not indicate altered sensitivity systemically (thumb) compared to the vulva. Others have suggested differences in heat pain threshold and tolerance [3, 25]. Reasons for these differences may be related to their use of more severe cases – those with pain confined to the introitus, or use of inclusion criteria that required vulvar sensitivity to pressure at the vulvar vestibule, and erythema in the same area [3, 25] – criteria that are not included in the more recent consensus statements on vulvodynia definitions [19, 20], and which may select for a specific subset of vulvodynia sufferers.

Vibration thresholds were not found to differ between those with vulvodynia and asymptomatic controls. Our findings were consistent with the negative findings of others assessing vibratory sensory thresholds in asymptomatic women [26], and vibratory pain thresholds in vulvodynia [3] and in fibromyalgia (a chronic pain condition associated with vulvodynia) [27].

Increased sensitivity to electrical stimulation among women with vulvodynia was demonstrated in this study. Unlike other stimuli that activated specific receptors, electrical stimuli bypass the receptor and directly stimulate primary afferent axons. Studies have suggested electrical sensitivity can differentiate those with other neurologic alterations, including fibromyalgia and migraine headaches [28], and those with urinary symptoms associated with retention [29]. However, little has been known about the response of women with vulvodynia to electrical stimulation. Our data confirm that electrical sensitivity is substantially increased in women with vulvodynia, both systemically (thumb) and locally.

Subgroups within the vulvodynia diagnosis have been suggested, with dichotomies of primary versus secondary, generalized versus localized, and spontaneous versus provoked-only vulvodynia being the most notable [19, 30]. However, little data support a physiologic basis for these subgroupings [31, 32]. Despite the prominence of the “generalized” versus “localized” dichotomy in the literature, this distinction continues to be questioned in light of little evidence to support the importance of this dichotomy [31, 32]. In our previous study, pressure sensitivity differences at the thumb and vulva between cases and controls were not different between those with localized versus those with generalized vulvar pain [4]. In this report, we similarly did not find these groups to be differentiated by pressure or electrical

stimulation thresholds – further questioning the physiologic basis for this subgroup. Our findings that the electrical sensitivity at the vulva differentiated cases versus controls in general and also differentiated those cases who reported spontaneous pain, compared to those with only provoked-pain, have not previously been reported. The finding that cases with spontaneous vulvar pain were more sensitive than cases with provoked-only pain when tested at the thumb with pressure stimuli further suggested a more widespread sensitivity in this subgroup. These results suggest a generalized A β fiber condition of mechanical allodynia that is consistent with reports of sensitivity to cotton swab testing. Observed during spinal central sensitization, A β fibers, which under normal conditions mediate only nonpainful sensations, change phenotype and behave as nociceptors. The increased sensitivity at suprathreshold pain levels suggest an A δ fiber sensitivity similar to pin prick hyperalgesia also found in central sensitization. This sensitization is a consequence of persistent nociceptor input that would be expected to result in spontaneous pain. Similarly, we demonstrated differences in pressure sensitivity among those cases with primary vs secondary vulvodynia. Others have indicated similar differences between those with primary versus secondary vulvodynia in QST (pressure), in fMRI findings, and in gray matter density [7].

Much remains to be learned about the value of QST testing in patients with altered pain sensitivity. Using a combination of QST modalities has been suggested by Neziri et al [33], who found different modalities (electrical, heat, cold, pressure, etc.) represented distinct individual uncorrelated measures of pain perception that are likely to identify specific pain dimensions; hence use in combination may be informative. Furthermore, treatment responses may vary depending on the differing sensory findings of individuals with a specific disorder, as has been found in other neurologic disorders [29]. At this point, a combination of pressure and electrical sensitivity testing might be considered in studies of pathophysiology and of treatment responses in women with vulvodynia. However, further work is needed to define these issues within the vulvodynia cohort.

Limitations to this study exist. The number of women studied was small. Further investigation with a larger number of subjects is needed. In addition, this study was conducted on clinically diagnosed vulvodynia cases presenting to vulvovaginal specialty clinics – whether findings would be similar in a community-based cohort is unknown. Lastly, we excluded women with fibromyalgia or chronic fatigue syndrome – comorbid conditions that may further alter sensitivity measures in those with and without vulvodynia. Future studies should include these women.

Conclusion

We found women with vulvodynia demonstrate increased sensitivity to pressure and electrical stimulation at the vulva and at the thumbnail, suggesting a central sensitization component is likely. In addition, the vulvodynia subgroups of primary vs. secondary, and presence of spontaneous pain versus provoked-only pain were shown to differ in QST findings, but the generalized versus localized dichotomy did not similarly differ, further adding evidence that this dichotomy may lack an evidence basis.

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Abbreviations and acronyms

mA	milliampere
QST	quantitative sensory testing
°C	degrees Centigrade
Aβ	A beta
Aδ	A delta

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Table 1

Characteristics of women participants by case control status.

	Vulvodynia Cases (N=41) (%)	Controls (N=43) (%)	OR (95% CI)	P value [^]	Adjusted P value [*]
Education 16 years	73.2	53.5	2.37 (0.95, 5.92)	0.062	0.209
Caucasian	70.7	90.7	0.25 (0.07, 0.85)	0.020	0.073
Nulliparous	72.5	39.5	4.03 (1.60, 10.20)	0.003	0.041
Married or living as married	61.0	46.5	1.80 (0.76, 4.28)	0.184	0.025
Currently taking oral contraceptives	40.0	17.1	3.24 (1.16, 9.08)	0.022	0.109
Ever used oral contraceptives	87.5	86.0	1.13 (0.32, 4.06)	0.845	0.578
Current smoker	7.3	9.3	0.77 (0.16, 3.67)	0.742	0.676
Ever smoked > 100 cigarettes	24.4	44.2	0.41 (0.16, 1.04)	0.056	0.759
Depression					
Ever	43.9	44.2	0.99 (0.42, 2.34)	0.979	0.437
Current treatment for depression	17.1	26.2	0.58 (0.20, 1.68)	0.314	0.467
History of abuse					
Sexual abuse	15.8	26.8	0.51 (0.17, 1.56)	0.233	0.536
Physical abuse	10.0	10.0	1.00 (0.23, 4.31)	1.000	0.828
First intercourse involuntary	7.3	12.2	1.76 (0.39, 7.90)	0.457	0.676
Any intercourse involuntary	26.8	30.8	0.83 (0.31, 2.18)	0.697	0.852

[^] Univariate logistic regression^{*} Logistic regression with age, nulliparity, current oral contraceptive use, and ethnicity included in the model.

Table 2

Pain characteristics of women with vulvar pain (N=41).

	Overall
Age at vulvar pain onset (years $\pm$ S.D.)	27.9 $\pm$ 12.6
Duration of vulvar pain (years $\pm$ S.D.)	5.1 $\pm$ 5.0
Pain after intercourse	72.2%
McGill Pain Questionnaire score (mean $\pm$ S.D.)	25.2 $\pm$ 13.2
Primary versus secondary	
Primary vulvodynia (pain 1 st intercourse or 1 st tampon insertion)	51.3%
Secondary vulvodynia (pain started later)	48.7%
Location of tenderness	
Localized to vestibule *	63.4%
Generalized beyond vestibule	36.6%
Spontaneous pain versus provoked-only	
Spontaneous pain $\pm$ provoked pain	36.6%
Provoked only pain	63.4%

* None had pain localized to clitoris only.

Table 3

Comparisons of sensitivity of cases and controls to sensory testing at the thumb and vulva.*

		Cases (Median)	Controls (Median)	Hazard Ratio** (95% CI)	P value
Pressure					
Vulva	Posterior vestibule (grams)				
	Mild discomfort	22.0	230.0	7.56 (4.14, 13.81)	<0.001
	Moderately severe discomfort	22.0	356.0	7.41 (4.10, 13.40)	<0.001
Thumbnail	Random staircase (grams)				
	Faint discomfort	250	625	1.37 (0.86, 2.17)	0.181
	Mild discomfort	2500	4250	1.97 (1.21, 3.19)	0.006
	Slightly intense discomfort	4500	6375	1.76 (1.05, 2.96)	0.033
Electrical (mA)					
Vulva	Threshold	0.487	0.682	2.74 (1.68, 4.48)	<0.001
	Moderate discomfort	0.491	0.714	2.89 (1.77, 4.70)	<0.001
	Intense discomfort	0.495	0.769	4.67 (2.21, 6.09)	<0.001
Hymen	Threshold	0.464	0.653	3.55 (2.13, 5.91)	<0.001
	Moderate discomfort	0.469	0.671	2.85 (1.78, 4.56)	<0.001
	Intense discomfort	0.472	0.758	3.81 (2.31, 6.29)	<0.001
Thumbnail	Mild discomfort	0.558	0.740	3.64 (2.19, 6.06)	<0.001
	Moderate discomfort	0.578	0.764	4.50 (2.62, 7.74)	<0.001
	Intense discomfort	0.617	0.772	2.63 (1.63, 4.24)	<0.001
Heat (degrees C)					
Vulva	Threshold	37.9	37.5	1.02 (0.65, 1.61)	0.923
	Moderately severe discomfort	41.2	42.9	1.66 (1.04, 2.66)	0.036
Hymen	Threshold	38.2	39.1	1.26 (0.80, 1.97)	0.316
Thumbnail	Threshold	34.7	34.4	0.97 (0.63, 1.51)	0.904
	Moderately severe discomfort	48.8	44.7	1.57 (1.00, 2.47)	0.049
Cold (degrees C)					
Vulva	Threshold	27.7	27.3	1.07 (0.69, 1.65)	0.773
	Moderately severe discomfort	14.0	11.8	0.65 (0.41, 1.03)	0.064
Hymen	Threshold	26.8	26.1	0.78 (0.50, 1.21)	0.264
Thumbnail	Threshold	28.8	28.8	1.24 (0.79, 1.95)	0.341
	Moderately severe discomfort	10.0	8.0	1.15 (0.69, 1.90)	0.592
Vibration (microns)					
Vulva	Threshold	0.61	0.85	1.16 (0.75, 1.81)	0.506
Hymen	Threshold	0.56	0.74	1.42 (0.91, 2.21)	0.118
Thumbnail	Threshold	0.44	0.46	1.20 (0.78, 1.85)	0.419

Bold = p value <0.025.

* Cox regression, controlled for age and censoring.

** Referent group = control women.

Table 4

Previously proposed subgroups and their relationship to pain characteristics and to psychophysical findings.^{*}

	Controls		Primary or secondary vulvodynia		Generalized or localized location		Spontaneous or provoked-only pain						
	Primary	Secondary [^]	Generalized [^]		Localized [^]		Spontaneous	Provoked-only pain [^]					
			Median	P value	Median	Hazard rate (95% CI)			Median	Hazard rate (95% CI)	P value		
Psychophysical characteristics													
Pressure sensitivity (grams)													
Pressure to vulva													
Mild discomfort	230.0	22.0	22.0	0.94 (0.49, 1.84)	0.866	22.0	39.5	1.43 (0.73, 2.79)	0.300	57.2	22.0	1.50 (0.74, 3.02)	0.263
Moderately severe discomfort	356.0	250.0	22.0	0.87 (0.45, 1.71)	0.694	22.0	39.5	1.26 (0.66, 2.44)	0.484	57.2	22.0	1.64 (0.81, 3.34)	0.171
Pressure to thumb (Random staircase in grams)													
Faint discomfort	625	250	250	0.92 (0.46, 1.86)	0.818	250	250	1.13 (0.57, 2.27)	0.722	250	375	2.01 (0.92, 4.40)	0.079
Mild discomfort	4250	2438	3125	3.34 (1.45, 7.65)	0.004	2125	2615	1.56 (0.81, 3.03)	0.184	1850	2690	2.41 (1.15, 5.05)	0.020
Slightly intense discomfort	6375	4375	6000	2.63 (1.19, 5.82)	0.017	4375	4625	1.63 (0.81, 3.28)	0.168	3875	4625	1.62 (0.77, 3.41)	0.202
Electrical Sensitivity (mA)													
Electricity to vulva													
Mild discomfort	0.682	0.477	0.582	1.63 (0.80, 3.34)	0.180	0.465	0.581	1.15 (0.59, 2.23)	0.681	0.445	0.596	2.50 (1.16, 5.37)	0.019
Moderate discomfort	0.714	0.482	0.588	1.28 (0.65, 2.52)	0.482	0.471	0.589	1.30 (0.67, 2.52)	0.435	0.450	0.608	2.70 (1.26, 5.79)	0.011
Intense discomfort	0.769	0.487	0.580	1.25 (0.63, 2.47)	0.562	0.477	0.594	1.30 (0.67, 2.53)	0.432	0.461	0.617	2.46 (1.18, 5.15)	0.017
Electricity to hymen													
Mild discomfort	0.653	.0456	0.488	1.15 (0.55, 2.39)	0.713	0.452	0.499	1.40 (0.73, 2.68)	0.314	0.374	0.551	2.40 (1.14, 5.02)	0.021
Moderate discomfort	0.671	0.464	0.490	1.04 (0.51, 2.11)	0.923	0.459	0.507	1.45 (0.75, 2.80)	0.266	0.441	0.559	2.49 (1.19, 5.23)	0.016
Intense discomfort	0.758	0.467	0.490	1.04 (0.51, 2.12)	0.908	0.462	0.516	1.41 (0.73, 2.73)	0.301	0.446	0.563	2.42 (1.15, 5.08)	0.020
Electricity to thumb													
Mild discomfort	0.740	0.577	0.564	1.08 (0.53, 2.18)	0.839	0.612	0.558	0.97 (0.50, 1.88)	0.929	0.466	0.568	1.46 (0.73, 2.94)	0.287
Moderate discomfort	0.764	0.602	0.578	1.07 (0.53, 2.17)	0.848	0.642	0.573	0.93 (0.48, 1.81)	0.839	0.564	0.590	1.16 (0.58, 2.29)	0.679
Intense discomfort	0.772	0.600	0.580	0.80 (0.40, 1.59)	0.526	0.648	0.607	1.19 (0.62, 2.31)	0.598	0.576	0.641	0.92 (0.47, 1.80)	0.801

Bold = p<0.025.

^{*} Cox regression with censoring, controlled for age.

[^] Referent category.