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Genetic Predisposition to Provoked Vestibulodynia

By Terry K. Morgan, M.D., Ph.D.

Terry Morgan, M.D., Ph.D., associate professor of pathology and obstetrics and gynecology at Oregon Health and Science University, received his Ph.D. in human genetics. His group's recent genetic studies of provoked vestibulodynia may lead to new insights into its causes.

Although research is ongoing, the underlying causes of provoked vestibulodynia (PVD) have not been identified. Our group and others have suggested PVD may run in families and shared genetic variants may increase a woman's risk of developing PVD when triggered by infection, allergy, autoimmune disease, etc. There are now four separate lines of evidence to suggest PVD may have a genetic predisposition. First, one in five women with PVD also has interstitial cystitis, which a number of good studies suggest is a genetic condition. Second, seasonal allergies are known to have a genetic predisposition and women with

PVD are two times more likely to have seasonal allergies than controls. Third, screening for specific "candidate genes" involved in inflammation and hormonal regulation suggests that some women with PVD share uncommon genetic variants that may make them more susceptible to environmental triggers. Finally, our group published the first familial pedigree study to test whether PVD runs in families. We restricted analysis to severe cases treated by vestibulectomy, because studying extreme phenotypes is an approach that yields results.

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Remission, Relapse, and Persistence in Vulvodynia

By Barbara D. Reed, M.D., M.S.P.H.

Barbara D. Reed, M.D., M.S.P.H., is a professor in family medicine at the University of Michigan Medical School and has been active in vulvodynia research for the past 17 years.

This article summarizes the key findings of our longitudinal vulvodynia study recently published in the Journal of Women's Health. (See cite in reference section.)

Those of us in clinical medicine often see women who have had symptoms of vulvodynia for years – and even decades. Similarly, women enrolling in studies on vulvar pain also report various durations of symptoms, but years of symptoms and first onset long ago is quite common. Hence, vulvodynia has been considered a chronic

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Genetics and Environment

We have to be careful when we say a disease runs in families. Infections run through families. Environmental risk factors run through families. Word of mouth referrals about doctors who can accurately diagnose PVD may run in families. To prove nature versus nurture, geneticists take a number of approaches. Typically, the first approach is to test for associations between the disease of interest and candidate genes that appeal to our selection bias for the most likely potential mechanisms. For example, if we think PVD is caused by an abnormally robust inflammatory response to vaginal infection, we may test for associations between genetic variants of inflammatory signals and the presence of disease. Candidate gene association studies are especially useful when studying common disorders like asthma, autoimmune diseases and PVD. It is generally accepted that these types of disease processes are multifactorial with both environmental triggers and a genetic predisposition. There are often numerous genetic variants that contribute to the genetic risk and these “major genes” may be different in different families.

Indeed, it is very unlikely that PVD is caused by a single genetic variant. Instead, like most common multifactorial diseases, more than one PVD susceptibility gene will likely be involved. They will likely increase a woman’s risk by *lowering the threshold* for triggering the cascade of events culminating in the clinical symptoms of PVD. In our view, a simple examination of a family tree for recessive or dominant inheritance (pedigree analysis) will likely fail. Recessive genetic diseases are usually very rare and when they show up in a family, they occur in 25 percent of children. In contrast, dominant genetic diseases are more common and affect 50 percent of the children --depending on the “penetrance,” a term used to describe the percentage of people who both carry the gene and develop the disease in their lifetime. We think PVD is multifactorial, involving multiple genes and environmental triggers, so a more complex approach to finding PVD genes is needed.

Finding Genes

Because common diseases are prevalent in the population, familial analysis of a disease process like PVD is very challenging. Multiple family members may be affected simply by chance. Proof of familial inheritance depends on showing that the rate of PVD is greater in the mothers, sisters, daughters, and/or granddaughters of affected patients, without an increased rate in the female in-laws of these affected women. Twin concordance studies also provide evidence for or against genetic risk. This is done by comparing the frequency of disease in identical twins with fraternal twins—they share the same environments, but identical twins share 100 percent of each other’s

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genes, while fraternal twins share 50 percent. Of course, the best proof of genetic risk is to find genetic variants known to affect a gene's function that are shared by related women with PVD, but not their unaffected female siblings. So far, only candidate gene association studies and one familial analysis of PVD-affected women treated by vestibulectomy have been done. No twin studies have been done and no PVD gene(s) have been identified by unbiased familial linkage studies.

Since PVD is unlikely to show simple recessive or dominant inheritance, the approach we took was to compare the frequency of PVD treated by vestibulectomy in the first-, second-, third-degree, out to distantly related female relatives documented within large Utah Mormon families as part of their genealogy incorporated into the Utah Population Database (UPDB). This database is a powerful genetic resource. It contains computerized genealogic data from the Mormon Utah pioneers and their descendants (from the mid 1800s to the present), which has been linked to diagnoses and procedural outcomes of patients treated at the University of Utah Health Sciences Center since 1994. The genealogy includes over eight million unique individual records; 1.3 million of these individuals have at least three generations of genealogy data. Inclusion criteria for familial clustering analyses requires all subjects (cases and matched population controls) to have genealogy information available for at least 12 of 14 of their immediate ancestors (i.e., parents, all grandparents, and at least 6 of 8 great-grandparents). These inclusion criteria have been determined to provide sufficient sensitivity to reasonably detect affected first-, second-, and third-degree relatives. Of course, all data is coded without patient identifiers and strictly regulated by multiple agencies, including the Institutional Review Board of the University of Utah.

Once evidence for a genetic contribution to disease risk is determined, affected individuals may be compared with unaffected family members to find candidate genes that are then validated in separate kindred families. The more distantly related an affected pair of

PVD patients, the more likely the genetic variants they share may be the genes that cause the disease. (See Figure, p. 4.)

Genetic Variation

Let us be clear about what we mean when we talk about genetic variation. In brief, one may think of the genome as a book that is copied each generation. The book is never copied exactly and the misprints within a gene may be considered minor genetic variants (uncommon genetic differences within a given gene). If there is positive selective pressure for the minor variant, it may become a more common genetic variant in a population. With each generation, chapters in the book are exchanged between those contributed by the mother and those contributed by the father. After many generations, or if relatives within a generation, e.g., millennials, are distantly related, we would expect that very few minor genetic variants would be preserved between distantly related women with PVD.

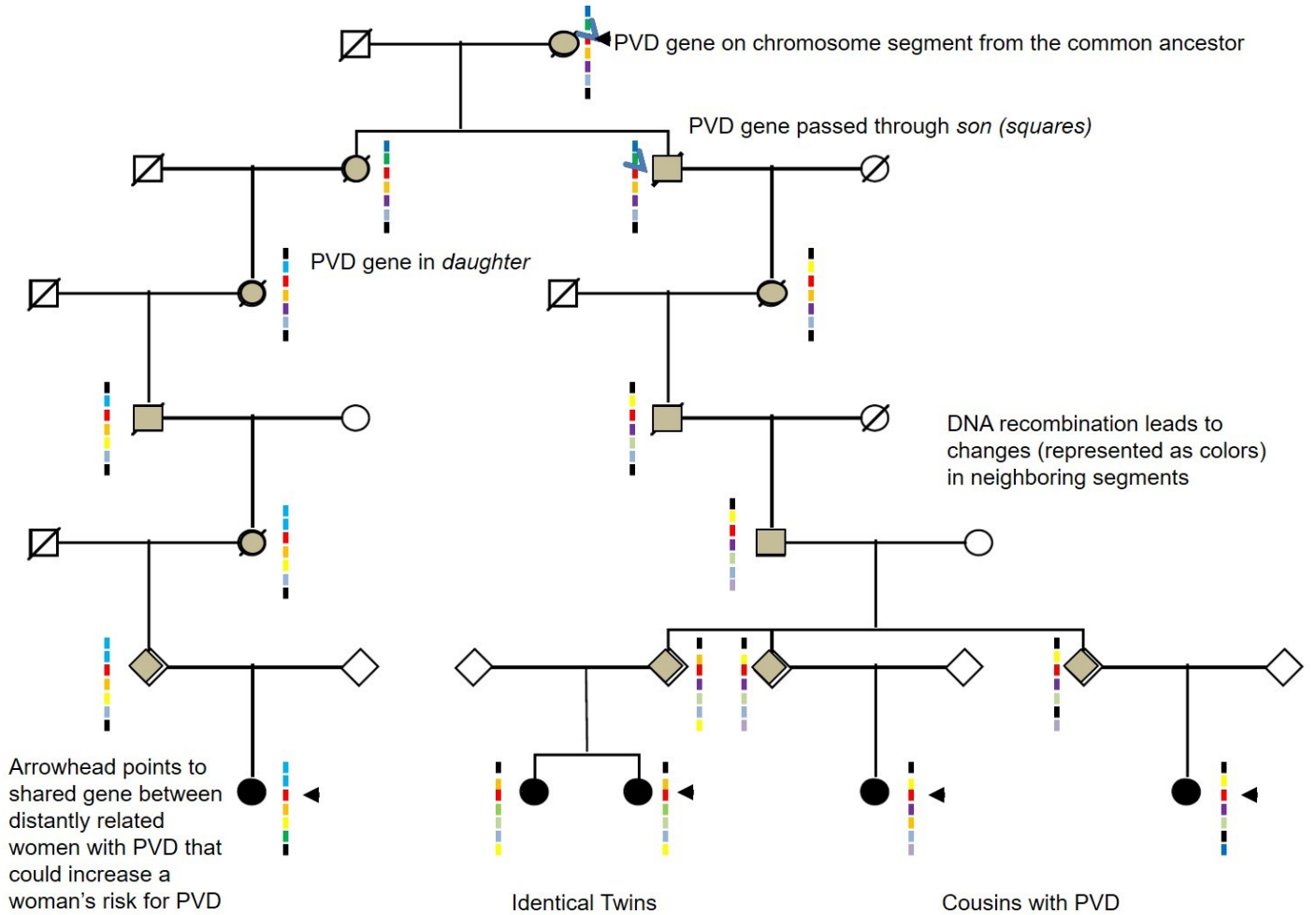
Race and genetic variation is an outdated political concept, but knowing the patient's race is important for this type of minor genetic variant analysis. Numerous whole genome studies have now shown extensive sharing and mixing of genes between individuals that may appear more or less "white" or "black" or other. However, there remain clear differences in genetic variant frequencies between races within population studies and this potential covariate should always be included in genetic analysis. For example the minor gene frequency of a genetic variant like Interleukin-4, associated with hypersensitive reactions like painful bladder, is very different in a Northern European white population than in an African-American population. If PVD is more common in one race compared with the other, we may be fooled by studying a minor gene that is also more common in one race.

The Need for Detailed Clinical Diagnosis

Ultimately, how specifically we describe the clinical features of a disease (the phenotype) will affect the

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Vestibulodynia Family Tree



Legend	
Square = Male	Diagonal line = Deceased
Circle = Female	Gray = May carry PVD gene
Diamond = Unknown sex	Black circle = Female diagnosed with PVD

Figure: Large Utah family with five affected women treated by vestibulectomy (black circles) linked to each other through the Utah Population Database. This large pedigree identified a common ancestor (top of figure) who may have transmitted PVD-related candidate gene(s) to these two branches of her family. The right side of the pedigree reveals a branch of the family with four cousins with PVD treated by vestibulectomy, including one pair of identical twins.

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ability of geneticists to find the genes that contribute to that clinical diagnosis. The more precise and extreme the phenotype, the more likely we are to find susceptibility genes. We have made progress defining vestibulodynia, but further progress in this field may begin with a clear distinction between primary and secondary PVD and assessment of the severity of disease. Primary PVD, vestibular pain since the first attempt of penetration, appears to begin earlier in life. Most of these women have had symptoms for years before accurate clinical diagnosis. Secondary PVD, pain that starts after a period of pain-free penetration, usually presents later in life, e.g., postpartum or postmenopausal. The underlying pathophysiology of the disease process is very likely different in these two PVD diagnostic classifications. Genetic studies should take this into account. In addition, we think this phenotypic distinction may be magnified in women whose pain is recalcitrant to conservative therapies and undergo a vestibulectomy. Using the more severe cases optimizes our studies and helps us find the most likely genetic risk factors.

Our group and others have shown that the vestibular tissue from women with primary PVD looks very different from that of women with secondary PVD, especially if the latter samples are from postmenopausal women. A lot more work needs to be done, including a better characterization of “normal” vestibular tissue and vestibular biopsies from women who respond to medical interventions. Our data suggest that the pain of PVD is related to an abnormal triggering of chronic inflammation and increased nerve growth in this tissue. To a pathologist, PVD vestibular biopsies look a lot like those from women with interstitial cystitis (painful bladder)—another common disease process often associated with PVD. Both the vulvar vestibule and bladder wall arise from the same embryonic tissue and both diseases show marked neurogenic (nerve-related) inflammation. This could be important to our efforts to find PVD risk genes. Perhaps these two common diseases share genetic risk factors and pathogenic triggers? Interstitial cystitis has been shown to have a

genetic risk by twin studies and to be familial by the UPDB. Association studies of interstitial cystitis have revealed promising candidate genes involved in immune regulation, but like PVD, no unbiased linkage analysis has been done to identify shared genetic variants between distantly related affected women.

PVD is Familial

We recently reported on dozens of separate Utah families with statistically more frequent PVD than what is observed in the general Utah population. Overall, the familial association was statistically significant out past third-degree relatives, who were very unlikely to share common environments or share clinical information. Female population controls were randomly selected from Utah patients that were matched to PVD cases based on sex, birth place (urban/rural based on Utah birth county residence), and birth year (5 year birth cohorts), similar to other publications using the UPDB to test for familiarity of various diseases. We estimated the risk of PVD in the female relatives of our affected patients as the number of confirmed PVD cases in these relatives divided by the expected frequency of PVD in the overall Utah female population. We could do this for each degree of relatedness: first-degree, second-, third-, on so on. Since first- and second-degree relatives likely share environments and word of mouth clinical referrals (sampling bias), the strongest data in support of familial genetic risk is relatedness of affected PVD patients out past cousins and aunts in the affected woman’s family. We also tested for a number of potentially comorbid conditions, including interstitial cystitis, fibromyalgia, autoimmune diseases, and asthma.

Our study was the first familial-based population study of PVD, but it will not be the last. Employing high-risk Utah pedigrees for linkage analysis and genomic sequencing of distantly related affected women will finally enable us to elucidate the genetic pathways

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Tips for Recovering from a Vestibulectomy

The most common surgical procedure for women with PVD is a vestibulectomy with vaginal advancement, which involves the removal of a portion (or all) of the vestibule, including the hymen, and then covering the excised area with vaginal tissue. Some doctors perform a modified vestibulectomy, in which only the superficial painful tissue is removed and there is no vaginal advancement. Most published results are based on vestibulectomy with vaginal advancement. Overall success rates for both procedures range from 60 to 93 percent. After surgery, physical therapy and the use of dilators is often recommended to help eliminate remaining pelvic floor muscle dysfunction.

A young woman who had a vestibulectomy last year thought that other women facing surgery could benefit from her experience, so she provided the suggestions below.

Before Surgery

Preparation is very important. Since it will be difficult to bend down for a few weeks, move everything you will need from lower shelves and drawers to a higher location. In addition, if your bed is far from the bathroom, consider if it's possible to rearrange your furniture to reduce the distance you have to walk. You will need towels to lay on in bed to catch the blood for the first few days. Try disposable medical towels, training pads from a pet store, or old cloth towels. You may also want to use a waterproof mattress pad.

During the first week after surgery you'll need to use a lot of ice. Prepare ice cubes double bagged in zip lock bags or fill non-lubricated condoms with water and put them in the freezer. If you don't have a bathtub at home, arrange to stay in a place that has one. You will need to take frequent baths, which are very soothing.

It is helpful to install a shower head on a flexible cord/line that dismounts and can be hand-held. That way, you can pee standing up in the shower and use the removable shower head to wash with warm water.

Another option is to crouch over the toilet, but hold your weight up with your hands so you're not fully sitting. It is important to drink enough water and eat well to avoid constipation. You will need a laxative, e.g., Miralax, to keep your stool soft, since you won't be able to bear down for weeks. A couple of enemas should be kept on hand just in case.

Make sure you have clothing that will be comfortable, such as long skirts, house dresses, or baggy pants to wear for the first few weeks. Surgical underwear is comfortable and easy to wash. This type of underwear collects excess blood and covers your skin while applying ice. Order a few pairs online prior to surgery.

Since you will be home-based for awhile, be sure to have some fun things to read and watch on television. An over-the-bed table on wheels that tilts is great for eating or working on a laptop in bed and a donut pillow makes it more comfortable to sit after your initial recovery. The pillow can be wrapped in a scarf and carried in a tote bag to use outside your home.

You will need support full-time for the first two weeks after surgery. Arrange for a parent, friend, partner or home health aide to stay with you or schedule a mix of people. Finally, make a chart to schedule and track your pain medication.

Recovery

After some healing has occurred, it is very important to use dilators. Although you start with the smallest one, it will hurt at first. Don't get discouraged! Keep doing your physical therapy exercises and inserting the dilators will become easier. It may help to use the dilator while taking a bath and/or warming it in a jar of hot water first. (Make sure it's not too hot.)

Having the surgery was difficult, but not as painful as I had feared. It may take six to 12 months until you can comfortably have sex after surgery, but in my experience, it was worth the wait! ■

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condition, and until recently, it was thought that once vulvodynia developed it would persist. However, a small number of recent longitudinal studies have demonstrated that, in follow-up, a substantial proportion of women with vulvodynia report no current vulvar symptoms, and at times even deny past symptoms, suggesting remission is occurring, and may be under-reported based on retrospective recall alone.

In the University of Michigan Woman to Woman Study, a longitudinal, population-based study of women living in southeast Michigan, we assessed the frequency of persistence, remission, and relapse, and risk factors associated with these clinical trajectories, using recurring surveys over a 36-month period. Results of that study were recently published and demonstrated that both remission and relapse are quite common among women meeting criteria for vulvodynia, and that those with persistent symptoms are the minority of women with this disorder.

Method

Methods for enrollment in the Woman to Woman Health Study have been published previously. We enrolled women ages 18 years and older living in a four-county area in southeast Michigan using random digit dialing. Participants completed a short interview, and were then sent a 26-page survey, which included previously validated screens for vulvodynia, fibromyalgia, interstitial cystitis, irritable bowel disorder, depression, and PTSD, as well as questions about demographic characteristics, health history, exposures, current symptoms, and other potential risk factors. Additional follow-up surveys were sent every six months and the first 36 months of follow-up were included in the report.

Since the possibility of relapse increases over time, only the data for those with at least four surveys after a positive vulvodynia screen were presented for remission and relapse rates and factors associated with outcomes. This provided a consistent yet maximum follow-up period for each included participant.

The vulvodynia screen used was verified previously and included the current presence of pain at the opening to the vagina, with or without provocation, that had been present for at least three months and had not resolved. Remission was defined as a subsequent negative screen (no longer meeting criteria for vulvodynia) following a positive screen. Relapse was defined as again screening positive for vulvodynia following such a remission. Persistence was defined as continuing to have positive vulvodynia screens at every follow-up after the initial positive screen.

Rates for remission and relapse were calculated using Poisson regression analysis (calculated from the time of the initial positive vulvodynia screen for remission rates, and from time of first remission for relapse rates). The relationship between clinical outcome and whether the participant was currently taking medication for either pain or depression was also analyzed. Additionally, the association between potential risk factors and the categories of remission without relapse, relapse, and persistence were assessed, with potential risk factors measured at the time of a first positive vulvodynia screen.

Results

Of the 2542 women enrolled in the Woman to Woman Health Study, 2193 completed the baseline survey and all questions on the vulvodynia screen. Of these, 441 screened positive for vulvodynia either at baseline or on one of the subsequent five follow-up surveys. Most women with vulvodynia completed all surveys. Of the 441 women screening positive, 239 (54.2%) completed four surveys after their first positive vulvodynia screen, and were included in the analyses.

Remission, Relapse, and Persistence Prevalence

The proportion of women demonstrating a remission without relapse, a relapse, or persistence of a positive screen varied depending on how many follow-up

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surveys were completed or considered in the analysis. The remission rate was substantial within two surveys of the initial positive survey (67%), but over time more than half of women reporting remission had a relapse. This confirmed the importance of ongoing follow-up in assessing the clinical trajectories, and the importance of limiting the analyses to those completing four surveys over time after the first positive screen. Among the 239 women meeting these criteria, over 50 percent had a remission without relapse, almost 40 percent had a remission with relapse documented, and 9.6 percent had vulvodynia symptoms that persisted during the entire study period. These clinical course outcomes didn't differ by demographic characteristics of the women, including age, ethnicity, or ability to pay for basics (food, shelter), although those with persistent symptoms were more likely to be married.

Rates of Remission and Relapse

Among the 239 women screening positive for vulvodynia and having four additional surveys in follow-up, the average time followed after a positive screen was 593.3 ± 62.2 days and over 90 percent had a remission during that time. Similar to previous studies reporting remission rates, we found some women who initially screened positive for vulvodynia (reporting many details of pain characteristics, severity, duration, etc.) and subsequently screened negative for vulvodynia (remission), who reported no recall of vulvar pain in the past. Of the 103 women with a remission (with or without relapse) at or after the 12-month survey (at which time the question about past pain was again asked), 38 percent reported no history of vulvar pain, despite previously screening positive in the study.

Factors Associated with Vulvodynia Remission, Relapse, or Persistence

Women with remission, relapse, or persistence did not differ by self-health rating, rating of physical pain in general, or general pain interference as reported at the time of the first positive vulvodynia screen. Prognosis was, however, associated with a number of factors

regarding pain characteristics, severity, and duration, and with some comorbid conditions, but not with primary versus secondary onset. (See table p. 9.)

Association with Current Treatment and Outcome

Concurrent treatments are rarely reported in studies of vulvodynia. We determined from the surveys whether the participants were taking medication (analgesics or neurotransmitter-altering drugs) at the time of the first positive vulvodynia screen or at the time of first remission, since these could potentially alter vulvar pain. Clinical outcome was not associated with use of medications for pain or neurotransmitter-altering drugs. In addition, when asked whether they were on a treatment for the vulvar pain, only 12.5 percent reported taking medication for the pain at the time of their first positive screen. Reported treatments included estrogen (with or without progesterone) in 50 percent, antifungals in about 13 percent, topical steroids in 20 percent, topical cream or moisturizer in 23 percent, and miscellaneous treatments in 13 percent. No one reported taking antidepressants, anticonvulsants, or pain medication for their vulvar pain.

Summary of Main Findings

In one of the first longitudinal population-based studies to prospectively determine probabilities of remission, relapse, and persistence among women screening positive for vulvodynia, we found the probability of remission was quite high, but that approximately 50 percent of those whose symptoms resolved had a relapse of symptoms within a short period of time. With even longer follow-up, relapse rates may be greater than those demonstrated in this study. Persistence of symptoms at every screening was only present in less than 10 percent of those with a positive survey who were followed for at least four additional surveys.

Interpretation

Although vulvodynia has traditionally been considered a chronic disorder, with little recognition of remissions

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or relapse, the literature has been supporting suggestions of remission for some time. Peckham (1986) was one of the first to report remission after a woman was diagnosed with vulvodynia; over 15 years, 50 percent of his 67 cases reported no further symptoms, with most remissions occurring in the first six months after diagnosis.

More recent studies assessing non-clinic-based populations suggest that a substantial proportion of women who report past vulvodynia deny ongoing symptoms. Cross-sectional surveys conducted online estimated that 16 to 28 percent of the populations had met survey-based criteria for vulvodynia at some point, but only 2 to 8 percent reported current symptoms,

suggesting remission may be common. Remission rates of more than 30 percent have been reported by others. These rates may have been underestimated by study designs that excluded women who later denied having past symptoms or that included only women with current symptoms, thereby excluding those who remitted and did not relapse. Improvement over time has also been demonstrated even without treatment, again demonstrating remission is not rare.

We again found inconsistent reporting of the history of vulvar symptoms. Previously, in one of the first prospective assessments of vulvodynia remission, our group reported a 22 percent remission rate over two

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Table. Risk factors for various clinical courses (remission, relapse, and persistence) after screening positive for vulvodynia (age-adjusted) (N=239). Arrows indicate decreased ↓ or increased ↑ odds ratio ($p \leq 0.05$), or no association × ($p > 0.05$).

	Remission only	Relapse after remission	Persistence	No association with clinical course
Provokable pain only	↓	↑		
Spontaneous pain as well				×
Pain with intercourse		↑	↑	
Pain after intercourse		↑	↑	
Pain with oral sex or with partner touch			↑	
Pain with masturbation or having an orgasm				×
More severe rating of “worst pain ever”		↑	↑	
Longer reported duration of pain		↑	↑	
Age at onset of pain				×
Primary versus secondary onset				×
Pain quality (sharp, stabbing, burning, or itching)				×
Presence of Fibromyalgia or Interstitial Cystitis by screen			↑	
Presence of IBS on screen				×
Depression by screen			↑	
PTSD by screen				×

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years among women identified from a Women's Health Registry, 60 percent of whom denied previous symptoms despite having screened positive two years previously. Similarly, in a nationwide population-based study, Sutton and colleagues found that over 51 percent of women meeting criteria for vulvodynia at their baseline survey denied having had these symptoms a year later. In the current study, women with symptoms that resolved were included in the remission statistics even when they reported no previous symptoms, while Sutton excluded these women from their analysis, explaining their lower remission rate of about 31 percent.

We found that the type of treatment being used was not associated with remission or relapse. Interestingly, very few women were taking any medication for their vulvar pain. No one reported using antidepressants or anticonvulsants, medications often used for neuropathic pain. The most common treatment was estrogen, with or without progesterone.

Risk Factors for Remission or Relapse

Little has been written about factors associated with remission of symptoms. The study reported here indicated a number of factors associated with vulvodynia outcome, including the presence of provoked pain, more severe pain with or after intercourse, pain with oral sex or partner touch, higher rating of worse pain ever, longer duration of pain, or screening positive for fibromyalgia, interstitial cystitis or depression. Some of these factors have been suggested in prior studies, and others diverge from previous reports. In our earlier study of women participating in a health registry, we assessed risk factors associated with remission and found that increased severity of past vulvar pain, longer duration of symptoms, and presence of pain after intercourse were associated with less improvement over time, consistent with the current study. Nguyen assessed reports by participants with vulvodynia in a community-based study about recollection of previous periods of no vulvar pain and found that

those with primary vulvodynia were less likely to report a remission than those with secondary vulvodynia. We proposed two reasons these results might vary. Based on the study design, the results of Nguyen reflect remissions reported by women who have subsequently undergone a relapse, thereby not including characteristics of those who had a remission without relapse. In addition, to fulfill their definition of primary vulvodynia the woman agreed that she "always had pain on contact," thereby excluding those who may have had remissions, a bias that might exist in that study. Further study of factors associated with the clinical trajectory are clearly needed, and may further indicate differences among these women that may impact treatment response, and/or probability of spontaneous resolution.

Conclusion

In summary, this longitudinal, population-based study indicated that remission of symptoms following vulvodynia diagnosis by a survey-based screening test is common, but approximately half of those with remission then undergo a relapse within a short period of time. Consistent reporting of vulvodynia symptoms (persistence) only occurs in the minority of those screening positive. Factors associated with outcome include several characteristics of the pain, its duration, and associated comorbid conditions, but not demographic characteristics.

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involved in PVD susceptibility. This approach is important because, unlike genetic studies that start with an assumption that a specific gene is the cause of PVD (candidate gene association study), we can sequence *all of the genes* in distantly related pairs of women with PVD and use vigorous statistical analysis to determine which specific genetic variants are shared by affected patients. The more families we sequence, the shorter the genomic region of interest and the more likely the genes in that region play a role in PVD. The candidate genes will then be validated against multicenter PVD databases from Oregon, Utah, and any other well-described cohorts from around the world. Finally, one can imagine animal models that will (i) introduce the genetic risk and test for PVD phenotype, and (ii) block the genetic risk and test for improvement of the PVD phenotype.

Conclusion

Whole genome sequencing is costly and a lot of sequencing data is needed to complete this important work. However, the weight of the evidence now suggests it is worth it. And if we are successful, this approach will provide new tools to help clinicians make early diagnoses before the tissue has been irreversibly remodeled and lead to more effective targeted-based therapies to stop disease progression once triggered.

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Letter to the Editor

Dear Editor,

I have just finished reading the treatment article by Andrew Goldstein and colleagues in your Fall 2016 newsletter.

I'm concerned that the authors recommend Capsaicin and Botox as possible treatments for provoked vestibulodynia, but specifically do not recommend tricyclic antidepressants. I don't think you can make such a strong statement based on the two tricyclic studies presented. Dr. Foster's randomized controlled trial found that desipramine was no more effective than a placebo, but one cannot then assume amitriptyline and nortriptyline are also ineffective. Dr. Brown's study on amitriptyline used low doses that seldom work in clinical practice.

In short, I don't think a blanket statement that tricyclic antidepressants are not recommended is supported by the full literature. My concern is that it does a disservice to women with vulvodynia by removing an option commonly used in clinical practice.

Thank you for considering my comments.

Sincerely yours,
Paul Nyirjesy, M.D.
Professor of Obstetrics and Gynecology
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Select References

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(Editor's note: To obtain the footnoted version of this article, with a full set of references, please contact Gigi Brecheen at gigi@nva.org or 301-949-5114.)■

Important Update

We are making some changes in 2017 so we can continue to serve both patient and professional members. In April, our past executive director and current President, Phyllis Mate, will return to the position of volunteer executive director.

After the spring 2017 newsletter issue, we will switch to sending all information digitally. Instead of a formatted newsletter three times per year, we will email individual major articles every 3 months, in addition to shorter articles and important news several times a year. You will be able to print everything we send.

It is very important that we have your current email address. If you do not have an email address, please contact Gigi Brecheen at 301-949-5114. She will send you photocopies of future articles.