National Vulvodynia Association

NVA News

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Why Oral Contraceptive Pills Can Cause Vulvodynia

By Andrew Goldstein, MD, Jill Krapf, MD, Zoe Belkin

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The debate about the role of oral contraceptive pills (OCPs) in vulvodynia has been underway for almost two decades. More than a dozen different research articles have been written on the topic, both supporting and refuting the association. In this article we will examine this important issue. We will begin our discussion by describing basic anatomy of the vulva, how OCPs work, and the potential mechanisms by which hormonal contraceptive might cause vulvodynia. This foundation will allow us to review the studies previously published on this topic. Finally, we will look at the results of our new genetic study, which provides overwhelming evidence for the impact of OCPs on vulvodynia.

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Superficial Pelvic Floor Muscles and Vulvar Pain

By Dr. Pamela Morrison Wiles, PT, MS, DPT, BCB-PMD, IMTC

Dr. Pamela Morrison Wiles has a private physical therapy practice in New York City specializing in women's and men's pelvic health. She is cited as an expert in pelvic floor muscle dysfunction by the American Physical Therapy Association, and has presented research on physical therapy for clitoral and vulvar pain at international conferences. Dr. Morrison Wiles was inducted as a Fellow into the International Society for the Study of Vulvovaginal Diseases in 2007 and is an Executive Board Member of the NVA.

Pelvic floor muscle (PFM) dysfunction, which usually includes pain and overactivity of the deep PFMs, has been confirmed as an adjunctive diagnosis with vulvar pain syndromes, including vulvodynia, vestibulodynia, and clitorodynia.[1, 2] Anatomically the deep PFMs refer to the levator ani, which is comprised of the pubococcygeus, iliococcygeus, and puborectalis muscles. Some authors and anatomists also consider the coccygeus muscle to be a part of the levator ani complex. Collectively, these deep PFMs form the pelvic diaphragm. The levator ani muscles are innervated by two nerves, the pudendal and the levator ani nerve. The pubococcygeus muscle is innervated by the levator ani nerve S3-5 and the perineal branch of the pudendal nerve

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The vulva and vagina can be thought of as three separate and distinct organs due to their embryological (prenatal) development. Very early after conception the cells divide into three tissue types: ectoderm, endoderm, and mesoderm. The ectoderm forms the tissue of the outer vulva, which includes the labia majora, the interlabial sulcus, the outer labia minora, the hood of the clitoris, the clitoris, and the perineum. The vulvar vestibule, which starts at Hart's line on the inner aspect of the labia minora and extends to just inside the hymen, is derived from the endoderm. The vagina is mostly comprised from tissue coming from cells of mesodermal origin. Because these tissues are derived from three different origins, it is logical that they would respond differently to varying hormonal states (such as too much, too little, or an imbalance in hormones) and to specific insults such as infections, allergic reactions, chemical irritation, and trauma. A recent study presented by our group at the International Society for the Study of Women's Sexual Health Annual Meeting showed that more than 90 percent of women with vulvodynia have pain confined to the tissue of the vulvar vestibule, and not the outside vestibule or inside the vagina. The historical name for this pain, vulvar vestibulitis, has been recently discarded, as we now understand that there are several causes of this localized pain, and most of them are not due to inflammation, i.e. an "itis." The new name "vestibulodynia" is a more inclusive term, literally meaning any abnormal pain sensation confined to the vestibule. The new name, however, still does not address the issue of the cause/causes of the pain.

With the understanding that the vestibule is comprised of tissue distinct from that of the outer vulva and the vagina, we can now ask how this difference affects its function. The tissue of the vestibule contains openings of several glands: the Skene's glands, the Bartholin's glands, and the minor vestibular glands. These glands, when stimulated by hormones, make mucin, an extremely slippery substance that acts as the primary lubricant during intercourse, giving women the sensation of feeling "wet" during arousal. When most people think of the hormone that is most necessary for vulvar or vaginal health, they think of estrogen. Interestingly, these glands don't rely on estrogen, or progesterone, but instead depend on testosterone and other similar hormones that we collectively call "androgens." These androgens act on a hormone receptor called the "androgen receptor" in the cells of these glands to cause the production of mucin. To visualize this, you may think of the androgens as a key that fits into a lock (androgen receptors) which open factory doors to allow the machines (the glands) to make mucin. Unfortunately, this system may malfunction in several ways. First, you can imagine that if there are not enough keys - low levels of androgens - then the locks cannot open and the factory will not work. Secondly, if the locks are rusty or sticky - a poorly functioning androgen receptor - then the doors of the factories will not open and the machines will not work.

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The National Vulvodynia Association is a nonprofit organization that strives to improve women's lives through education, support advocacy and research funding.

The NVA is not a medical authority and strongly recommends that you consult your own health care provider regarding any course of treatment or medication.

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Use of OCPs can cause both low androgens and "sticky" androgen receptors. Additionally, some women genetically have "stickier" or "inefficient" androgen receptors which make them even more susceptible to the negative effects of OCPs.

So now that we know that the glands (and the rest of the mucosa of the vestibule) are dependent on androgens and working androgen receptors to function properly, we will now discuss how OCPs work and how they can "throw a wrench" into the mucin factory.

Almost all OCPs currently being used contain a combination of two synthetic hormones, a synthetic estrogen and synthetic progesterone (a progestin). All pills contain the same synthetic estrogen, Ethinyl Estradiol (EE). The primary way in which the dozens of brands of OCPs differ is that they contain varying types of progestins and variable amounts of EE. The OCPs that have come to market in the last 15 years typically contain a "3rd generation" progestin such as desogestrol, norgestimate, and drosperinone. In fact, OCPs containing drosperinone became so popular after the turn of the century that they comprised more than 40 percent of all OCPs prescribed in the United States. In addition, there has been a trend toward lower doses of EE. While any pill that contains 35 micrograms of EE is considered a low dose OCP, recent pills contain as little as 10 micrograms of EE. While this may seem like a good idea, it should be noted that OCPs with lower doses of EE and the progestin drosperinone significantly increase the risk of developing vestibulodynia. Before we discuss how that happens, we will finish the description of how OCPs work.

Oral contraceptive pills prevent the pituitary gland from producing normal levels of two important hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). As a result, ovulation is inhibited and pregnancy is prevented. The inhibition of LH and FSH also causes a very significant reduction in the ovarian production of estrogen, progesterone, and androgens. In addition, the synthetic hormones in OCPs that are metabolized in the liver induce the liver to increase production of a protein called Sex Hormone Binding Globulin (SHBG). This substance binds to sex hormones, preferentially to androgens, rendering them inactive. The progestins, drosperinone and etonogestrel (which is in the vaginal contraceptive ring, NuvaRing), are especially effective at raising SHBG levels. The combined effect of decreased ovarian production of androgen from the ovary and increased production of SHBG results in a reduction of greater than 75 percent of "bioavailable" or "free" androgens. In our key, lock, and factory analogy, this means that OCPs reduce the number of keys by at least 75 percent. The drosperinone also binds to the androgen receptor rendering it inactive or "sticky."

While we discussed earlier that low androgen levels or a "sticky" androgen receptor could theoretically cause problems in the vulvar vestibule, we have already demonstrated these results in medical research. A recent study by Battaglia showed that women who took the OCP Yasmin had shrinkage of their labia minora, a reduction in the diameter of the vulvar vestibule, and a reduction in clitoral blood flow as measured by ultrasound after just three months of taking this OCP.[1] Another study by Johannesson showed that women on OCPs develop microscopic structural changes in the mucosa of the vulvar vestibule rendering them more susceptible to tears and fissures when exposed to trauma.[2] In addition, a study by Bohm-Starke showed that women without vulvodynia on OCPs sense pain in their vestibules at a much lower pressure i.e., have a lower pain threshold than women who do not take OCPs.[3]

So what about published studies looking at OCPs and vulvodynia? The results are contradictory. Let's look at the individual studies to examine why.

In a prospective study, Bazin showed that women who started taking OCPs before the age of 17 were 11 times more likely to develop vestibulodynia in comparison to women who had never taken OCPs.[4] In addition, a study by Bouchard in Quebec showed that women who were examined in a vulvar specialty clinic and found to have vestibulodynia were 9.6 times more likely to develop vestibulodynia if they started OCPs prior to the age of 16. They also showed an increasing risk of developing vestibulodynia with longer duration of OCP use.[5]

In addition, we recently published in The Journal of Sexual Medicine a case series of 50 consecutive wom-

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en who developed vestibulodynia while taking OCPs.[6] Women with other potential identifiable causes of vulvodynia, such as tight pelvic floor muscles or pudendal nerve injury were excluded from this study. The women were treated by having them stop OCPs and by applying a compound that contained topical estrogen and testosterone to the vestibule. On average their vestibular pain dropped from 7.5 to 2 on a ten-point pain scale after three months of treatment. Although this was not a placebo controlled study, the results are so compelling that it is our opinion that women who developed vestibulodynia while taking OCPs should consider this a first line treatment.

In contrast, a study recently published by Reed in the British Journal of Obstetrics and Gynecology concluded that "for women aged < 50, OCP use did not increase the risk of developing vulvodynia."[7] Unlike the three studies discussed above whose participants were all examined in vulvar specialty clinics and found to have pain localized to the vestibule, the women in the Reed study were identified as having vulvodynia from a questionnaire and were never physically examined. Furthermore, Reed acknowledges in the conclusion of her paper that, "further work is needed to assess these findings in a prospective study including subgroups that may differ in risk."

In addition, is it common practice, even among physicians, to consider all forms of OCPs as simply the "The Pill." As discussed earlier, however, OCPs are a vastly heterogeneous group of medications with different synthetic hormonal components in varying dosages. Also, in investigating the relationship between vulvodynia and OCP use, it is crucial to distinguish between pill types in order to not overlook important associations. While Reed did not differentiate between pill types in her study, Greenstein did differentiate and showed that women taking OCPs containing only 20 micrograms of EE were more likely to develop vestibulodynia than women taking OCPs with higher doses of EE.[8]

Given that the majority of studies discussed above have shown that OCPs increase the risk of developing vestibulodynia, our group wanted to determine why some women develop pain from OCPs while others do not. We hypothesized that women who genetically have inefficient androgen receptors would be more susceptible to developing vestibulodynia from the hormonal changes that occur by taking OCPs. As mentioned earlier, an inefficient androgen receptor ("sticky lock") won't work well if there are low levels of free androgens ("less keys"). The efficiency of an androgen receptor is determined by the length of the androgen receptor gene, which is located on the X chromosome. Women have two X chromosomes and have two androgen receptor genes, one from each parent, but men only have one from their mother. The longer the androgen receptor gene, the more inefficient the androgen receptor. In order to confirm this hypothesis, we looked at two groups: a study group and a control group. The study group consisted of 30 women who developed vestibulodynia while taking OCPs and had complete resolution of symptoms with cessation of OCPs and application of topical estradiol and testosterone to the vestibule. All women in this group were taking OCPs at their initial presentation. Of these 30 women, 21 were taking OCPs that contained the progestin drospirenone. The control group consisted of 17 women who were currently taking OCPs containing the progestin drospirenone. They did not complain of vulvar pain or pain with sex, nor did they have any evidence of vestibulodynia upon physical examination. Blood samples from both groups of women were then used for genetic analysis.

As you can see in Fig. 1, our hypothesis was correct. Let's explain what this graph shows. As you move from left to right on the graph, the length of the androgen receptor gene is increasing (the androgen receptor is becoming more inefficient). As you move from bottom to top, the percentage of women with a given androgen receptor gene length increases. So the women in the study who had developed vestibulodynia from OCPs (the blue line) have significantly longer androgen receptor genes (and therefore more inefficient androgen receptors) than women who don't develop vestibulodynia from OCPs (the red line).

Another analogy might help to crystallize these results in your mind. Take two groups of women. The women in the first group all drive a gas guzzling huge SUV (Hummer) and the women in the second group all drive a very fuel efficient compact car (Prius). Now if there is plenty of gas to go around, both groups of women have no problems driving as much as they want. But, if there

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is a gas shortage, then the women who drive a Hummer will run out of gas well before the women who drive a Prius. Women with long androgen receptor gene are "driving a Hummer" and there is a gas shortage caused by taking OCPs.

There are several questions that we have been asked many times when we have presented these results and we think that it would be useful to answer them now before we present our conclusions.

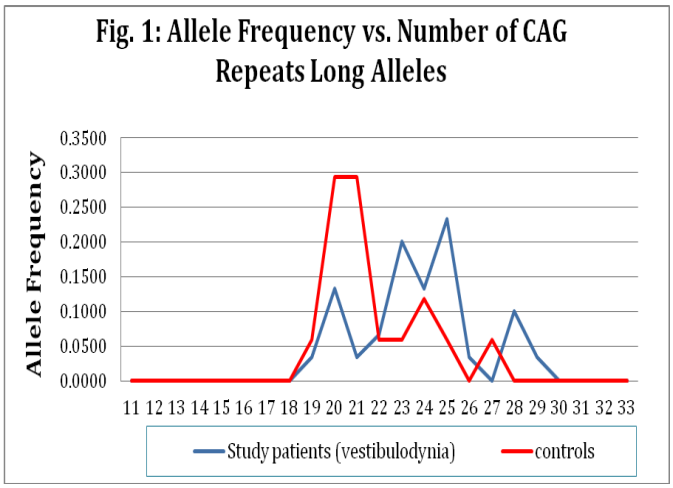
1) Is a longer androgen receptor gene the only genetic defect that can cause women to develop vulvodynia from OCPs? No, it is likely that there are other genetic defects in the androgen receptor gene and possibly defects in the SHBG gene and the estrogen receptor gene that also may play a role. We will look for these genetic changes in the future. It is our hope that in the future there will be a quick and inexpensive test that examines all of the possible negative genetic changes so that women will be able to determine if they are at risk before starting OCPs. As the cost of genetic testing continues to drop, this could happen within the not too distant future.

2) If OCPs are the cause of my vulvodynia, won't just stopping the OCPs allow the vulvodynia to go away? Unfortunately, for many women, just stopping OCPs does not cause the vulvodynia to resolve. This is because, even after stopping OCPs, the levels of SHBG often do not recede to their original levels before the women started taking OCPs. This leads to consistently low free androgens and the persistence of vestibulodynia. In our experience, the only way to overcome the persistently low hormone levels is to apply a compound of topical testosterone and estrogen to the vestibule.

3) Can I remain on OCPs and just use topical hormones as treatment? Unfortunately, the progestin in OCPs can inhibit the androgen receptor, so using topical hormones without stopping OCPs typically does not work.

4) If my vulvodynia goes away after the combination of stopping OCPs and using topical hormones, will I ever be able to go back on OCPs? In our experience, the pain returns after restarting OCPs. We typically recommend intrauterine devices (IUDs) for our patients who need contraception.

5) Can my health care provider order the genetic test that you used in your study? To our knowledge, the test



is not currently offered by any commercial clinical laboratory.

6) If this is the cause of my vulvodynia, is my daughter at risk for developing vulvodynia? Should she not take OCPs? If the combination of a genetic change, such as a longer androgen receptor gene, and OCPs caused your vulvodynia, your daughter may also be at increased risk. It is possible that her risk could be lower than your risk, however, because one of her two androgen receptor genes comes from her father and it may be shorter and more efficient than either of your two genes.

In conclusion, the most exciting result of our research and the other studies discussed above is that we can finally end the controversy regarding the role of OCPs in vulvodynia.

1) We clearly know that all women who take OCPs don't develop vulvodynia, but some women do develop vulvodynia from OCPs.

2) Women may be genetically susceptible to developing vestibulodynia from OCPs. Women with longer androgen receptor genes are more likely to develop vestibulodynia from OCPs than women with shorter genes.

3) OCPs that contain either of the progestins, drosperinone or etonogestrel, appear to cause a greater risk than OCPs that contain progestins with less "anti-androgenic" properties.

4) OCPs with lower levels of EE might cause a greater risk of developing vestibulodynia than OCPs with higher doses of EE.

Editor's Note: Dr. Goldstein is co-author of When Sex Hurts: A Woman's Guide to Banishing Sexual Pain. All proceeds from the sale of this book are donated to NVA.

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In Her Own Words: "Hope"

By Sherrie Utley

Sherrie is a young wife and mother of three children living in Oregon. In 2005, she was diagnosed with lichen sclerosus, a vulvar dermatological disorder that causes vulvar skin alterations and pain. Her daughter was also diagnosed with lichen sclerosus two years ago. Sherrie's experiences have inspired her to speak out about the condition and her struggles through her blog, and to provide support and encouragement to other women and girls suffering from vulvar dermatologic conditions and pain.

My father Rex is an amazing man. I cannot remember a time in my life that I was not aware that my dad was sick. However, he is a great example of a person that accepts his fate and pushes forward. My father was diagnosed with Parkinson's in his thirties and over the years I've watched his health decline. He's had three brain surgeries and numerous struggles with his disorder. Yet he has always been an example of a person who would do anything for a friend, loved one or complete stranger. He would literally give you the shirt off his back.

He's always been a hard-worker, can be stubborn most of the time and is quiet, but he has a great sense of humor and has always believed in and supported me. He's never given in to his disease. He's always fighting and trying to do things that most people take for granted because he wants to be independent. I will never know completely the heartache he has gone through, but I am aware of all the things he's had to give up, such as driving, a good night's sleep, working, fishing, hobbies and even the ability to get around without falling. Although my dad has never broken down in front of me, I'm sure he's had moments of despair and fear. Like my dad, I don't bemoan my disease either.

In my darkest hours, I sit and think about how I've suffered and will continue to suffer, how at best I'll have remissions followed by flare-ups, but will never be completely cured. However, I've been raised by a dad that taught me how to gracefully go through life with a disease. I come from a family of survivors who endure and continue to have hope. I am my father's daughter.

Wallowing in despair drains from me all that is vibrant and joyful in my life. It kills my ambition, pollutes my soul and breaks my heart. Hope inspires me to trust that I am strong enough to handle my disease and not let it dictate my life. Instead of having *hope for* a cure, I have *hope* that no matter how unbearable my current pain may be, there will always be beautiful things all around me – my children, family, friends and nature – that I treasure while coping with pain.

For me, hope and charity go hand-in-hand. I love doing things for other people because it not only distracts me from thinking only of myself and my chronic pain, but it urges me to care for other people without expectation of reward. I've been devoted to charity and good works since I was a child. It is weaved into the fabric of my being.

If you are suffering with lichen sclerosus, vulvodynia, or some other sickness or trial in your life, *never* surrender and *never* allow despair to overcome you. Press forward and know that tomorrow is a new day – full of possibility and hope. ■

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References

1. Battaglia C, Battaglia B, Mancini F, Busacchi P, Paganotto MC, Morotti E, et al. Sexual behavior and oral contraception: a pilot study. J Sex Med 2012;9:550-7.
2. Johannesson U, Blomgren B, Hilliges M, Rylander E, Bohm-Starke N. The vulval vestibular mucosa-morphological effects of oral contraceptives and menstrual cycle. Br J Dermatol 2007;157:487-93.
3. Bohm-Starke N, Johannesson U, Hilliges M, Rylander E, Torebjörk E. Decreased mechanical pain threshold in the vestibular mucosa of women using oral contraceptives: a contributing factor in vulvar vestibulitis? J Reprod Med 2004;49:888-92.
4. Bazin S, Bouchard C, Brisson J, Morin C, Meisels A, Fortier M. Vulvar vestibulitis syndrome: an exploratory case-control study. Obstet Gynecol 1994;83:47-50.
5. Bouchard C, Brisson J, Fortier M, Morin C, Blanchette C. Use of oral contraceptive pills and vulvar vestibulitis: a case-control study. Am J Epidemiol 2002;156:254-61.
6. Burrows LJ, Goldstein AT. The treatment of vestibulodynia with topical estradiol and testosterone. Sex Med 2013;1:30-3.
7. Reed B, Harlow S, Legocki L, et al. Oral contraceptive use and risk of vulvodynia: a population-based longitudinal study. BJOG 2013;120:1678-84.
8. Greenstein A, Ben-Aroya Z, Fass O, Militscher I, Roslik Y, Chen J, et al. Vulvar vestibulitis syndrome and estrogen dose of oral contraceptive pills. J Sex Med 2007;4:1679-83. ■

NVA 2013 Research Grant Recipients

Terry K. Morgan, MD, PhD - Oregon Health & Science University

It has been shown by using vestibular tissue biopsies that women with provoked localized vulvodynia (PLV) have significantly more nerve branches and chronic inflammation than unaffected women. This so-called "neurogenic inflammation" is known to be painful, especially when touched. The objective of this study is to understand *why* there is neurogenic inflammation in PLV patients. Dr. Morgan will complete a prospective matched case-control analysis of fresh vestibular biopsies from at least 10 women with primary PLV (always had PLV), 10 women with secondary PLV (symptoms usually start postpartum or after menopause), and 10-20 matched unaffected controls. He hypothesizes that PLV may be triggered by an infection, allergy, or autoimmune process. His group has recently shown that the CD4 type of lymphocytes (certain white blood cells) that mediates the reaction to these triggers is more common in vestibular biopsies from women with PLV. CD4 cells may be further subtyped into Th1, Th2, and Th17 using molecular labeling of the lymphocytes and flow cytometric analysis. To further test for CD4 subtype polarization in vestibular biopsies, expression analysis of markers including γIFN (Th1), IL-4 (Th2), and IL-17 (Th17) will be used in this study. If PLV has an infectious trigger, either past or current, the researchers anticipate Th1 dominance. If it is an allergic trigger, Th2 cells should predominate; and, if PLV has an underlying autoimmune etiology, Th17 cells will be more common. The results will lead to a better understanding of the role of CD4 lymphocytes in PLV and may provide a new method for individualized diagnoses and targeted therapies.

Lee Hullender Rubin, DAOM, Lac - Oregon College of Oriental Medicine

Provoked, localized vulvodynia (PLV) is a poorly understood and treated female sexual pain disorder for which there is limited evidence on acupuncture's effectiveness. We aim to investigate the feasibility and acceptability of adjuvant acupuncture to lidocaine as a treatment for PLV pain. This study will determine acceptability, feasibility of acupuncture and lidocaine therapy, and estimate effect size to prepare for a larger randomized, controlled trial. Thirty subjects with PLV, as diagnosed by physicians in the OHSU Program for Vulvar Health, will be recruited and randomized into two arms. Fifteen subjects will be allocated to the classical acupuncture and lidocaine 5% cream group and fifteen to the non-classical acupuncture and lidocaine 5% cream group. The course of classical acupuncture treatment includes electroacupuncture and manual acupuncture using a protocol derived from previous pilot studies. The non-classical treatment will receive minimal needling and sham electroacupuncture on points located away from classically described acupoints and acupuncture vessels and are not classically known to be associated with vulvar pain. The duration of treatment for both arms is twelve weeks. The primary outcome measure is pain reduction assessed by the Tampon Test. Our secondary goals are to assess pain reduction assessed by the cotton swab test, patient satisfaction, and changes as measured by the Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires on global health, vaginal discomfort, pain intensity, sexual function, anxiety, depression, pain behavior and interference, and patient characteristics of the Traditional Chinese Medicine diagnosis. We expect acupuncture will be feasible and acceptable to PLV patients and significantly decrease pain and improve quality of life. This study will generate the preliminary evidence required to estimate the effect size for an adequately powered efficacy study.

Devavani Chatterjea, PhD - Macalester College

Epidemiological evidence points to a history of seasonal allergies as a risk factor for vulvodynia. Clinical studies indicate that mast cells potentially are critical mediators of vulvodynia in conjunction with observed hyperinnervation in the vestibular tissue of patients. Mast cell-mediated mechanisms underlying skin allergies have been extensively studied in rodent models using exposures to chemical allergens such as oxazolone. Dr. Chatterjea and colleagues have successfully established a model of both acute and lasting vulvar mechanical pain in response to one to three applications of oxazolone in the labiar skin of female mice that have been previously exposed to oxazolone. They also found that oxazolone-induced vulvar pain is accompanied by persistent hyperinnervation of the labiar tissue. In this study, the researchers propose to characterize nerve mast cell connections in the hyper-innervated tissue by identifying

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key molecular players that maintain these connections and understanding the contributions of both nerves and mast cells to pain pathways. Through this study, they aim to identify biomarkers and therapeutic targets that can be used to develop better classification, management and treatment strategies for patients suffering from allergy-associated vulvodynia.

Gerard Ahern, PhD - Georgetown University

A major impediment to better treatment is our poor understanding of "pain" (nociceptive) nerves and receptors in the vulva/vagina. The goal of this project is two -fold. First, Dr. Ahern and colleagues plan to precisely map nociceptive nerves that project to the vulva and distal vagina. They will utilize mice engineered to selectively express a fluorescent, tomato reporter in pain nerves. The exceptionally bright tomato fluorescence will allow them to directly image these nerves in the vulva/vagina to monitor how the localization and density of these nerves change under pathological conditions. Second, they aim to measure expression of two pivotal pain receptors, TRPV1 and TRPA1, in the vulva/vagina. These proteins are key pain detectors found throughout the body, but they are yet to be characterized in the vulva/vagina. They will use mice engineered to selectively label TRPV1 and TRPA1 to readily visualize their localization in neuronal and non-neuronal tissue. As there is evidence that ovarian hormones are a potential contributing factor to vulvar pain, they propose to study both reproductive aged mice and mice at several time points post-ovariectomy to determine changes associated with ovarian hormone deprivation. The results will reveal fundamental knowledge regarding nociceptive signaling pathways in the vulva/vagina needed to expand our understanding of unexplained vulvar pain.

Melissa Farmer, PhD - Northwestern University

The overarching goal of this project is the evaluation of physiological changes that characterize the onset of vulvodynia. Vulvodynia is characterized by a variety of sensory abnormalities that may differentially contribute to the onset versus persistence of vulvar pain. A longitudinal evaluation of sensory and brain characteristics in a group of women with subacute (lasting ≥ 3 months but < 6 months) vulvar pain may permit the dissociation between different types of mechanisms that can inform the assessment and treatment of women at varying stages of vulvodynia development. Subacute characteristics will be used to predict whether vulvar pain will become chronic. Early identification of traits associated with chronic pain can direct prompt treatments that address the configuration of symptoms. This strategy, which has no precedent in the pelvic pain field, can transform our current understanding of female pelvic pain by identifying important sensory and brain changes that can facilitate the development of novel therapies to treat (and ultimately prevent) the development of vulvodynia.

Steven Witkin, PhD - Weill Cornell Medical College

The mechanisms leading to allodynia and hyperalgesia in women with vestibulodynia remain incompletely defined. Recent evidence from the cancer field implicates the activity of serine proteases as a key intermediate in a previously unidentified mechanism for the induction of allodynia and hyperalgesia. Based on these findings, Dr. Witkin and colleagues have initiated an investigation of proteases and serine protease inhibitors in vaginal secretions of women with vestibulodynia and matched controls. Their initial results indicate that the concentrations of two serine protease inhibitors, secretory leukocyte protease inhibitor (SLPI) and human epididymal protein-4 (HE-4) are markedly reduced in women with vestibulodynia. They propose to test the hypothesis that a decrease in serine protease inhibitor concentrations in the vagina leads to an elevation in unopposed serine protease activity and an increased sensitivity of local peripheral nerves to pro-inflammatory signals. This results in an elevated susceptibility to develop vestibulodynia. Their specific study objectives are to determine whether (i) decreases in vaginal levels of SLPI and HE-4 and/or increases in the vaginal serine protease, kallikrein, or the cysteine protease, cathepsin, are associated with primary and/or secondary vestibulodynia, (ii) this deficit is present in a specific subset(s) of patients and (iii) successful treatment is associated with an increase in SLPI and/or HE-4 concentrations and/or a decrease in kallikrein or cathepsin levels. They expect that the successful diminution of vestibulodynia-related symptoms will be associated with local elevations in SLPI and/or HE-4 levels and/or decreases in kallikrein or cathepsin. This is an initial study of a novel, biologically plausible and previously unexplored mechanism that may be involved in the development and perpetuation of vestibulodynia. ■

New Appointment to NVA Executive Board

For more than 20 years, Dr. Pamela Morrison Wiles has been practicing physical therapy (PT) in the areas of orthopedics and women's and men's pelvic health issues and has a private practice in Manhattan. She earned a BS in PT from Downstate Medical Center in NY and then an Advanced Master's degree in orthopedic PT from Touro College in New York in 1999. Dr Morrison Wiles also achieved a Doctorate at Touro College in 2006, with research completed in common PT evaluative findings in patients with chronic vulvar pain. A trained specialist in surface EMG pelvic muscle dysfunction biofeedback, she has also completed training in rehabilitative ultrasound imaging for lumbar and pelvic dysfunction. She earned a Certification in Integrative Manual Therapy at the Connecticut School for Integrative Manual Therapy in 2006.

In 2001, Dr. Morrison Wiles was inducted as a Fellow into the International Society for the Study of Vulvovaginal Diseases as an expert in her field. As a member of their Vulvar Pain Task Force, she devised PT algorithms for the evaluation and treatment of vulvar pain. She also was a primary instructor and curriculum editor for the advanced course in pelvic pain for the Section on Women's Health of the American Physical Therapy Association (APTA). Dr. Morrison Wiles has lectured nationally and internationally on the topics of vulvodynia, interstitial cystitis, treatment of pelvic and sexual pain, surface EMG pelvic floor muscle biofeedback, and pelvic floor muscle dysfunction. She is a member of many organizations such as the International Pelvic Pain Society; Interstitial Cystitis Association; International Society for the Study of Women's Sexual Health; American Association of Sexuality, Educators, Counselors, and Therapists; and the APTA. She has been cited as an expert in her field by PT magazines, the Interstitial Cystitis Association, the APTA, and on medical radio talk shows. Dr. Morrison Wiles reviews papers and research studies for the Journal of Sexual Medicine and the NVA. Above all, she is committed to providing the best possible care for her patients. We welcome her to the NVA Board of Directors. ■

(*PELVIC FLOOR MUSCLES from page 1*)

S3-4. The iliococcygeus is innervated by the levator ani nerve S3-4 and the puborectalis is innervated by the inferior rectal branches of the pudendal nerve S2-4. The coccygeus is innervated by direct nerve roots S3-4.

The functions of the deep PFMs include supporting the abdominal viscera or organs, providing pelvic and spinal stability, assisting in respiration, providing sphincteric closure for bowel and bladder function, as well as playing a role in sexual function.[3] There is, however, an entire superficial layer of PFMs, also referred to as the urogenital diaphragm, that needs to be considered in the assessment and treatment of vulvar and sexual pain. This layer is on the outside of the vagina directly under the perineum and vulvar tissue and includes the external anal and urethral sphincter muscles, superficial transverse perineal muscles, bulbocavernosus muscles, and ischiocavernosus muscles.[3] The functions of the superficial PFMs include a role in sexual responses such as clitoral engorgement, assisting in vaginal closure, reflexive response to enhance sexual pleasure, and facilitating closure of the urethra and anus for continence.[4] Although the individual muscles of the superficial layer are much smaller than the deep PFMs, their potential role in vulvar pain syndromes requires equal attention. (See Fig. 1, p.10.)

Anatomy and Function of the Superficial Layer

It is important to understand the anatomy of the superficial PFMs for proper diagnosis and to design an effective treatment plan. The external anal sphincter encircles the anus and its main function is to contract voluntarily to inhibit defecation. It attaches to the perineal body, superficial transverse perineal muscles, and anococcygeal liga-

(See PELVIC FLOOR MUSCLES, page 10)

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ment (raphae).[5] The external urethra sphincter is a voluntary muscle that surrounds the urethra and upon contraction compresses the urethra to stop the flow of urine. The superficial transverse perineal muscle runs across the perineum from the vagina and anus and has been referred to as the "bowtie" of the perineum.[6] Its function is to provide support to the perineal body. The perineal body is considered the central tendon to which most of the deep and superficial PFMs attach. Its essential role is to maintain pelvic floor integrity. This muscle is commonly injured during childbirth due to tearing or an episiotomy. The bulbocavernosus muscles, (also known as bulbospongiosus) muscles, surround the urethra and the vagina and cover the vestibule bulbs. The bulbocavernosus aids in clitoral erection and closure of the vagina. The ischiocavernosus muscles run lateral to the bulbocavernosus muscles along the pubic rim, making palpation challenging. The ischiocavernosus attaches to the medial part of the ischial tuberosity and originates in the crura of the clitoris. The crura are the V-shaped erectile tissue attaching to the clitoral body, that help promote clitoral erection. The superficial PFMs are innervated by the perineal branch of the pudendal nerve S2-4.

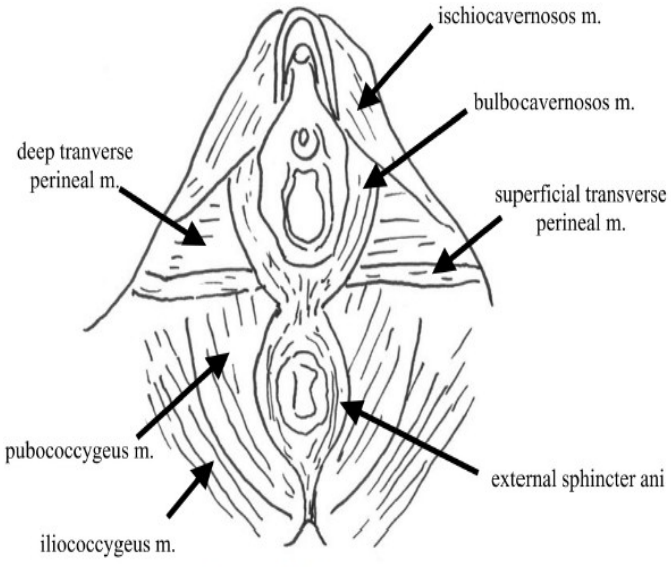

Fig 1: Pelvic Floor Musculature
Reproduced with permission from Reissing et al.

Evaluation of the Superficial Layer

Close evaluation of the superficial layer of PFMs through palpation and strength testing are components of the PFM examination along with assessment of the deeper layer, the levator ani. Digital palpation assesses for pain, myofascial trigger points, tone, symmetry, and strength. The clinician systematically palpates each superficial PFM individually comparing sides as the patient informs of any pain experienced using a verbal scale of absent, mild, moderate, or severe pain. The clinician should palpate along the entire lengths of the muscles from proximal to distal and lateral to medial to ensure no hidden tender points or myofascial trigger point (MTP) exist. Tender points are specific areas of tenderness or pain in a muscle and can feel like a taut band, whereas MTPs are painful taut bands within a muscle that have a referral pattern of pain away from the site being touched. When compressed, MTPs can have a twitch response. According to trigger point expert Janet Travell, MTPs from the ischiocavernosus and bulbocavernosus refer pain to genital structures, including the clitoris, vulva, and vagina in females.[7] Vulvovaginal pain can also arise from MTPs in the deep PFMs. Therefore, both superficial and deep PFMs need to be assessed.

Strength testing of the superficial PFMs is next. Using a gloved finger, the clinician inserts one finger into the vaginal entrance at the level of the distal phalangeal joint only. A manual muscle test of the superficial layer collectively is performed by asking the patient to contract layer 1, the outermost layer, pulling "up and in". The strength is rated using an adapted Oxford Scale 0 to 5, with 0 = no contraction; 1 = flicker or twitch; 2 = weak squeeze without lift; 3 = fair squeeze with definite lift; 4 = good with a palpable lift, able to hold against resistance; 5 = strong squeeze, able to hold against strong resistance.[8] A score of 5 is ideal.

The anal sphincter is assessed via digital palpating and manual strength testing. The ability of the patient to volitionally close the anal sphincter and the amount of pressure felt upon removal of the finger should be noted. The strength of the anal sphincter is rated on an Oxford Scale 0 to 5, with 0 = no contraction; 1 = trace or flicker contraction; 2 = minimum contraction; 3 = fair contraction; 4 = good contraction; and 5 = ideal or strong contraction. Palpation should also include assessing symmetry between the right and left sides and noting any divots or scar tissue from prior surgeries or

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tearing from childbirth. Sensation deficits to light touch of the anal sphincter should also be assessed. The anal wink reflex can be tested when the clinician gently yet swiftly strokes the tissue adjacent to the anal sphincter with a cotton swab to view an involuntary contraction of the anal sphincter. This is tested on both sides. Clues regarding function of sacral nerve roots may be revealed.

Associated Musculoskeletal Evaluation

The alignment, function, and soft tissue of the pubic symphysis joint, hip joints, and coccyx may have an influence on the resting tone, length, and function of the superficial PFMs because of the myofascial relationships. A pubic symphysis malalignment may cause abnormal tensions and pain in structures that attach onto the pubis by way of ligaments or fascia such as the mons soft tissue, urethra, clitoris, and bulbocavernosus and ischiocavernosus muscles. Malalignment of the pubic symphysis, hip impingement syndrome, or hip labral tears can cause abnormal tensions of the hip adductor muscles that attach adjacent to the superficial PFMs and share myofascial connections. The anal sphincter attaches onto the coccyx via the anococcygeal ligament, and thus a coccyx malalignment (rotated, sidebent, or flexed/extended) can influence the myofascial tensions at the anal sphincter, perineal body, and superficial transverse perineal muscles. Persistent abnormal tensions in the fascia and muscles can be a cause of adverse tensions placed on the nerves supplying the area such as the pudendal and levator ani nerves. This can become a pain source. Eventually these abnormal tensions also result in the production of tender points, trigger points and/or MTPs in the superficial PFMs. Thus, close inspection and evaluation of these musculoskeletal components associated with vulvar pain is prudent.

Research

Studies have confirmed the involvement of the superficial PFMs in vulvar pain. Higher tone or overactivity of the superficial PFMs has been noted in women with provoked vestibulodynia as per Reissing.[9] In this study, tone was assessed by a passive stretch placed on the bulbocavernosus, ischiocavernosus, and superficial transverse perineal muscles and the physical therapist recorded the findings on a scale of + 3 for severe hypertonicity to -3 for severe hypotonicity, with 0 being normal tone. The women with vulvar pain presented with significantly more hypertonicity at the superficial layer compared to the deeper layer. Reissing suggests that both the superficial and deep muscles collectively contract against attempted penetration when pain is experienced during intercourse, decreasing the size of the vaginal opening. This results in increased pressure at the vulvar vestibule. Furthermore, contracted muscles adjacent to the distal vagina most likely contribute to chronic vulvar pain.[10]

Another study by Gentilore-Saulnier [4] had similar findings. Women with vulvar pain demonstrated altered PFM behavior compared with controls. Gentilore-

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(*PELVIC FLOOR MUSCLES from page 11*)
Saulnier noted heightened responsiveness to pain in the superficial layer upon stimulation, hypertonicity, decreased flexibility, and impaired relaxation after a contraction. Assessment occurred via surface electromyography (sEMG) with placement of self adhesive disposable electrodes on the patients' bulbocavernosus muscles and an intravaginal probe was placed to assess the response of the deep PFMs. A baseline resting tone of 10 seconds was observed and then the patients performed one maximal voluntary contraction. Patients had increased tonic sEMG in their superficial PFMs as compared with the control group and there were no differences found in the deep PFMs. Patients underwent physical therapy treatment comprised of soft tissue mobilization, manual stretches, sEMG biofeedback, internal PFM electrical stimulation, and a home exercise program of PFM exercises. After treatment, the patients demonstrated resolution of hypertonicity, pain, and improved flexibility and relaxation post-contraction.

Treatment

Medical treatment options available for deep PFM dysfunction include oral and/or vaginal or rectal suppository muscle relaxants, Botox injections and trigger point injections.[1, 11, 12] Medical treatment options for the superficial PFMs may include oral and/or topical muscle relaxants, Botox injections, or trigger point injections. If anxiety is also a component, SSRIs may be prescribed. Physicians specializing in vulvar pain and pelvic floor dysfunction such as gynecologists, urogynecologists, nurse practitioners, urologists, physiatrists (rehabilitation medicine doctors), osteopaths, and pain management doctors may offer these treatments. Physical therapy treatment options for the superficial PFM layer may include soft tissue mobilization, including myofascial release, massage, trigger point release techniques, and neural mobilization; joint mobilization; manual stretching; therapeutic ultrasound; neuromuscular re-education techniques; external electrical stimulation, sEMG PFM biofeedback; specific PFM and lower quarter therapeutic and motor control exercises; and transcutaneous electrical nerve stimulation. Cryotherapy or heat therapy may also be utilized. Skin rolling, another myofascial release technique, may also be employed systematically over the entire perineum, hip adductors, mons pubis, and suprapubic region. Treatment that addresses both superficial and deep PFMs, as well as dysfunction and associated musculoskeletal issues, may be the most comprehensive and effective approach because multiple dysfunctions can occur simultaneously and perpetuate chronic vulvar pain.

References

1. Fischer G. Management of vulvar pain. Dermatol Ther 2004;17:134-9.
2. Gordon A. Clitoral pain: the unexplored pain in women. J Sex Marital Ther 2002;28(suppl 1):123-8.
3. Bo K, Sherburn M. Evaluation of female pelvic-floor muscle function and strength. Phys Ther 2005;85:269-82.
4. Gentilore-Saulnier E, Mclean L, Goldfinger C, Pukall CF, Chamberlain S. Pelvic floor muscle assessment outcomes in women with and without provoked vestibulodynia and the impact of a physical therapy program. J Sex Med 2010;7:1003-22.
5. Raizada V, Mittal RV. Pelvic floor anatomy and applied physiology. Gastroenterol Clin North Am 2008;37:493-509, vii.
6. Bates F. Assessment of the female patient with urinary incontinence. Urol Nurs 2002;22:305-14, 317.
7. Travell JG, Simmons DG. Myofascial pain and dysfunction: the trigger point manual; vol. 2, the lower extremities. Media (PA): Williams & Wilkins; 1992.
8. Laycock J, Haslem J, editors. Therapeutic management of incontinence and pelvic pain: pelvic organ disorders. 2nd ed. London: Springer-Verlag; 2008.
9. Reissing ED, Brown C, Lord MJ, Binik YM, Khalife S. Pelvic floor muscle functioning in women with vulvar vestibulitis syndrome. J Psychosom Obstet Gynaecol 2005;26:107-13.
10. Bohm-Starke N. Medical and physical predictors of localized provoked vulvodynia. Acta Obstet Gynecol Scand 2010;89:1504-10.
11. Abbott J. Gynecological indications for the use of botulinum toxin in women with chronic pelvic pain. Toxicon 2009;54:647-53.
12. Rogalski MJ, Kellogg-Spadt S, Hoffman AR, Fariello JY, Whitmore KE. Retrospective chart review of vaginal diazepam suppository use in high-tone pelvic floor dysfunction. Int Urogynecol J 2010;21:895-9.■