

## NVA RESEARCH UPDATE NEWSLETTER

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This newsletter is quarterly and contains abstracts from medical journals published between March and June 2008. Abstracts presented at scientific meetings may also be included. Please direct any comments regarding this newsletter to [chris@nva.org](mailto:chris@nva.org).

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### Vulvodynia

#### **Influence of dietary oxalates on the risk of adult-onset vulvodynia.**

Harlow BL, Abenhaim HA, Vitonis AF, Harnack L  
J Reprod Med. 2008 Mar;53(3):171-8

**OBJECTIVE:** To examine the relationship between dietary oxalates and the development of vulvodynia. **STUDY DESIGN:** We conducted a population-based, case-control study of women with and without vulvodynia from 9 ethnically diverse Boston-area communities. Conditional logistic regression analyses were used to estimate the odds of developing vulvodynia as a consequence of self-reported consumption patterns of high-oxalate foods and total weekly dietary oxalate. Oxalate consumption was referenced prior to the onset of symptoms in cases and to a matched reference date among controls. **RESULTS:** Baseline clinical characteristics were similar among the 242 cases and 242 controls except for a higher reported incidence of pain/difficulty with first tampon insertion among cases (46.3% vs. 32.2%,  $p < 0.01$ ). After adjusting for potential confounders, no differences were observed in consumption patterns of different high-oxalate foods between cases and controls, and there was no increase in risk of developing vulvodynia with increasing tertiles of estimated oxalate intake. In addition, we saw no association between increasing consumption of various food items high in oxalate content and the risk of vulvodynia. **CONCLUSION:** Dietary oxalate consumption does not appear to be associated with an elevated risk of vulvodynia.

#### **Vulvar vestibulitis syndrome: A clinicopathological study of 14 cases.**

[article in French]

Perrigouard C, Dreval A, Cribier B, Lipsker D  
Ann Dermatol Venereol. 2008 May;135(5):367-372.

**BACKGROUND:** Vulvar vestibulitis syndrome (VVS) is one of the most frequent causes of superficial dyspareunia in young women. VVS has a pronounced psychological impact. The results of pathological studies published thus far are controversial. **PATIENTS AND METHODS:** Fourteen women with VVS were included in this study and underwent vestibular biopsy. Vulvar biopsies were taken from the orifice of Bartholin's gland. The biopsy samples were stained with a standard stain and PAS and 25 serial sections were prepared for each specimen. **RESULTS:** The mean patient age was 26 years and VVS had been present for a mean 30 months. Extensive inflammation of mononuclear cells was observed in the vulvar chorionic epithelium. This inflammation was seen mainly around the minor vestibular glands. Mild exocytosis of lymphocytes was noted in the vestibular glands and ducts. **DISCUSSION:** Most studies concerning this disease report chronic inflammation of the vulvar vestibular mucosa. This inflammation is seen mainly around the minor vestibular glands. We report the same pattern in our study. Moreover, we

observed some exocytosis into the epithelium of minor vestibular glands and the excretory duct. This aspect has not been reported to date, further supporting the individual nature of this entity.

### **The use of amielle vaginal trainers as adjuvant in the treatment of vestibulodynia: an observational multicentric study.**

Murina F, Bernorio R, Palmiotto R

Mescape J Med. 2008 Jan 30;10(1):23

**OBJECTIVE:** To assess the effectiveness of a specific set of vaginal dilators (Amielle Comfort) as a part of vestibulodynia therapy. **STUDY DESIGN:** Fifteen women referred for vestibulodynia, localized vulvodynia, were advised to use vaginal dilators (Amielle Comfort) accompanied by standardized instructions, after previously receiving 1 or more therapies for the vestibulodynia. **RESULTS:** The post-treatment Marinoff scale for dyspareunia significantly improved in patients after vaginal dilator treatment compared with baseline values (2.2 +/- 0.4 vs 1.1 +/- 0.9;  $P < .01$ ), and the Female Sexual Function Index scores were significantly improved compared with the prestudy values (16.3 +/- 5.5 vs 25.3 +/- 7.5;  $P < .01$ ). **CONCLUSION:** Among women with previous therapy for vestibulodynia, vaginal dilator use was associated with improvement in symptoms. Vaginal dilators can play an important role in overcoming pelvic floor muscular responses that remain and sometimes increase after pain perception has decreased.

### **Vulvodynia: A review of pathophysiological factors and treatment options**

Pukall CF, Bergon S, Goldfinger C

Basic and Clinical Medicine, 28(4), 421-436

Vulvodynia, or chronic vulvar pain, affects 16% of women in the general population and has negative effects on numerous aspects of a woman's life. The purpose of this paper is to review the literature on the etiology and treatment of vulvodynia. Since relatively little research has been carried out on unprovoked generalized vulvodynia (UGVD), this review focuses on provoked vestibulodynia (PVD), a subtype of vulvodynia characterized by a severe, burning/sharp pain that occurs in response to pressure localized to the vestibule. Research examining the pathophysiology of PVD provides evidence that both peripheral (e.g., vestibular tissue abnormalities, pelvic floor hypertonicity) and central (e.g., increased neural activation) factors are involved in the development and maintenance of PVD. Additionally, psychological reactions to the pain may vary and influence the expression and course of the pain. Despite the multitude of factors involved in PVD, most treatment studies to date are unimodal in nature, retrospective, and uncontrolled. A review of treatment studies targeting peripheral (e.g., topical applications, vestibulectomy) and central (e.g., antidepressants, pain management therapy) components of PVD is provided, and the need for multimodal treatment plans which target both levels of pain processing is discussed. Given the complexity of PVD, a biopsychosocial approach is recommended for future research endeavors and treatment plans.

### **Vulvodynia.**

Ventolini G, Barham SM

Dermatol Online J. 2008 Jan 15;14(1):2.

Vulvodynia or vulvar pain syndrome is a chronic, heterogeneous, and multifactorial disease with a high prevalence. This condition affects Caucasians, African Americans, Africans and Hispanic women, particularly those sexually active at child-bearing age. The etiology of this condition is complex and remains elusive. An accurate diagnosis requires a comprehensive history, physical examination and targeted diagnostic tests. Although many treatment options have been utilized, a rational therapeutic strategy is still under research. Psychological counseling and group support should be considered in all cases.

## **The role of pelvic floor physical therapy in the treatment of pelvic and genital pain-related sexual dysfunction.**

Rosenbaum TY, Owen A  
J Sex Med 2008;5:513–523

*Introduction.* Chronic pelvic pain (CPP) in women and men is associated with significant sexual dysfunction. Recently, musculoskeletal factors have been recognized as significant contributors to the mechanism of pelvic pain and associated sexual dysfunction, and in particular, pelvic floor muscle hypertonus has been implicated. *Aim.* The purpose of this Continuing Medical Education article is to describe the musculoskeletal components involved in pelvic and genital pain syndromes and associated sexual dysfunction, introduce specific physical therapy assessment and intervention techniques, and provide suggestions for facilitating an effective working relationship among practitioners involved in treating these conditions. *Methods.* A review of the relevant literature was performed, clarifying current definitions of pelvic pain, elucidating the role of musculoskeletal factors, and determining the efficacy of physical therapy interventions. *Results.* A review of the role of physical therapy for the treatment of pelvic pain and related sexual dysfunction. *Conclusions.* Physical therapy treatment of pelvic pain is an integral component of the multidisciplinary approach to CPP and associated sexual dysfunction.

## **Vulvar pain: a comprehensive review.**

Strauhal MJ, Frahm J, Morrison P, Featherstone W, Hartman D, Florendo J, Parker S  
Journal of Women's Health Physical Therapy, 31:3, Winter 2007; 6-22.

Background: Vulvar pain or vulvodynia is a poorly understood, understudied, and devastating condition affecting the lives of many women. A subset of vulvar pain known as local provoked vestibulodynia (LPV), previously known as vulvar vestibulitis syndrome (VVS), is a condition defined by symptoms and the exclusion of identifiable pathologies. There is little in the way of evidence-based literature to guide the physical therapist in the evaluation and management of LPV. Purpose/Method: To review current theory and evidence for the diagnosis of LPV by a review of literature and use of surveys to practitioners. Results: The Vulvar Pain Task Force makes recommendations for physical therapy evaluation and management of LPV. Recommendations address the need for physical therapy in the field of vulvar pain. Conclusion: Many different interventions for LPV exist with a paucity of evidence for their effectiveness. Physical therapists are encouraged to seek ongoing educational opportunities and interdisciplinary interactions in the area of vulvar pain conditions, to study and use appropriate measurement tools and outcome measures, and to engage in research to add the physical therapy perspective to the growing body of evidence in the literature.

## **Vaginal pressure-pain thresholds: initial validation and reliability assessment in healthy women.**

Tu FF, Fitzgerald CM, Kuiken T, Farrell T, Norman Harden R  
Clin J Pain. 2008 Jan;24(1):45-50

OBJECTIVES: Pelvic muscle pain syndromes are poorly understood and lack reliable diagnostic criteria. Furthermore, animal models suggest that somatic pain can influence the development of pelvic visceral pain dysfunction. To develop psychophysical measures to facilitate diagnosis of pelvic floor myofascial pain syndromes, this pilot was designed to preliminarily test the feasibility, reliability, and validity of pressure-pain thresholds (PPTs) to identify and quantify pelvic floor pain sensitivity. METHODS: We conducted a cross-sectional study of pelvic floor PPTs using 19 healthy women. Using a prototype vaginal pressure algometer, we measured PPTs and calculated intraclass correlations for short-term and intermediate-term reliability. Validity was assessed by correlating numerical rating scores for pain (0 to 100) at standard pressure levels applied to the right iliococcygeus muscle. RESULTS: The mean PPT of all pelvic floor sites was 1.52 kg/cm (SD=0.62), whereas thresholds of nonmuscle vaginal sites (anterior and posterior wall) were 1.65 kg/cm (SD=0.64). Pain numerical rating scores were positively correlated with stimulus intensity at the right iliococcygeus (Pearson  $r=0.61$ ). Intraclass correlation demonstrated good short-term reliability at this same site for the first versus second, and second versus third measurements (0.75, 0.64); 1-week repeat reliability was also good for the right pubococcygeus,

iliococcygeus, and obturator (0.69, 0.84, and 0.61, respectively), and both nonmuscle vaginal sites. DISCUSSION: These data suggest that PPTs may prove to be valid and reliable measures of pelvic floor somatic pain sensitivity in healthy women. Broader studies including a pelvic pain cohort should be conducted to corroborate these results and determine the technique's external validity and clinical relevance.

### **Physical therapy evaluation of patients with chronic pelvic pain: a controlled study.**

Tu FF, Holt J, Gonzales J, Fitzgerald CM  
Am J Obstet Gynecol. 2008 Mar;198(3):272.e1-7

OBJECTIVE: The purpose of this study was to determine the relative frequency of positive musculoskeletal exam findings between patients with chronic pelvic pain (CPP) and healthy control subjects. STUDY DESIGN: We conducted a masked, prospective, cross-sectional study of abnormal pelvic, abdominal, and back examination findings in 19 women with CPP vs 20 healthy control subjects. RESULTS: Women with CPP had more frequent abnormal musculoskeletal findings than did control subjects asymmetric iliac crests (61% vs 25%), pubic symphysis heights (50% vs 10%), and positive posterior pelvic provocation testing (37% vs 5%; all  $P < .05$ ). Patients with pain exhibited more tenderness at several abdominal muscle sites, had higher median total pelvic floor tenderness scores (3/24 vs 0/24;  $P < .05$ ), and less control of the pelvic floor (unable to maintain 10 seconds of relaxation, 78% vs 20%;  $P < .001$ ). CONCLUSION: The higher frequency of positive pelvic musculoskeletal findings in CPP suggests that an investigation of somatic pain generators is warranted in these patients.

### **Perineal pain and inferior cluneal nerves: anatomy and surgery.**

Darnis B, Robert R, Labat JJ, Riant T, Gaudin C, Hamel A, Hamel O  
Surg Radiol Anat. 2008 May;30(3):177-183. Epub 2008 Feb 28

Neuropathic perineal pains are generally linked to suffering of the pudendal nerve. But some patients present pains described as a type of burning sensation located more laterally on the anal margin and on areas including the scrotum or the labiae majorae, the caudal and medial parts of the buttock and the upper part of the thigh. These pains extend beyond the territory of the pudendal nerve. It is interesting to note that the inferior cluneal nerves are responsible for the cutaneous sensitivity in the inferior part of the buttock. We wanted to check if these nerves, or some of their branches, could be responsible for such pains. An anatomic study, containing six dissections on corpse, has been conducted. The inferior cluneal nerves, emerging from the posterior femoral cutaneous nerve have some branches joining the perineum, especially by a perineal ramus. However, two conflict areas have been identified on the path of these nerves and on the perineal ramus: one at the level of the sacrotuberal ligament, and the other being the passage under the ischium. Two surgical approaches have been established from these observations with the aim of suppressing the conflicts.

### **Do psychosexual factors play a role in the etiology of provoked vestibulodynia? A critical review.**

Desrochers G, Bergeron S, Landry T, Jodoin M  
J Sex Marital Ther. 2008 May-Jun;34(3):198-226

The aim of this review was to critically examine published studies concerning the psychosexual aspects of provoked vestibulodynia. Despite the presence of several methodological limitations, some findings were consistently replicated. Overall, women with vestibulodynia demonstrate impaired sexual functioning, namely, lower levels of sexual desire, arousal, and frequency of intercourse. Childhood physical and sexual abuse represent potential risk factors for the development of this condition. Additionally, specific psychological states such as anxiety, fear of pain, hypervigilance, catastrophizing, and depression, are more frequently reported by these women. More rigorous studies are needed to establish which psychosexual variables may exacerbate and/or maintain vestibulodynia.

### **Neuropathic pain: emerging treatments.**

Dray A

Br J Anaesth. 2008 May 28. [Epub ahead of print]

Neuropathic pain remains one of the most challenging of all neurological diseases and presents a large unmet need for improved therapies. Many mechanistic details are still lacking, but greater knowledge of overlapping mechanisms and disease comorbidities has highlighted key areas for intervention. These include peripheral and central hyperexcitability. Among the molecular drivers are ion channels (Nav1.7, Nav1.8, Nav1.3, Cav2.2, and alpha2-delta subunits) whose expression is changed during neuropathic pain and their block shows therapeutic utility. Block of a number of ligand-gated channels [transient receptor potential (TRP)V1, TRPM8, and neuronal nicotinic receptors (NNRs)], important in neural sensitization, may also prove beneficial. Other approaches, such as the modulation of peripheral excitability via CB1 receptors, reduction of spinal excitability through block of glutamate receptors (metabotropic glutamate receptor 5 and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate), block of activated spinal neuroglial (CCR2 and P2X7), or increasing spinal inhibition by enhancing monoaminergic activity, all offer exciting opportunities currently being validated in the clinic. Finally of note is the emergence of biological approaches, for example, antibodies, siRNA, gene therapy, offering powerful therapeutic additions with which to redress the neurological disease imbalances causing neuropathic pain.

### **Evidence for the use of botulinum toxin in the chronic pain setting – a review of the literature.**

Jeynes LC, Gauci CA

Pain Pract. 2008 May 23. [Epub ahead of print]

A significant proportion of chronic pain is of musculoskeletal origin. Botulinum toxin (BTX) has been successfully used in the treatment of spasmodic torticollis, limb dystonia, and spasticity. Investigators have, thus, become interested in its potential use in treating many chronic pain conditions. Practitioners have used BTX, outside the product license, in the treatment of refractory myofascial pain syndrome and neck and low back pain (LBP). This article reviews the current evidence relating to chronic pain practice. There is evidence supporting the use of both BTX type A and type B in the treatment of cervical dystonias. The weight of evidence is in favor of BTX type A as a treatment in: pelvic pain, plantar fasciitis, temporomandibular joint dysfunction associated facial pain, chronic LBP, carpal tunnel syndrome, joint pain, and in complex regional pain syndrome and selected neuropathic pain syndromes. The weight of evidence is also in favor of BTX type A and type B in piriformis syndrome. There is conflicting evidence relating to the use of BTX in the treatment whiplash, myofascial pain, and myogenous jaw pain. It does appear that BTX is useful in selected patients, and its duration of action may exceed that of conventional treatments. This seems a promising treatment that must be further evaluated.

### **Cutaneous amitriptyline in human volunteers: differential effects on the components of sensory information.**

Duale C, Daveau J, Cardot JM, Boyer-Grand A, Schoeffler P, Dubray C

Anesthesiology. 2008 Apr;108(4):714-21

**BACKGROUND:** Amitriptyline is effective in relieving neuropathic pain. Its site of action is thought to be supraspinal and spinal, but a peripheral effect on fibers is also suggested. **METHODS:** This double-blind study examined the effects of transcutaneous amitriptyline diluted in hydroalcoholic solution in healthy young male volunteers. Six treatments were randomly applied on different areas of the skin of the back: amitriptyline at 0 (vehicle), 25, 50, and 100 mg; saline (control); and lidocaine-prilocaine cream as a positive control. Up to 24 h after application, mechanical thresholds for touch and nociception, and thermal thresholds for cold, warm, and heat sensation were recorded for each area. Blood samples were collected to assess plasma levels of amitriptyline. A late recording of the tactile thresholds was performed 1 and 3 weeks after the treatment session. **RESULTS:** The thresholds for all sensations did not differ between the vehicle and saline. Lidocaine-prilocaine cream displayed a short-lasting anesthetic effect for

all sensations, although this was not significant for warm sensation. Amitriptyline, at the three concentrations studied, induced a mild and short-lasting increase of the tactile and mechanical nociceptive thresholds. It significantly decreased cold thresholds (down to 21.8 degrees C, P = 0.01 vs. 27.5 degrees C for control) and heat thresholds (down to 40.1 degrees C, P = 0.004 vs. 43.4 degrees C for control). These two effects were no longer significant after the fourth hour of observation. Amitriptyline did not change warm thresholds. There was no apparent systemic absorption effect of the drug. CONCLUSION: It is hypothesized that amitriptyline has a differential effect on different fiber structures.

## **Other Vulvovaginal Disorders**

### **Relationship between clinical diagnosis of recurrent vulvovaginal candidiasis and detection of Candida species by culture and polymerase chain reaction.**

Weissenbacher T, Witkin SS, Ledger WJ, Tolbert V, Gingelmaier A, Scholz C, Weissenbacher ER, Friese K, Mylonas I  
Arch Gynecol Obstet. 2008 May 28. [Epub ahead of print]

**BACKGROUND:** Recurring vulvovaginal candidiasis (RVVC) is a common vaginal discharge affecting 75% of all women at least once in their life. In 5% of these women, infection is recurring. Aim of the study was to determine the sensitivity of detecting Candida species by culture and polymerase chain reaction (PCR) in women with a clinical diagnosis of RVVC. **METHODS:** A total number of 104 patients referred with a clinical diagnosis of RVVC and therefore at least four episodes in the previous year were evaluated. In order to detect Candida, vaginal swabs were cultured on Sabouraud and chromagar. Furthermore, the supernatant from the vaginal lavage was examined for the presence of Candida by PCR. **RESULTS:** When the culture was analyzed, only 31 (29.8%) of the 104 patients diagnosed with RVVC were positive for Candida species in their vagina. Candida albicans was identified in 25 women and six were positive for Candida glabrata. When analyzed by PCR, 44 (42.3%) patients were positive for Candida species. In 13 women (12.5%) only the PCR was positive, while in 31 patients both culture and PCR were positive. **CONCLUSION:** The diagnostic method of PCR is more sensitive than culture in detecting Candida species in the vagina. The results also suggest further investigation to verify the complaints of the negative tested patients.

### **Preliminary evaluation of a vaginal cream containing lactoferrin in the treatment of vulvovaginal candidosis.**

Costantino D, Guaraldi C  
Minerva Ginecol. 2008 Apr;60(2):121-125

**AIM:** The objective of the study is to verify the clinical effectiveness of a cream containing lactoferrin in the treatment of acute vulvovaginal candidiasis. **METHODS:** The study enrolled 34 patients aged 25-45 years and presenting signs and symptoms of acute vulvovaginal candidiasis. The patients have been treated with a cream containing lactoferrin 4%, 5 g of cream in vagina and 2 cm applied on the vulva twice a day for 7 days. At the end of the treatment the patients a clinical and microscopical examination was performed in order to evaluate the effectiveness of the therapy. **RESULTS:** The results obtained showed that 27 women completely recovered, 5 showed a good improvement and only 2 women were still suffering from vulvovaginitis at the end of treatment. **CONCLUSION:** From the data of our study, a cream containing lactoferrin seems to be clinically effective in the treatment of acute vulvovaginal candidiasis, with a good response on all the characteristic symptoms of this infection.

### **pH-balanced tampons: do they effectively control vaginal pH?**

Melvin L, Glasier A, Elton R, Cameron ST  
BJOG. 2008 Apr;115(5):639-45

**OBJECTIVE:** To determine if tampons lubricated with pH-balanced gel are effective at maintaining normal vaginal pH. **DESIGN:** Randomised controlled trial. **SETTING:** Urban family planning clinic and teaching hospital. **POPULATION:** Healthy volunteers using the combined oral contraceptive pill. **METHODS:** Women were randomised to use an existing lubricating gel (pH 5.1) or a lactic acid-buffered gel (pH 3.8-4.2) with regular size, non-applicator tampons. In the preceding control cycle, women used identical tampons without gel. **MAIN OUTCOME MEASURES:** Vaginal pH  $\leq$  4.5, microbiology (candida and bacterial vaginosis [BV]) and colposcopic appearance within 72 hours of tampon use, subject acceptability and symptoms. **RESULTS:** Eighty-one out of 98 (83%) women completed the study. No significant difference was observed between tampons with the standard gel formulation, the pH-balanced gel and nonlubricated tampons in terms of vaginal pH, microbiological evidence of candida or BV, or colposcopic appearance. Acceptability scores were significantly higher for lubricated tampons compared with nonlubricated tampons ( $P < 0.05$ ), although there was no difference in reported symptoms. **CONCLUSIONS:** Tampons lubricated with pH-balanced gel do not control vaginal pH. There was no evidence of measurable health benefits of lubricated tampons, but women preferred tampons without lubrication.

## **Basic Science**

### **Convergence of nociceptive information in the forebrain of female rats: reproductive organ response variations with stage of estrus.**

Chadha HK, Hubscher CH  
Exp Neurol. 2008 Apr;210(2):375-87.

Neurons in the preoptic area (POA) of the hypothalamus and the bed nucleus of stria terminalis (BST) play an important role in the neuroendocrine control of the reproductive cycle, mating behaviors and nociception. Single unit extracellular recordings were performed in the POA and BST region of 20 urethane anesthetized female rats during either the proestrus (elevated levels of estrogen/progesterone) or metestrus (low circulating hormones) stage of the estrous cycle. A total of 118 neurons in the POA and 65 neurons in the BST responded to the search stimuli, bilateral electrical stimulation of the viscerocutaneous branch of the pelvic nerve and/or sensory branch of the pudendal nerve (i.e., dorsal nerve of clitoris). Most of the neurons responding to the electrical search stimuli received a high degree of somatovisceral convergence, including inputs from the abdominal branches of the vagus, cervix, vagina, colon and skin territories on the perineum and trunk. Mean neuronal response thresholds for vaginal and cervical stimulation but not colon distention were significantly higher for animals tested during proestrus. Also, there was a shift in POA and BST neuronal responsiveness towards more inhibition and less excitation during proestrus for a variety of somatovisceral inputs. These data demonstrate that the changes in hormonal status affect the properties of POA and BST neurons, which likely relates not only to the functional importance of these inputs for reproductive behaviors but also for nociceptive processing as well.