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This newsletter is quarterly and contains abstracts from medical journals published between March and June 2007 (abstracts presented at scientific meetings may also be included). Please direct any comments regarding this newsletter to chris@nva.org.

Vulvodynia / Pain

Vulvovaginal Infection.
Ledger, WJ, Witkin, SS
(contains chapter on vulvodynia)

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Enhanced synthesis of proinflammatory cytokines by vulvar vestibular fibroblasts: implications for vulvar vestibulitis.
Foster DC, Piekarz KH, Murant TI, LaPoint R, Haidaris CG, Phipps RP
Am J Obstet Gynecol. 2007 Apr;196(4):346.e1-8

OBJECTIVE: The objective of the study was to determine whether vestibular fibroblasts from vulvar vestibulitis (VVS) patients produce higher proinflammatory cytokine levels when provoked with Candida albicans (yeast) and alpha-melanocyte-stimulating hormone (alpha-MSH) in vitro. STUDY DESIGN: Twenty anatomically defined fibroblast strains from patients and age-matched controls were stimulated with 5 regimens: no stimulus, alpha-MSH, heat-killed yeast, alpha-MSH plus yeast, and interleukin (IL)-1beta. Supernatant products included the following: granulocyte macrophage colony-stimulating factor, interferon-gamma, IL-10, IL-12, IL-1beta, IL-2, IL-4, IL-6, IL-8, and tumor necrosis factor-alpha were assayed. RESULTS: Coincubation with alpha-MSH plus yeast significantly increased IL-6 (3-fold) and IL-8 (greater than 40-fold) production in patients and controls. Vestibular fibroblast exceeded external vulvar fibroblast production of IL-1beta, IL-6, and IL-8 following yeast alone and alpha-MSH plus yeast stimuli in patients and controls. Substratified by anatomic origin, vestibular fibroblasts from VVS patients produced the highest relative levels of IL-1beta, IL-6, and IL-8 at baseline and following the yeast-alone regimen. CONCLUSION: Localized pain of VVS may results from regionally elevated cytokines produced by vulvar vestibule-specific fibroblasts.

Evaluation of gabapentin in the treatment of generalized vulvodynia, unprovoked.
Harris G, Horowitz B, Borgida A
J Reprod Med. 2007 Feb;52(2):103-6

OBJECTIVE: To determine the efficacy of gabapentin in the treatment of generalized vulvodynia, unprovoked, to determine the most common presenting symptoms in patients with this diagnosis, to evaluate the prevalence of comorbidities in these patients and to determine the possibility of

comorbidities or specific presenting symptoms that decrease the efficacy of this drug. STUDY DESIGN: The charts of all women seen in our facility with a diagnosis of generalized vulvodynia between January 1, 2002, and September 30, 2004, were reviewed. A total of 601 charts were reviewed. Patients were included in the study if they had a diagnosis of generalized vulvodynia, they were treated with single-agent gabapentin, had follow-up for 30 months or more and had adequately documented follow-up. RESULTS: A total of 152 patients were included in the study. Ninety-eight (64%) patients treated with gabapentin had resolution of at least 80% of their symptoms during the study period. Forty-nine (32%) did not have adequate resolution. There was a high percentage of comorbidities in patients with generalized vulvodynia. Sleep disturbance was the only comorbidity that negatively affected the efficacy of gabapentin. In addition, there appeared to be a trend toward a less favorable response in patients with a longer period of untreated illness (p value not less than 0.05). Side effects of gabapentin were few. Forty (26%) reported some side effects. Fatigue was the most common complaint. Seventeen patients (11%) discontinued the medication secondary to side effects. CONCLUSION: Gabapentin appears to be very effective in the treatment of generalized vulvodynia, unprovoked. It has a very low side effect profile. Certain patients may be less likely to benefit from gabapentin, including those with the comorbidity of sleep disturbance. Patients with symptoms of longer-standing generalized vulvodynia, unprovoked, may also be less likely to benefit from this treatment.

Effect of test order on sensitivity in vulvodynia.
Reed BD, Sen A, Gracely RH
J Reprod Med. 2007 Mar;52(3):199-206.

OBJECTIVE: To assess the effect of order of sensitivity testing at the vulva and thumb on the sensitivity determined at the second site tested among women with and without vulvodynia. STUDY DESIGN: We evaluated the stability of sensitivity measurements to pressure at the vulva and thumb when the order of testing was randomized to vulva first vs. thumb first; we repeated testing 1 week later in the opposite order. RESULTS: Stability of results over time and the influence of the order of testing were determined among 13 women with vulvodynia and 20 asymptomatic control women. We found a strong correlation between results compared between the first and second visits as well as no order effect. CONCLUSION: The order of testing at vulvar and peripheral sites has little impact on the results of pressure-responsive sensitivity testing among women with and without vulvodynia.

Effectiveness of hypnosis for the treatment of vulvar vestibulitis syndrome: a preliminary investigation.
Pukall C, Kandyba K, Amsel R, Khalife S, Binik Y
J Sex Med. 2007 Mar;4(2):417-25.

INTRODUCTION: Vulvar vestibulitis syndrome (VVS) is a common cause of vulvar pain. Therapeutic options target different pain systems believed to be involved in its development and maintenance. Most treatments target the pain component with the assumption that sexual function will increase once the pain has decreased, yet this is not necessarily the case. AIMS: Research has supported the effectiveness of hypnosis for many chronic pain disorders, and a case report demonstrated pain reduction and an increase in intercourse pleasure in a woman with VVS. This preliminary study examined the effectiveness of hypnosis on pain and psychosexual function in VVS. METHODS; Eight women suffering from VVS completed a hypnosis screening assessment, an interview, pain and psychosexual questionnaires, a gynecologic examination, vestibular pain threshold measurement, a psychosexual assessment, and six hypnotherapy sessions. The physical examinations, interview, and questionnaires were repeated at 1 and 6 months posttreatment. MAIN OUTCOME MEASURES: These included pain ratings during the gynecologic examination, vestibular pain thresholds, scores on the McGill Pain Questionnaire and Pain Catastrophizing Scale, and responses to questions on intercourse-related and nonintercourse-related pain. Measures of psychosexual function included the Female Sexual Function Index, State-Trait Anxiety Scale, Beck Depression Inventory-II, and the Brief Symptom Inventory. RESULTS: Results indicated significant decreases in gynecologic examination pain and in several measures assessing intercourse pain, and nonsignificant increases in threshold. Some indices of noncoital vulvar pain decreased. Overall

sexual function, particularly sexual satisfaction, increased at posttreatment. There were no differences on any psychological measure. Participants reported satisfaction with the treatment and rated their VVS pain reduction as average. CONCLUSIONS: Hypnotherapy appears to be a promising treatment for reducing intercourse pain and some aspects of noncoital vulvar pain, and for restoring sexual function in women with VVS. These results suggest that a large controlled trial should be considered.

Itch and burning pain in women with partial vaginismus with or without vulvar vestibulitis.
Engman M, Wijma K, Wijma B
J Sex Marital Ther. 2007 Mar-Apr;33(2):171-86

Fifty-three women with partial vaginismus with or without vulvar vestibulitis and 27 asymptomatic women estimated sensations of burning pain and itch at 20 standardized moments during a standardized penetration situation, including vaginal muscle contractions. Forty-three women with partial vaginismus (81.1%) reported burning pain, 23 (43.4%) itch, and 22 (41.5%) both complaints, compared to 0% of the asymptomatic women. In 17 of 22 cases, burning pain preceded the appearance of itch and in four cases the two complaints coincided. The median time from the moment when burning pain started until itch appeared was 150 seconds.

Effects of sexual arousal on genital and non-genital sensation: a comparison of women with vulvar vestibulitis syndrome and healthy controls.
Payne KA, Binik YM, Pukall CF, Thaler L, Amsel R, Khalife S
Arch Sex Behav. 2007 Apr;36(2):289-300. Epub 2006 Nov 30

The relationship between sexual arousal and sensory perception has been a topic largely neglected within the realm of human sexuality research. The present study assessed the influence of sexual arousal on genital and non-genital sensation in women. It also examined the theory that painful intercourse is associated with insufficient sexual arousal. A total of 20 healthy women and 20 women with Vulvar Vestibulitis Syndrome (VVS) underwent genital and non-genital sensory testing at baseline and in response to erotic and neutral stimulus films. Touch and pain thresholds were assessed at the vulvar vestibule, inside the labia minora, and on the volar surface of the forearm. Sexual arousal was assessed via the measurement of surface skin temperature changes of the labia minora using a labial thermistor clip. Participants also completed questionnaires pertaining to mood, pain, and sexual functioning. In response to the erotic stimulus, both groups evidenced a significant increase in physiological sexual arousal and vulvar sensitivity. Women with VVS reported a significantly lower desire to engage in intercourse after having viewed the erotic film and reported lower levels of desire and arousal on questionnaire measures. Women with VVS also exhibited significantly more genital and non-genital pain sensitivity than healthy women across all conditions, in addition to more catastrophizing, hypervigilance, and fear of pain. Contrary to some theories, these data suggest that women with VVS are not lacking in physiological sexual arousal, and that physiological sexual arousal may actually increase vulvar sensation. Lack of subjective sexual arousal, however, may yet be implicated in vulvar pain during intercourse.

Management of dyspareunia and associated levator ani muscle overactivity.
Fisher KA
Phys Ther. 2007 May 1; [Epub ahead of print]

BACKGROUND AND PURPOSE: Musculoskeletal dysfunction is a known cause of dyspareunia and a reason for referral for physical therapist management. The purpose of this case report is to describe the physical therapist management of a patient with dyspareunia and overactivity of the pelvic-floor muscles with a limited number of visits and a focus on self-management strategies. CASE DESCRIPTION: This case involved a 30-year-old married woman with levator ani muscle overactivity and dyspareunia that was 1 year in duration. Intervention The therapist explained the anatomy and function of the pelvic-floor muscles during intercourse, instructed the patient on how to control the levator ani muscles, and

instructed her on vaginal self-dilation techniques. OUTCOMES: The patient attended 3 physical therapy sessions over a period of 9 weeks. She performed vaginal self-dilation at home. She rated pain during intercourse as 0/10 on a verbal rating scale and had no remaining tenderness in the levator ani muscles at discharge. DISCUSSION: Some women with dyspareunia may improve with an intervention that emphasizes education and vaginal self-dilation techniques. Future research should compare home-based and clinic-based treatments.

Simultaneous measurement of pelvic floor muscle activity and vaginal blood flow: a pilot study.
Both S, Laan E
J Sex Med. 2007 May;4(3):690-701. Epub 2007 Apr 13

Introduction. Dyspareunia, defined as persistent or recurrent genital pain associated with sexual intercourse, is hypothesized to be related to pelvic floor hyperactivity and to diminished sexual arousal. Empirical research to support these hypotheses is scarce and concentrates mostly on the role of either pelvic floor activity or genital arousal in female dyspareunia. Currently, however, there is no measurement device to assess pelvic floor activity and genital response simultaneously. Aim. The aim of this study was to investigate the validity of a new device that enables simultaneous measurement of pelvic floor activity and genital response in women. Main Outcome Measures. Genital arousal measured as vaginal pulse amplitude, and vaginal surface electromyogram (EMG). Method. Thirty sexually functional women participated. To investigate the accuracy of genital response measurement with the adapted photoplethysmograph, and the sensitivity of the device for involuntary changes in pelvic floor activity, vaginal pulse amplitude and vaginal surface EMG were monitored during exposure to emotional, including erotic, films. In addition, vaginal surface EMG was monitored during instructed pelvic floor contractions. Results. The genital data obtained during emotional films proved accurate measurement of genital response. EMG values during the emotional films indicated limited sensitivity of the device for small, involuntary changes in pelvic floor activity due to emotional state. The EMG measurements during the instructed pelvic floor contractions proved sensitivity of the new probe to voluntary pelvic floor activity. Conclusion. It is concluded that following improvement of the sensitivity of the EMG measurement for small, involuntary changes in pelvic floor activity, the device will be a valuable tool in research on superficial dyspareunia.

Pudendal entrapment as an etiology of chronic perineal pain: diagnosis and treatment.
Popeney C, Ansell V, Renney K
Neurourol Urodyn. 2007 May 4; [Epub ahead of print]

AIMS: This study was conducted to evaluate pudendal entrapment as an etiology of chronic pain, a diagnostic protocol for pudendal entrapment, and clinical response to surgical decompression. METHODS: A case series of 58 consecutive patients with a diagnosis of pudendal entrapment, based on clinical factors, neurophysiologic studies, and response to pudendal nerve infiltrations, is described. All patients were refractory to other treatment modalities. Patients were assessed before and after surgical decompression: degree of pain was assessed by visual analog scale (VAS) score, percent global overall improvement, and improved function and quality of life before surgery and 12 months or longer after surgery. RESULTS: The primary presenting feature was progressive, chronic, intractable neuropathic pain in the perineum (ano-rectal and/or urogenital) that worsened with sitting. Other symptoms included urinary hesitancy, frequency, urgency, constipation/painful bowel movements, and sexual dysfunction. After surgical decompression, 35 (60%) patients were classified as responders, based on one of the following three criteria: a greater than 50% reduction in VAS score, a greater than 50% improvement in global assessment of pain, or a greater than 50% improvement in function and quality of life. CONCLUSIONS: Pudendal entrapment can be a cause of chronic, disabling perineal pain in both men and women. Since symptomatic patients seek medical care from many different medical specialists, a reliable diagnostic protocol should be established. For patients refractory to conventional interventions, surgical decompression of the pudendal nerve can improve pain-related symptoms and disability. With ongoing work on this subject, which is a difficult disorder to accurately diagnose and treat, a better awareness of pudendal entrapment across specialties will emerge.

Vulvar Dermatoses

Pimecrolimus 1% cream in the treatment of vulvar lichen sclerosus in postmenopausal women.
Oskay T, Kaya Sezer H, Genc C, Kutluay L
Int J Dermatol. 2007 May;46(5):527-32

Background: Vulvar lichen sclerosus (LS), a poorly recognized chronic inflammatory skin disease, may represent a therapeutic challenge. Pimecrolimus cream 1% is a nonsteroidal, selective inflammatory cytokine inhibitor that has recently been indicated for some inflammatory cutaneous diseases. Objective: To investigate the efficacy, tolerability, and safety of 1% pimecrolimus cream therapy in postmenopausal women with LS. Methods A total of 16 patients applied pimecrolimus cream 1% twice a day over the first 3 months and then as required. All the patients completed this study and were then followed up over the next 12 months. The symptoms and clinical appearance of the lesions in every subject were recorded before and after treatment using a severity scale. Results: Using pimecrolimus, most of the patients exhibited a significant improvement with respect to symptoms and the clinical appearance of the disease. After 3 months of treatment, complete remission was seen in 11 patients, partial remission in four, whereas one patient experienced no response at all. Over the subsequent 12 months of follow-up, 10 patients exhibited complete remission while five had partial remission. Four cases with complete remission experienced a few relapses during the follow-up period. Older patients and those with an advanced stage of the disease responded poorly. No significant side effects were observed. Conclusions: Pimecrolimus cream 1% appears to be an effective and well-tolerated therapeutic alternative option in the treatment of early stage of vulvar LS. Pimecrolimus may reduce the incidence of flare ups, improve long-term disease control, and enhance the patients' quality of life, especially in postmenopausal women.

Open-label trial of cyclosporine for vulvar lichen sclerosus.
Bulbul Baskan E, Turan H, Tunali S, Toker SC, Saricaoglu H
J Am Acad Dermatol. 2007 Apr 16; [Epub ahead of print]

BACKGROUND: Lichen sclerosus (LS) is a chronic inflammatory disease of skin and mucosal surfaces which is generally difficult to treat. OBJECTIVE: We evaluated the efficacy of oral cyclosporine in refractory vulvar LS. METHODS: Five patients with refractory vulvar LS were treated with oral cyclosporine (3-4 mg/kg/d) for 3 months. They were followed up on a monthly basis. RESULTS: At the end of the treatment, the mean total symptom score regressed significantly and clinical findings such as erythema and erosion showed marked improvement. Mild adverse effects were seen in 3 patients. LIMITATIONS: The patients did not give consent to rebiopsy at the end of the treatment. CONCLUSION: Moderate dose of oral cyclosporine could be an effective alternative in the treatment of refractory vulvar LS.

Detection of perforin and granzyme B mRNA expressing cells in lichen sclerosus.
Hunger RE, Bronnimann M, Kappeler A, Mueller C, Braathen LR, Yawalkar N
Exp Dermatol. 2007 May:16(5):416-20

Granzyme B and perforin messenger RNA (mRNA) expression has been shown to be a specific in vivo activation marker for cytotoxic cells. The aim of this study was to assess the contribution of cell-mediated cytotoxicity in the pathogenesis of lichen sclerosus. In situ hybridization and immunohistochemistry were performed on serial tissue sections of lesional skin biopsies and normal skin as control. Immunohistochemical staining showed that the cellular infiltrate of diseased skin consisted predominantly of T cells (CD3+) and some B cells (CD20+). Among T cells CD4+ and CD8+ cells were found in about equal numbers. In normal skin samples perforin and granzyme B mRNA expressing cells were only rarely found. In contrast, in biopsies from diseased skin a high percentage of infiltrating cells expressed mRNA for perforin and granzyme B. The perforin and granzyme B expressing cells were found in the dermal infiltrate and intraepidermally in close proximity to keratinocytes suggesting in situ activation of these

cells. These findings provide evidence that cell-mediated cytotoxicity plays a significant role in tissue destruction in lichen sclerosus.

Infectious Disease

Mannose-binding lectin gene polymorphism, vulvovaginal candidiasis, and bacterial vaginosis.
Giraldo PC, Babula O, Goncalves AK, Linhares IM, Amaral RL, Ledger WJ, Witkin SS
Obstet Gynecol. 2007 May;109(5):1123-1128

OBJECTIVE: To evaluate associations between polymorphisms in the gene coding for mannose-binding lectin (MBL) and the diagnosis of acute or recurrent vulvovaginal candidiasis and bacterial vaginosis METHODS: Women at two outpatient clinics in Brazil filled out a questionnaire and were examined for the presence of vulvovaginal candidiasis or bacterial vaginosis. A buccal swab was blindly tested for codons 54 and 57 MBL2 gene polymorphisms by polymerase chain reaction and endonuclease digestion. RESULTS: A total of 177 women were enrolled. Vulvovaginal candidiasis was identified in 78 (44.1%) women, 33 (18.6%) had bacterial vaginosis, and 66 (37.3%) were normal controls. Recurrent vulvovaginal candidiasis was present in 50 (64.1%) of the women with vulvovaginal candidiasis; 20 (60.6%) of the bacterial vaginosis patients had recurrent disease. Vulvovaginal candidiasis was associated with white race (P=.007), bacterial vaginosis was associated with nonwhite race (P=.05), and both were associated with a history of allergy (P</=.02) and having sexual intercourse at least three times a week (P<.001). Carriage of the variant MBL2 codon 54 allele B was more frequent in women with recurrent vulvovaginal candidiasis (25.0%) than in the women with acute vulvovaginal candidiasis (17.9%) or controls (10.6%) (P=.004). Allele B was also more prevalent in women with recurrent bacterial vaginosis (22.5%) than in those with acute bacterial vaginosis (0%) (P=.009). The MBL2 codon 57 polymorphism was infrequent and not associated with vulvovaginal candidiasis or bacterial vaginosis. CONCLUSION: The incidence of vulvovaginal candidiasis and bacterial vaginosis differs by ethnicity in Brazilian women. The MBL2 codon 54 gene polymorphism is associated with both recurrent vulvovaginal candidiasis and recurrent bacterial vaginosis. LEVEL OF EVIDENCE: III.

Rapid testing for vaginal yeast detection: a prospective study.
Chatwani AJ, Mehta R, Hassan S, Rahimi S, Jeronis S, Dandolu V
Am J Obstet Gyencol. 2007 Apr;196(4):309.e1-4

OBJECTIVE: The purpose of this study was to determine the accuracy of rapid vaginal yeast detection assay compared with yeast cultures for the diagnosis of vulvovaginal candidiasis. STUDY DESIGN: This was a prospective study that involved 104 subjects, 34 asymptomatic women and 70 symptomatic women with vaginitis. Vaginal swabs were obtained from all subjects for wet mount, yeast culture, and the rapid yeast detection test. Overall, the prevalence rate was 39.4%, based on positive yeast cultures. The rapid yeast test performed by the physician was positive in 30 of 41 subjects with positive cultures and 13 of 63 subjects with negative cultures. RESULTS: The rapid yeast test had 73.1% sensitivity and 82.0% negative predictive value compared with the wet mount, which had 43.9% sensitivity and 70.9% negative predictive value. In symptomatic patients, the test had 77.4% sensitivity and 81% negative predictive value compared with wet mount, which had 51.6% sensitivity. Patient-performed test results were identical to the tests that were performed by the physicians. The cost of the rapid yeast test kit is estimated to be <$10, compared with a mean of $65 for the yeast culture. CONCLUSION: Rapid yeast detection assay is accurate and affordable compared with the gold standard yeast culture in the diagnosis of vulvovaginal candidiasis. Relative to the wet mount, it is more sensitive, cheaper, and accurate for the rapid diagnosis of vaginal yeast infection.

Clinical aspects and luteal phase assessment in patients with recurrent vulvovaginal candidiasis.
Spacek J, Buchta V, Jilek P, Forstl M
Eur J Obstet Gynecol Reprod Biol. 2007 Apr;131(2):198-202. Epub 2006 May 9

OBJECTIVE: This study was undertaken to characterize the patients with recurrent vulvovaginal candidiasis. STUDY DESIGN: Basic data of personal history and history of recurrent vulvovaginal candidiasis, lower genital tract symptoms and signs in 50 patients were analyzed in this longitudinal follow-up study including the determination of midluteal serum progesterone and urinary pregnanediol levels during the luteal phase in 84 cycles (recurrent vulvovaginal candidiasis) and 60 cycles (healthy controls). RESULTS: All patients suffered primary idiopathic form of recurrent vulvovaginal candidiasis. Frequently, there was a striking discrepancy between severe symptoms and clinical finding, which was often negligible or normal. There was no redness and no or minimum discharge in 52% of culture documented attacks. In contrast to the healthy controls, the patients had significantly lower levels of progesterone ($p<0.01$) as well as those of urinary pregnanediol ($p<0.05$). CONCLUSION: Culture positive attacks in patients with recurrent vulvovaginal candidiasis represented rather a form of vulvovaginal discomfort than attacks of vulvovaginal candidiasis with typical inflammatory changes. Significantly lower progesterone levels in the RVVC patients as compared to the healthy controls suggest a link between an altered hormonal status and one of possible causes of RVVC in these women.

Basic Science

None.