NVA RESEARCH UPDATE NEWSLETTER
September 2007

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This newsletter has been supported, in part, through a grant from the **Enterprise Rent-A-Car Foundation**.

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

Vulvodynia / Pain

The result of treatment on vestibular and general pain thresholds in women with provoked vestibulodynia.
Bohm-Starke N, Brodda-Jansen G, Linder J, Danielsson I
Clin J Pain. 2007 Sep;23(7):598-604

OBJECTIVE: To correlate changes in vestibular pain thresholds to general pain thresholds in a subgroup of women with provoked vestibulodynia taking part in a treatment study. METHODS: Thirty-five women with provoked vestibulodynia were randomized to 4 months' treatment with either electromyographic biofeedback (n=17) or topical lidocaine (n=18). Vestibular and general pressure pain thresholds (PPTs) were measured and the health survey Short Form-36 (SF-36) was filled out before treatment and at a 6-month follow-up. Subjective treatment outcome and bodily pain were analyzed. Thirty healthy women of the same age served as controls for general PPTs and SF-36. RESULTS: No differences in outcome measures were observed between the 2 treatments. Vestibular pain thresholds increased from median 30 g before to 70 g after treatment in the anterior vestibule (P<0.001) and from median 20 to 30 g in the posterior vestibule (P<0.001). PPTs on the leg and arm were lower in the patients as compared with controls both before and at the 6-month follow-up. Patients reporting total cure were 3/35; 25/35 were improved. The number of patients who frequently reported of other bodily pain was reduced after the treatment. The patients had lower scores for SF-36 (General Health, Vitality) before treatment, which was restored at the 6-month follow-up. DISCUSSION: Treating provoked vestibulodynia by either topical lidocaine or electromyographic biofeedback increased vestibular pain thresholds, reduced dyspareunia, and improved bodily pain. The patients showed a general hypersensitivity to pressure pain compared with controls and in this study the hypersensitivity did not seem to be affected by treating the superficial dyspareunia.

Vulvar vestibulitis and risk factors: a population-based case-control study in Oslo.
Edgardh K, Abdelnoor M
Acta Derm Venereol. 2007;87(4):350-4

Vulvar vestibulitis is a major cause of entry dyspareunia in young women. The aim of this study was to evaluate a self-reported history of bacterial vaginosis, candidiasis, use of oral contraception and nulli-pregnancy as risk factors for vestibulitis. A retrospective examination of medical records was performed for 45 patients with vestibulitis from a vulvar clinic in Oslo, median age 24 years, age range 19-49 years. Four controls per case were selected randomly from the same Oslo source population as the cases. Age-matching was not performed, as matching does not control for confounding in the case-control design. Controls anonymously answered a postal questionnaire, response rate 61%. The crude effect for the major potential predictors for vulvar vestibulitis was estimated, and stratification on age for the major

potential predictors. The method of Mantel Haenszel was used to quantify confounders, and control for multi-confounders and the gradient effect of different covariates was performed. The major confounder was age. Independent risk factors for vestibulitis were nulli-pregnancy, odds ratio (OR) 8.4 (95% confidence interval (CI) 2.8-25.2) and bacterial vaginosis, OR 3.37 (95% CI 1.06-10.6). Adjusting for age diluted the effect of oral contraception and frequent treatment for candidiasis. This study is the third case-control study identifying bacterial vaginosis as a risk factor for vestibulitis. Thus, it remains to be investigated whether abnormal vulvo-vaginal microbiota belongs to the aetiology of vulvar vestibulitis.

Predictors of genital pain in young women.
Farmer MA, Meston CM
Arch Sex Behav. 2007 Aug 3; [Epub ahead of print]

Despite the high prevalence of genital pain in healthy young adult women, limited research has addressed genital pain during intercourse using contemporary models of multidimensional sexual function. The objectives of this study were threefold: (1) to identify differences in sexual functioning in women who experience genital pain compared to pain free women; (2) to identify predictors of sexual functioning in women with and without genital pain; and (3) to identify predictors of sexual satisfaction in women with and without genital pain. Sexually active female undergraduates (n = 651) were administered the Female Sexual Function Index and the Derogatis Sexual Functioning Inventory. We evaluated the sexual factors that impact the sexual function of women with any pain (including high and low pain groups) versus women with no history of pain. Women with genital pain reported greater rates of sexual dysfunction as compared to pain-free women; however, sexual functioning in the high versus low pain groups was distinguished primarily by vaginal lubrication. Women in the high pain group showed negative correlations between domains of sexual satisfaction and genital pain frequency and intensity that were not found in the low pain group. For pain-free women, intercourse played a strong role in sexual satisfaction, whereas non-intercourse sexual behavior was central to sexual satisfaction in women who reported pain. The evaluation of levels of genital pain may provide insight into the mechanisms underlying the impairment of sexual function, sexual behavior, and sexual satisfaction.

Vulvostomatodynia.
Petruzzi M, De Benedittis M, Pastore L, Serpico R
Maturitas. 2007 Sep 20;58(1):102-6. Epub 2007 Jun 29

Burning mouth syndrome associated to vulvodynia (Vulvostomatodynia) is a rare condition and is often difficult to diagnose and treat. Tongue, lips, vestibule and others mucosal sites may be affected by a tiresome burning sensation, especially in menopausal and postmenopausal women. Patients seldom report genital symptoms to the dentist and dentists do not generally investigate about genital symptoms. Delays in diagnosis may affect the quality of life. We report the clinical features of five new cases of vulvostomatodynia. A thorough multidisciplinary medical management is necessary to improve symptoms and prevent from psychologic distress. Counselling and an understanding between patient and clinician/therapist are important for long-term results.

Is localized, provoked vulvodynia an inflammatory condition?
Eva LJ, Rolfe KJ, MacLean AB, Reid WM, Fong AC, Crow J, Perrett CW
J Reprod Med. 2007 May;52(5):379-84

OBJECTIVE: To perform a pilot study to investigate the relationship between localized, provoked vulvodynia of the vestibule and inflammatory cytokine expression. STUDY DESIGN: Women with a diagnosis of localized, provoked vulvodynia had tissue samples taken for vulvar expression of Interleukin 1alpha and 1beta and tumor necrosis factor alpha and compared to those of a control group. RESULTS: The study group did not show a significant increase in expression of inflammatory markers. CONCLUSION: There was no evidence in this study that localized, provoked vulvodynia is an inflammatory condition, as previously thought. This may be helpful in explaining why some women are

resistant to medical or antiinflammatory treatment and may allow treatment to be prescribed more effectively.

Pregabalin-induced remission in a 62-year-old woman with a 20-year history of vulvodynia.
Jerome L
Pain Res Manag. 2007 Autumn;12(3):212-4

A case of a 62-year-old woman presenting with a 20-year history of vulvodynia previously unresponsive to medical treatment is described. The epidemiology, phenomenology and medical management of vulvodynia is reviewed. The case presentation illustrates the role of pregabalin in successful medical management of this chronic pain disorder, as well as the management of common psychiatric morbidities associated with this condition.

Human papillomavirus in vulvar vestibulitis syndrome.
Gaunt G, Good AE, McGovern RM, Stanhope CR, Gostout BS
J Reprod Med. 2007 Jun;52(6):485-9

OBJECTIVE: To investigate the prevalence of human papillomavirus (HPV) in patients with vulvar vestibulitis syndrome by using a recently developed polymerase chain reaction (PCR) primer set that detects known papillomavirus types. STUDY DESIGN: We retrospectively identified 38 patients with vulvar vestibulitis who underwent therapeutic surgical excision of the vestibule. Eleven controls without vestibulitis who underwent vestibular excision for conditions unrelated to HPV infection were identified prospectively. Surgical specimens were examined for the presence of HPV DNA by PCR amplification. DNA sequencing was used to determine HPV type. RESULTS: The prevalence of HPV among patients with vestibulitis was 21% vs. 36% among controls. Group B HPV types accounted for 4 of the 10 (40%) HPV types found in patients with vestibulitis. Overall, in both patient and control samples, a spectrum of HPV types was identified, encompassing many branches of the HPV phylogenetic tree. No etiologic association was apparent. CONCLUSION: This study did not support an association of HPV with vulvar vestibulitis. The low rate of observed infection in women with and without vestibulitis and the diversity of HPV types identified suggest incidental virus carriage rather than direct cause and effect. The underlying cause of this debilitating condition remains unknown.

Prevalence and genotyping of human papillomavirus infection in women with vulvodynia.
Orlandi A, Francesconi A, Angeloni C, Palmieri G, Fulvia G, Ciotti M, Criscuolo A, Sesti F, Spagnoli LG
Acta Obstet Gynecol Scand. 2007;86(8):1003-10

Background. Evidence of vulvar human papillomavirus infection varies and the frequency of the different genotypes has not been adequately assessed. Methods. Fifty consecutive sexually active healthy patients with vulvodynia and suspected of human papillomavirus infection underwent a vulvoscopy and biopsy. Ten normal vulvar samples were also enrolled as control. Histological and vulvoscopic findings were compared in relation to human papillomavirus-DNA presence and genotyping by a broad-spectrum polymerase chain reaction and reverse hybridization line probe assay. Results. Although the clinical and histological diagnoses did not always coincide, a good association was found ($p<0.0001$). Human papillomavirus-DNA was detected in 42% of all biopsies and in none of the controls, and less frequently in acetowhite-positive patients (33.3%, $p<0.03$). Squamous papillomatosis (74%) was the most frequent histological diagnosis, followed by condyloma (20%). Condyloma (90%) but not squamous papillomatosis (29.7%) was significantly associated with human papillomavirus-DNA presence. Out of the vulvoscopically normal patients, one (33%) was human papillomavirus-DNA positive. Out of the recorded microscopic features, only koilocytosis was associated with human papillomavirus-DNA presence. Eight different human papillomavirus genotypes were detected: high-risk 16 (43%), 31 (19%), 52 (14.3%), 68, and 59 (4.8% each), and low-risk types 6 (71.4%), 11, and 40 (4.8% each); 33.3% of infections were multiple, ranging from 2 to 4 genotypes. Out of the human papillomavirus-DNA positive squamous papillomatosis, 72.7% showed a high-risk type but the infection remained episomal. Conclusions. Our

data confirm human papillomavirus as a frequent cause of vulvodynia and its frequent association with squamous papillomatosis or condyloma. The high-risk human papillomavirus in squamous papillomatosis suggests screening for possible undiagnosed cervical infection.

The biochemical origin of pain: The origin of all pain is inflammation and the inflammatory response. Part 2 of 3 - Inflammatory profile of pain syndromes.
Omoigui S
Med Hypotheses. 2007 Aug 27; [Epub ahead of print]

Every pain syndrome has an inflammatory profile consisting of the inflammatory mediators that are present in the pain syndrome. The inflammatory profile may have variations from one person to another and may have variations in the same person at different times. The key to treatment of Pain Syndromes is an understanding of their inflammatory profile. Pain syndromes may be treated medically or surgically. The goal should be inhibition or suppression of production of the inflammatory mediators and inhibition, suppression or modulation of neuronal afferent and efferent (motor) transmission. A successful outcome is one that results in less inflammation and thus less pain. We hereby briefly describe the inflammatory profile for several pain syndromes including arthritis, back pain, neck pain, fibromyalgia, interstitial cystitis, migraine, neuropathic pain, complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD), bursitis, shoulder pain and vulvodynia. These profiles are derived from basic science and clinical research performed in the past by numerous investigators and serve as a Foundation to be built upon by other researchers and will be updated in the future by new technologies such as magnetic resonance spectroscopy. Our unifying theory or law of pain states: the origin of all pain is inflammation and the inflammatory response. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response. Activation of pain receptors, transmission and modulation of pain signals, neuro plasticity and central sensitization are all one continuum of inflammation and the inflammatory response. Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arise from inflammation and the inflammatory response. We are proposing a re-classification and treatment of pain syndromes based upon their inflammatory profile.

Vulvar Dermatoses

Open-label trial of cyclosporine for vulvar lichen sclerosus.
Bulbul Baskan E, Turan H, Tunali S, Toker SC, Sarifcaoglu H
J Am Acad Dermatol. 2007 Aug;57(2):276-8. Epub 2007 Apr 17

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.

A comparative analysis of lichen sclerosus of the vulva and lichen sclerosus that evolves to vulvar squamous cell carcinoma.
Raspollini MR, Asirelli G, Moncini D, Taddei GL
Am J Obstet Gynecol. 2007 Aug 20; [Epub ahead of print]

OBJECTIVE: The aim of this study was to determine whether the premalignant change in lichen sclerosus (LS) could be identified with immunohistochemical analyses. STUDY DESIGN: Eight cases of histologically diagnosed vulvar LS, which showed, after a period of 10 months-9 years, an evolution to carcinoma of the vulva that was histologically documented, were compared with 8 cases of vulvar LS, for which follow-up information was available for at least 9 years. The proliferative index and the expression of tumor suppressors p16 and p53 were analyzed. RESULTS: The difference of MIB1 labeling index of evolving or unchanged LS cases was significant (P = .005). The difference in the p53 of evolving or unchanged LS cases shows a trend towards association (P = .08). Both LS cases (evolving or unchanged) did not show p16 positive staining. CONCLUSION: The evaluation of MIB1 and p53 may identify those vulvar LS cases with a high likelihood of evolving into squamous cell carcinoma, which would need careful periodic checks or adjunctive biopsies. The study must be confirmed by a larger number of cases to substantiate this observation.

The role of angiogenesis and COX-2 expression in the evolution of vulvar lichen sclerosus to squamous cell carcinoma of the vulva.
Raspollini MR, Asirelli G, Taddei GL
Gynecol Oncol. 2007 Jun 7; [Epub ahead of print]

OBJECTIVES.: We aimed to determine whether premalignant changes in vulvar lichen sclerosus (LS) could be identified by analysing markers of angiogenesis and the expression of the enzyme cyclooxygenase-2 (COX-2). METHODS.: Eight cases of histologically diagnosed vulvar LS, which showed an evolution to carcinoma of the vulva histologically documented, were compared to 10 cases of vulvar LS, for which follow-up information was available for at least 9 years, and to 10 cases of LS adjacent to squamous cell carcinoma (SCC) of the vulva. The microvessel density (MVD), and the expression of vascular endothelial growth factor (VEGF) and of COX-2 were analysed. RESULTS.: Difference of MVD between unchanged LS cases and LS cases evolving to SCC and LS adjacent to SCC cases was statistically significant (P=0.008, Wilcoxon Mann-Whitney test). Difference of VEGF and COX-2 expression between unchanged LS cases and LS cases evolving to SCC and LS adjacent to SCC cases were statistically significant (P=0.007 and P=0.01, respectively; Fisher's exact test). CONCLUSIONS.: Our study addresses the possibility that immunohistochemical studies may add information to permit the identification of LS as a precursor lesion that has a greater potential to evolve into SCC. These data may identify characteristics of vulvar LS disclosing alterations that indicate the further development to cancer; therefore, it may allow the identification of a group of LS patients who need a careful follow-up and adjunctive biopsies.

Infectious Disease

Vulvovaginal candidosis.
Sobel JD
Lancet. 2007 Jun 9;369(9577):1961-71

Despite therapeutic advances, vulvovaginal candidosis remains a common problem worldwide, affecting all strata of society. Understanding of anti-candida host defence mechanisms in the vagina has developed slowly and, despite a growing list of recognised risk factors, a fundamental grasp of pathogenic mechanisms continues to elude us. The absence of rapid, simple, and inexpensive diagnostic tests continues to result in both overdiagnosis and underdiagnosis of vulvovaginal candidosis. I review the epidemiology and pathogenesis of this infection, and also discuss management strategies.

Comprehensive review of conventional and non-conventional methods of management of recurrent vulvovaginal candidiasis.
Watson C, Calabretto H
Aust N Z J Obstet Gynaecol. 2007 Aug;47(4):262-72

Recurrent vulvovaginal candidiasis (VVC) is a condition what causes women a great deal of discomfort, inconvenience, and sometimes has psychological sequelae.(1) This condition is notoriously difficult to manage. Conventional management is generally favoured by medical practitioners. Some practitioners prefer not to offer other options because of significant possible side-effects and the lack of research supporting alternative treatments. There are many studies and much available information surrounding uncomplicated VVC, including two systematic reviews.(2,3) In the area of recurrent VVC however, quality conclusive studies are scarce, and recurrent VVC is featured infrequently in randomised controlled trials (RCTs). Systematic reviews that strongly support a particular pharmacological method of conventional management of recurrent VVC over another are absent from medical literature. Recommendations are largely formed on the basis of scanty RCTs and expert opinion. There is even less conclusive evidence in the area of alternative therapies; yet despite this, anecdotally many practitioners (both alternative and mainstream) continue to advocate certain treatments in the absence of any reliable cure that can be confidently prescribed. As the use of methods other than mainstream medicine becomes more widespread, it is important to be aware of both conventional and non-conventional management of recurrent vulvovaginal candidiasis. Practitioners need to ascertain their patient's preference and treatment history. It is difficult to find comprehensive literature assessing both approaches. Giving women the most up-to-date and relevant information, and different management options, is essential in allowing them to make informed decisions. This review critically assesses both mainstream and less conventional approaches in the management of recurrent VVC.

Basic Science

Organ crosstalk modulates pelvic pain.
Rudick CN, Chen MC, Mongiu AK, Klumpp DJ
Am J Physiol Regul Integr Comp Physiol. 2007 Jul 11; [Epub ahead of print]

Interstitial cystitis (IC) is a chronic bladder inflammatory disease of unknown etiology that is often regarded as a neurogenic cystitis. IC is associated with urothelial lesions, voiding dysfunction, and pain in the pelvic/perineal area, and diet can exacerbate IC symptoms. Here, we used a murine neurogenic cystitis model to investigate the development of pelvic pain behavior. Neurogenic cystitis was induced by the injection of Barthas strain of pseudorabies virus (PRV) into the abductor caudalis dorsalis tail base muscle of female C57BL/6J mice. Infectious PRV virions were isolated only from the spinal cord, confirming the centrally-mediated nature of this neurogenic cystitis model. Pelvic pain was assessed using von Frey filament stimulation to the pelvic region, and mice infected with PRV developed progressive pelvic pain. Pelvic pain was alleviated by 2% lidocaine instillation into either the bladder or the colon but not following lidocaine instillation into the uterus. The bladders of PRV infected mice showed markers of inflammation and increased vascular permeability compared to controls. In contrast, colon histology was normal and vascular permeability was unchanged, suggesting that development of pelvic pain was due only to bladder inflammation. Bladder-induced pelvic pain was also exacerbated by colonic administration of a sub-threshold dose of capsaicin. These data indicate organ crosstalk in pelvic pain and modulation of pain responses by visceral inputs distinct from the inflamed site. Furthermore, these data suggest a mechanism by which dietary modification benefits pelvic pain symptoms. Key words: bladder, interstitial cystitis, pain, diet.

Innervation of the levator ani muscles: description of the nerve branches to the pubococcygeus, iliococcygeus, and puborectalis muscles.

Grigorescu BA, Lazarou G, Olson TR, Downie SA, Powers K, Greston WM, Mikhail MS

Int Urogynecol J Pelvic Floor Dysfunct. 2007 Jun 13; [Epub ahead of print]

We described the innervation of the levator ani muscles (LAM) in human female cadavers. Detailed pelvic dissections of the pubococcygeus (PCM), iliococcygeus (ICM), and puborectalis muscles (PRM) were performed on 17 formaldehyde-fixed cadavers. The pudendal nerve and the sacral nerves entering the pelvis were traced thoroughly, and nerve branches innervating the LAM were documented. Histological analysis of nerve branches entering the LAM confirmed myelinated nerve tissue. LAM were innervated by the pudendal nerve branches, perineal nerve, and inferior rectal nerve (IRN) in 15 (88.2%) and 6 (35.3%) cadavers, respectively, and by the direct sacral nerves S3 and/or S4 in 12 cadavers (70.6%). A variant IRN, independent of the pudendal nerve, was found to innervate the LAM in seven (41.2%) cadavers. The PCM and the PRM were both primarily innervated by the pudendal nerve branches in 13 cadavers (76.5%) each. The ICM was primarily innervated by the direct sacral nerves S3 and/or S4 in 11 cadavers (64.7%).