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This newsletter is quarterly and contains abstracts from medical journals published between March and June 2009. Abstracts presented at scientific meetings may also be included. Please direct any comments regarding this newsletter to chris@nva.org.

Vulvodynia/Pain

Investigation of the sensitivity of a cross-polarized light visualization system to detect subclinical erythema and dryness in women with vulvovaginitis.
Farage MA, Singh M, Ledger WJ
Am J Obstet Gynecol.2009 Apr 22. [Epub ahead of print]

OBJECTIVE: An enhanced visualization technique using polarized light (Syris v600 enhanced visualization system; Syris Scientific LLC, Gray, ME) detects surface and subsurface (approximately 1 mm depth) inflammation. We sought to compare the Syris v600 system with unaided visual inspection and colposcopy of the female genitalia. STUDY DESIGN: Erythema and dryness of the vulva, introitus, vagina, and cervix were visualized and scored by each method in patients with and without vulvitis. RESULTS: Subsurface visualization was more sensitive in detecting genital erythema and dryness at all sites whether or not symptoms were present. Subsurface inflammation of the introitus, vagina, and cervix only was detected uniquely in women with vulvar vestibulitis syndrome (VVS). A subset of women presenting with VVS exhibited subclinical inflammation of the vulva vestibule and vagina (designated VVS/lichen sclerosus subgroup). CONCLUSION: Enhanced visualization of the genital epithelial subsurface with cross-polarized light may assist in diagnosing subclinical inflammation in vulvar conditions heretofore characterized as sensory syndromes.

Polymorphism in a gene coding for the inflammasome component NALP3 and recurrent vulvovaginal candidiasis in women with vulvar vestibulitis syndrome.
Lev-Sagie A, Prus D, Linhares IM, Lavy Y, Ledger WJ, Witkin SS
Am J Obstet Gynecol. 2009 Mar;200(3):303.e1-6.

OBJECTIVE: Patients with vulvar vestibulitis syndrome (VVS) and control subjects were tested for a polymorphism in the gene coding for the NALP3 component of inflammasomes, cytoplasmic structures regulating interleukin (IL)-1beta production. STUDY DESIGN: DNA from 143 women with VVS and 182 control women were tested for a length polymorphism in intron 4 of the gene (CIAS1) that codes for NALP3. Vestibular tissue was examined for NALP3 expression. Whole blood cultures were tested for Candida albicans-induced IL-1beta production. RESULTS: The allele 12 frequency was higher in control subjects than in the patients with VVS (P = .02). Among patients with VVS and a self-reported history of recurrent vulvovaginal candidiasis (RVVC), the allele 7 frequency was 43.9% as compared with 30.8% in patients with no history of RVVC and 26.9% in control women (P = .035 vs other patients and .001 vs control subjects). NALP3 was identified in vestibular tissue. C albicans-induced IL-1beta production was reduced in samples from women with the 7,7 genotype (P = .030). CONCLUSION: Polymorphism in the CIAS1 gene may play a central role in the triggering of VVS in a subset of patients.

The tampon test for vulvodynia treatment outcomes research: reliability, construct validity, and responsiveness.
Foster DC, Kotok MB, Huang LS, Watts A, Oakes D, Howard FM, Stodgell CJ, Dworkin RH
Obstet Gynecol. 2009 Apr;113(4):825-32.

OBJECTIVE: A standardized tampon insertion and removal test, the Tampon Test provides an alternative to sexual intercourse pain as an outcome measure for vulvodynia research. We report upon the reliability, validity, and responsiveness to change of the Tampon Test as an outcome measure for vulvodynia clinical trials. METHODS: Outcome measures were assessed in women enrolled in the Vulvar Vestibulitis Clinical Trial, a randomized clinical trial of oral desipramine and topical lidocaine effectiveness. Reliability estimates of the Tampon Test using the Kappa statistic evaluated week-to-week measures at baseline. Tampon Test construct and discriminant validity were assessed through correlation with other outcome measures. Patients' ability to regularly perform the Tampon Test was compared with regularity of reporting intercourse pain. RESULTS: During the 2-week baseline phase, women with vulvodynia reported stable mean Tampon Test scores 4.6+/-2.6 (week -2); 4.6+/-2.7 (week -1); and 4.7+/-2.8 (week 0) with moderate week-to-week reliability (weighted Kappa 0.52). Over an 8-week phase of trial intervention, change in the Tampon Test measure significantly correlated to a number of outcome measures, including daily pain (r=0.42), intercourse pain (r=0.35), cotton swab vestibular pain (r=0.38), and the Brief Pain Inventory (r=0.49). Women with vulvodynia study participants performed the Tampon Test 96.3% of the requested time, which was twofold higher adherence than intercourse pain measurement (49.7%). CONCLUSION: The Tampon Test reflects a real life experience that is reliable, with good construct validity as shown by the breadth of correlated outcome measures. The Tampon Test is an appropriate outcome measure for vulvodynia research that can be considered for use as the primary efficacy endpoint in clinical trials of treatments for vulvodynia. LEVEL OF EVIDENCE: II.

Pain ratings, sensory thresholds, and psychosocial functioning in women with provoked vestibulodynia.
Sutton KS, Pukall CF, Chamberlain S
J Sex Marital Ther. 2009;35(4):262-81.

Psychosocial and psychophysical functioning in 25 women with and 25 without provoked vestibulodynia (PVD) were examined. Participants underwent quantitative sensory testing and completed psychosocial measures. Women with PVD displayed lower pain thresholds, higher pain ratings, lower sexual functioning and sexual self-efficacy, and higher levels of somatization and catastrophization than controls. Lower psychosocial functioning correlated with decreased vulvar pressure-pain threshold and increased cotton-swab test pain ratings. For PVD women, decreased sexual function and sexual self-efficacy were associated with higher vulvar pressure-pain ratings. Findings suggest that women with PVD would benefit from treatment that addresses pain-focused and psychosocial components.

A prospective study of pelvic floor physical therapy: Pain and psychosexual outcomes in provoked vestibulodynia.
Goldfinger C, Pukall CF, Gentilcore-Saulnier E, McLean L, Chamberlain S
J Sex Med. 2009 April 28 [Epub ahead of print]

Introduction. Research suggests that increased tension in the pelvic floor muscles of women with provoked vestibulodynia (PVD, the most common form of chronic vulvar pain) may play an important role in maintaining and exacerbating their pain. However, no prospective studies of pelvic floor physical therapy (PFPT) for PVD have been carried out. Aim. This study prospectively examined the effectiveness of a PFPT intervention in treating the pain and sexual and psychological components of PVD, and determined predictors of greater treatment success. Methods. Thirteen women with PVD completed eight sessions of PFPT. Participants were assessed at pre- and post-treatment via gynecological examinations, vestibular pain threshold testing, structured interviews, and standardized questionnaires. A 3-month follow-up interview assessed any further changes. Main Outcome Measures. Outcome measures included: vestibular pain thresholds, gynecological examination and intercourse pain ratings, sexual

function and intercourse frequency, mental health, negative pain cognitions, and success rates. Results. Following treatment, participants had significantly higher vestibular pain thresholds and significantly lower pain ratings during the gynecological examination. Participants reported significant reductions in pain intensity during intercourse and were able to engage in significantly more pain-free activities. Although overall sexual function significantly improved, various components of sexual function and frequency of intercourse did not. Participants' mental health did not significantly improve; however, pain catastrophizing and pain-related anxiety significantly decreased. The treatment was considered to be successful for 10 of the 13 participants, and predictors of greater treatment success included greater reductions in helplessness and a longer period of time in treatment. Conclusions. Results provide preliminary support for the effectiveness of PFPT in treating the pain of PVD, as well as some of the sexual and cognitive correlates of PVD. The results also indicate the need for large-scale, randomized studies of the effectiveness of PFPT in comparison and in conjunction with other treatment options.

Open-label trial of lamotrigine focusing on efficacy in vulvodynia.
Meltzer-Brody SE, Zolnoun D, Steege JF, Rinaldi KL, Leserman J
J Reprod Med. 2009 Mar;54(3):171-8.

OBJECTIVE: Chronic pelvic pain (CPP) affects 15% of women and has a high rate of psychiatric comorbidity. Vulvodynia, a vulvar pain syndrome that includes vulvar vestibulitis, is the most common subtype of CPP. This study examined the efficacy of lamotrigine for the treatment of CPP using an open-label design. STUDY DESIGN: Forty-three women with CPP were recruited from a specialty pelvic pain clinic. Of these, 31 completed 8 weeks of active treatment. Outcome variables included the McGill Pain Rating Index and subscales of pain intensity and the Hamilton Depression and Anxiety Rating Scales. RESULTS: We found significant reductions in all pain and mood measures at the 8-week visit compared to baseline. In particular, women with vulvodynia-type CPP (N = 17) had robust reductions in pain and mood symptoms. CONCLUSION: CPP is a heterogeneous disorder, with psychiatric comorbidity and poor treatment response. This open-label study suggests that treatment with lamotrigine in women with the vulvodynia subtype of CPP may be helpful in addressing both the pain and mood symptoms associated with this disorder.

Gynecological indications for the use of botulinum toxin in women with chronic pelvic pain.
Abbott J
Toxicon. 2009 Mar 3. [Epub ahead of print]

Chronic pelvic pain in women is a common symptom with a wide variety of etiologies that demand accurate diagnosis and appropriate treatment if pain reduction is to be effected. Superficial conditions such as provoked vestibulodynia and problems affecting deeper structures such as pelvic floor muscle spasm are difficult to treat and can have significant impacts on quality of life for the sufferer. Apart from daily pain, symptoms such as painful intercourse (dyspareunia), painful bowel motions (dyschesia) and exacerbation of period pain (dysmenorrhea) are commonly reported by patients. For inflammatory conditions, and in areas where muscle spasm is thought to contribute to pain, botulinum toxins (BoNT) are used with considerable success. For gynecological indications, there are limited data, in the form of case reports and small series, to indicate that BoNT used in the vulva may have a benefit for 3-6months after injection of 20-40U of BOTOX((R)); for women with provoked vestibulodynia. Re-treatment is reported to be successful and side effects are limited. Controlled studies are essential to further explore this indication. For pelvic floor muscle spasm, a greater number of women have been studied and a double blind, randomized controlled study has reported a significant reduction in pelvic floor pressures with significant pain reduction for some types of pelvic pain compared to baseline. There were no differences in pain compared to the control group who had physical therapy as an intervention. Physical therapy could be used as a non-invasive first line treatment, with BoNT injections reserved for those who are refractory to treatment. In summary, BoNT treatment for a variety of gynecological indications seems successful with limited side effects, although there are minimal data, particularly in superficial vulval conditions. To allow recommendation for wider utilization of this treatment, it is essential that more research is performed to add further evidence to our current knowledge.

Chronic stress in women with localised provoked vulvodynia.
Ehrstrom S, Kornfeld D, Rylander E, Bohm-Starke N
J Psychosom Obstet Gynaecol. 2009 Mar;30(1):73-9.

BACKGROUND: Localised provoked vulvodynia (former vulvar vestibulitis syndrome) is the most common cause of superficial dyspareunia among young women. In a clinical setting, it is obvious that many women with localised provoked vulvodynia show signs of chronic stress. The objective of this study was to compare chronic stress in a group of women with localised provoked vulvodynia, referred to the vulvar unit at the Division of Obstetrics and Gynecology, Danderyd Hospital, Stockholm, Sweden with control women of the same age and educational level, using two independent methods. METHODS: Forty-three women with localised provoked vulvodynia and 35 healthy control women underwent a gynecological examination, filled in a health questionnaire, and self-collected saliva for analysis of cortisol at awakening and after 15, 30 and 45 min (morning awakening cortisol). Thirty-three patients and 28 controls completed a stress questionnaire. RESULTS: Morning awakening cortisol was blunted in women with localised provoked vulvodynia ($p < 0.05$), indicating chronic stress. The stress questionnaire showed more signs of burnout ($p < 0.005$), and emotional ($p < 0.05$) and bodily symptoms of stress ($p < 0.005$) in women with localised provoked vulvodynia compared with control subjects (students t-test). CONCLUSION: More women with localised provoked vulvodynia showed blunted morning awakening cortisol and reported more symptoms of stress compared with healthy control women of the same age.

Incidence of Bartholin's duct occlusion after superficial localized vestibulectomy.
Goetsch MF
Am J Obstet Gynecol. 2009 Apr 17. [Epub ahead of print]

OBJECTIVE: The objective of the study was to analyze the incidence of occlusion of Bartholin's ducts after the procedure of superficial localized vestibulectomy for severe vulvar vestibulitis. STUDY DESIGN: One hundred fifty-five women underwent modified superficial vestibulectomy for severe primary or secondary vestibulitis between 1989 and 2007. Charts were reviewed and data were calculated regarding occlusion of Bartholin's ducts. Database software was FileMaker Pro 5 (FileMaker, Inc, Santa Clara, CA). SPSS 16.0 (SPSS, Inc, Chicago, IL) calculated means. RESULTS: Fourteen of 155 women (9%) had small blisters noted at a Bartholin's duct site after healing. Of these, 6 (43%) noted local symptoms related to sexual arousal. Surgical unroofing was attempted in 8 (62%) and corrected symptoms in all but 1. The subject with remaining symptoms notes deep pain with arousal suggestive of Bartholin's adenitis. CONCLUSION: The incidence of duct ostium occlusion after superficial modified vestibulectomy was 9%, and only half had symptoms. Methods of surgical treatment of the occlusion are compared.

Exploring clinical associations using '-omics' based enrichment analyses.
Hanauer DA, Rhodes DR, Chinnaiyan AM
PLoS ONE. 2009;4(4):e5203. Epub 2009 Apr 13.

BACKGROUND: The vast amounts of clinical data collected in electronic health records (EHR) is analogous to the data explosion from the "-omics" revolution. In the EHR clinicians often maintain patient-specific problem summary lists which are used to provide a concise overview of significant medical diagnoses. We hypothesized that by tapping into the collective wisdom generated by hundreds of physicians entering problems into the EHR we could detect significant associations among diagnoses that are not described in the literature. METHODOLOGY/PRINCIPAL FINDINGS: We employed an analytic approach original developed for detecting associations between sets of gene expression data, called Molecular Concept Map (MCM), to find significant associations among the 1.5 million clinical problem summary list entries in 327,000 patients from our institution's EHR. An odds ratio (OR) and p-value was calculated for each association. A subset of the 750,000 associations found were explored using the MCM tool. Expected associations were confirmed and recently reported but poorly known associations were uncovered. Novel associations which may warrant further exploration were also found. Examples of expected associations included non-insulin dependent diabetes mellitus and various diagnoses such as retinopathy, hypertension, and coronary artery disease. A recently reported association included irritable

bowel and vulvodynia (OR 2.9, p = 5.6x10(-4)). Associations that are currently unknown or very poorly known included those between granuloma annulare and osteoarthritis (OR 4.3, p = 1.1x10(-4)) and pyloric stenosis and ventricular septal defect (OR 12.1, p = 2.0x10(-3)). CONCLUSIONS/SIGNIFICANCE: Computer programs developed for analyses of "-omic" data can be successfully applied to the area of clinical medicine. The results of the analysis may be useful for hypothesis generation as well as supporting clinical care by reminding clinicians of likely problems associated with a patient's existing problems.

Pudendal neuralgia. Fact or fiction?
Stay K, Dwyer PL, Roberts L
Obstet Gynecol Surv. 2009 Mar;64(3):190-9.

PURPOSE: To review the condition of pudendal neuralgia (PN) and its role in chronic pelvic pain in women. METHODS: A Medline search for articles published before April, 2008 was done using a list of terms related to PN including: pudendal nerve, neuralgia, chronic pelvic pain syndromes, and entrapment neuropathies. RESULTS: The prevalence of PN is unknown and it seems to be a rare event. The main feature is neuralgic pain in the distribution of the pudendal nerve. The most common patient's profile is a patient who had seen multiple physicians, with no evidence of organ disease, normal urogynecological and colorectal evaluations, and failed multiple pharmacologic treatments. The cause of the PN is not always clear, but it is believed that neuronal insult caused by stretching or compression is the primary etiology. PN is said to be a diagnosis of exclusion and requires a high index of suspicion. Although there are no pathognomonic signs and symptoms, clinical diagnostic criteria were recently discussed and published by a multidisciplinary working party in Nantes (France 2006). Clinical neurophysiology tests have quite low diagnostic efficacy and must therefore be considered to be complementary investigations. Optional treatments include behavioral modifications, physical therapy, analgesics, pudendal nerve block, and surgical nerve decompression. CONCLUSIONS: PN does seem to exist as a clinical syndrome rather than a specific diagnosis. It is important to note that it does not have definite etiological implications, and there is no evidence to support equating the presence of this syndrome with a diagnosis of pudendal nerve entrapment although that may be 1 etiological condition.

Evaluation of diagnostic accuracy of colour duplex scanning, compared to electroneuromyography, diagnostic score and surgical outcomes, in pudendal neuralgia by entrapment: a prospective study on 96 patients.
Mollo M, Bautrant E, Rossi-Seignert AK, Collet S, Boyer R, Thiers-Bautrant D
Pain. 2009 Mar;142(1-2):159-63.

The objective of our study is to evaluate the detection capacity of Colour Duplex Scanning (CDS) in helping to diagnose Pudendal Neuralgia (PNa) by Pudendal Nerve Entrapment (PNE). This technique is being compared to complete Neurological Criteria (NC) based on Diagnostic Score (DS) and Electroneuromyography (ENMG) and secondly, to the results of surgery. This is a prospective study, on a consecutive series of 96 unselected patients evaluated by both CDS and NC. The CDS examinations were performed by the same operator who was unaware of the NC. The DS and the ENMG were read by a practitioner who was unaware of the CDS findings. The Peak Systolic Velocity (PSV) and the Systolic Ascension Time (AT) were the vascular criteria. Inadequate examinations were neither repeated nor removed from the analysis. Of 166 Internal Pudendal Arteries (IPAs) explored by CDS, 163 were visualised on their whole course, leading to a 98% feasibility. Of the 67 PNE identified by NC, 60 cases of Pudendal Vascular Entrapment (PVE) were detected by CDS, leading to a 89.6% sensitivity and a 67.4% specificity. Currently, there is no gold standard that can diagnose PNa by PNE with certainty. CDS is a non-invasive technique, demonstrating high diagnostic value to confirm PNE. In this study, we determined a new objective diagnostic criterion, the Pudendal Artery Ratio (PAR), which is very strong at diagnosing PNE but needs to be validated by further studies.

Role of interventional radiology in pudendal neuralgia: a description of techniques and review of the literature.
Fanucci E, Manenti G, Ursone A, Fusco N, Mylonakou I, D'Urso S, Simonetti G
Radiol Med. 2009 Mar 10. [Epub ahead of print]

PURPOSE: The authors sought to evaluate indications, technical feasibility and clinical efficacy of computed tomography (CT)-guided pudendal nerve infiltration in patients with chronic anoperineal pain by reviewing the role of the CT technique in their personal experience and in the recent interventional literature. MATERIALS AND METHODS: Twenty-eight women, mean age 50 years, and with a diagnosis of pudendal neuralgia on the basis of clinical and electromyographic criteria were enrolled in the study. CT-guided pudendal nerve injections were performed during three consecutive sessions held 2 weeks apart. In each session, patients received two percutaneous injections: one in the ischial spine, and the other in the pudendal (Alcock's) canal. RESULTS: One patient dropped out of the study after the first session. At clinical assessment, 24h h after treatment, 21/27 patients reported significant pain relief. At follow-up at 3, 6, 9 and 12 months, 24/27 patients reported a>/=20% improvement in the Quality of Life (QOL) index. Conclusions. In pudendal nerve entrapment, CT-guided perineural injection in the anatomical sites of nerve impingement is a safe and reproducible treatment with a clinical efficacy of 92% at 12 months.

Laparoscopic management of endopelvic etiologies of pudendal pain in 134 consecutive patients.
Possover M
J Urol. 2009 Apr;181(4):1732-6.

PURPOSE: The feasibility of the laparoscopic transperitoneal approach to the pelvic somatic nerves was determined for the diagnosis and treatment of anogenital pain caused by pudendal and/or sacral nerve root lesions. MATERIALS AND METHODS: The records of 134 consecutive patients who underwent laparoscopy for refractory anogenital pain were retrospectively reviewed. All neurosurgical procedures, such as neurolysis/decompression of the pudendal nerve and the sacral nerve roots or neuroelectrode implantation to the sacral plexus for postoperative neuromodulation, were done via the laparoscopic transperitoneal approach to the pelvic nerves. RESULTS: A total of 18 patients had Alcock's canal syndrome and decompression was successful in 15. Due to failed decompression 3 patients underwent secondary sacral laparoscopic neuroprosthesis implantation with a decrease of at least 50% on the pain visual analog scale. Sacral plexus lesions or radiculopathies, most commonly postoperative lesions and retroperitoneal endometriosis, were found in 109 patients who underwent laparoscopic neurolysis of the sacral plexus. The final outcome depended on the etiology. Of patients with postoperative nerve damage 62% had a decrease in the mean +/- SD preoperative visual analog scale score of from 8.9 +/- 2.9 (range 7 to 10) to 2.4 +/- 2.3 points (range 0 to 4) at the time of article submission at a mean followup of 17 months (range 3 to 39). Because of failed decompression, 8 patients underwent secondary sacral laparoscopic neuroprosthesis implantation and a decrease in the pain visual analog scale score was achieved in 5. Of patients with an endometriosis lesion of the sacral plexus 78% had a decrease in the mean preoperative visual analog scale score of 8.7 +/- 1.9 (range 8 to 10) to 1.1 +/- 0.7 points (range 0 to 2) at the time of article submission at a mean followup of 21 months (range 2 to 42). All 6 patients with vascular entrapment of pelvic nerves achieved complete relief. The last 7 patients underwent primary sacral laparoscopic neuroprosthesis implantation with at least a 50% decrease in the pain visual analog scale score in 4. CONCLUSIONS: Our findings emphasize that in patients with seemingly inexplicable anogenital pain, especially after failed treatment for Alcock's canal syndrome, laparoscopic exploration of the pelvic nerves must be done for further diagnosis and therapy before prematurely labeling the patients as refractory to treatment.

Chronic pelvic pain syndromes: clinical, urodynamic, and urothelial observations.
Butrick CW, Sanford D, Hou Q, Mahnken JD
Int Urogynecol J Pelvic Floor Dysfunct. 2009 May 21. [Epub ahead of print]

INTRODUCTION/METHODS: A cohort of 408 patients with bladder pain syndrome/interstitial cystitis (BPS/IC) was evaluated, and findings were discussed in this retrospective chart review. RESULTS: Based on the chief complaints, they were divided into four subgroups: BPS/IC (n = 157), CPP (n = 98), vulvodynia/dyspareunia (n = 40), and "other" (n = 113). Similar findings were found in all four subgroups: complaints of voiding dysfunction (70%), dyspareunia (54%), mean PUF score of 15.9 +/- 6.4, and a positive potassium sensitivity test in 83%. Urodynamics revealed a maximal urethral pressure of 131 cm of water and an abnormal uroflow in 80%. Urothelial therapy in the form of intravesical therapeutic anesthetic cocktails provided benefit in all groups (50%, 67%, 73%, and 77% for vulvodynia, CPP, BPS/IC, "other"). CONCLUSIONS: All subgroups had similar findings and response to therapy. Five to 10% of patients with chief complaints of stress or urge incontinence or prolapse were also found to have BPS/IC.

Differentiating interstitial cystitis from similar conditions commonly seen in gynecologic practice.
Dell JR, Mokrzycki ML, Jayne CJ
Eur J Obstet Gynecol Reprod Biol. 2009 Apr 29. [Epub ahead of print]

Interstitial cystitis is a syndrome characterized by pelvic pain, urinary urgency/frequency, nocturia, and dyspareunia, with no other identifiable etiology. The clinical presentation of interstitial cystitis is similar to that of many other conditions commonly seen in female patients, including recurrent urinary tract infections, endometriosis, chronic pelvic pain, vulvodynia, and overactive bladder. In addition, interstitial cystitis may exist concurrently with these conditions. Correct diagnosis is necessary for appropriate treatment and improved outcomes. Tools to assist in the diagnosis of interstitial cystitis, as well as effective therapies for this condition, are available. A diagnosis of interstitial cystitis should be considered in patients with irritative voiding symptoms and/or pelvic pain complaints.

Evaluation and treatment of dyspareunia.
Steege JF, Zolnoun DA
Obstet Gynecol.2009 May;113(5):1124-36.

Dyspareunia affects 8-22% of women at some point during their lives, making it one of the most common pain problems in gynecologic practice. A mixture of anatomic, endocrine, pathologic, and emotional factors combine to challenge the diagnostic, therapeutic, and empathetic skills of the physician. New understandings of pain in general require new interpretations concerning the origins of pain during intercourse, but also provide new avenues of treatment. The outcomes of medical and surgical treatments for common gynecologic problems should routinely go beyond measures of coital possibility, to include assessment of coital comfort, pleasure, and facilitation of intimacy. This review will discuss aspects of dyspareunia, including anatomy and neurophysiology, sexual physiology, functional changes, pain in response to disease states, and pain after gynecologic surgical procedures.

Other Vulvovaginal Disorders

Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally.
Bachmann G, Bouchard C, Hoppe D, Ranganath R, Altomare C, Vieweg A, Graepel J, Helzner E
Menopause. 2009 May 8. [Epub ahead of print]

OBJECTIVE: The aim of this study was to evaluate the efficacy and safety of low-dose conjugated estrogens (CE) cream for treatment of atrophic vaginitis. METHODS:: Postmenopausal women (N = 423)

with moderate-to-severe vaginal atrophy were randomized to CE cream 0.3 mg or placebo once daily (21 days on/7 days off) or twice weekly for 12 weeks, followed by open-label treatment with CE cream for 40 weeks consistent with their prior regimen. Primary endpoints were changes in vaginal maturation index (VMI; percentage of superficial cells), vaginal pH, and severity of participant-reported most bothersome symptom (vaginal dryness, itching, burning, or dyspareunia) at week 12. Endometrial safety was assessed by transvaginal ultrasound and endometrial biopsy for 52 weeks. RESULTS:: At week 12, improvements in VMI with daily and twice-weekly use of low-dose CE cream (27.9% and 25.8%, respectively) were significantly greater compared with placebo (3.0% and 1.0%, respectively; P < 0.001). Improvements in vaginal pH with daily and twice-weekly CE cream (-1.6 for both) were also significantly greater relative to placebo (-0.4 and -0.3, respectively; P < 0.001). VMI and vaginal pH responses were sustained through 52 weeks. Both CE cream regimens significantly reduced most bothersome symptom scores compared with placebo (P </= 0.001), including those for dyspareunia (P </= 0.01). There was no report of endometrial hyperplasia or carcinoma. Adverse events occurred with similar frequency among the active and placebo groups during the double-blind phase. CONCLUSIONS:: Daily and twice-weekly use of low-dose CE cream was equally effective in relieving symptoms of vulvovaginal atrophy. Both regimens showed endometrial safety and sustained efficacy during 1 year of therapy.

Urogenital atrophy.
Calleja-Agius J, Brincat MP
Climacteric. 2009 Apr 22:1-7. [Epub ahead of print]

The major cause of urogenital atrophy in menopausal women is estrogen loss. The symptoms are usually progressive in nature and deteriorate with time from the menopausal transition. The most prevalent urogenital symptoms are vaginal dryness, vaginal irritation and itching. The classical changes in an atrophic vulva include loss of labial and vulvar fullness, with narrowing of the introitus and inflamed mucosal surfaces. Dyspareunia and vaginal bleeding from fragile atrophic skin are common problems. Other urogenital complaints include frequency, nocturia, urgency, incontinence and urinary tract infections. Atrophic changes of the vulva, vagina and lower urinary tract can have a large impact on the quality of life of the menopausal woman. However, hormonal and non-hormonal treatments can provide patients with the solution to regain previous level of function. Therefore, clinicians should sensitively question and examine menopausal women, in order to correctly identify the pattern of changes in urogenital atrophy and manage them appropriately.

Longitudinal changes in sexual functioning as women transition through menopause: results from the Study of Women's Health Across the Nation.
Avis NE, Brockwell S, Randolph JF Jr, Shen S, Cain VS, Ory M, Greendale GA
Menopause. 2009 May-Jun;16(3):442-52.

OBJECTIVE: Sexual functioning is an important component of women's lives. The extent to which the menopausal transition is associated with decreased sexual functioning remains inconclusive. This study seeks to determine if advancing through the menopausal transition is associated with changes in sexual functioning. METHODS: This was a prospective, longitudinal cohort study of women aged 42 to 52 years at baseline recruited at seven US sites (N = 3,302) in the Study of Women's Health Across the Nation (SWAN). Cohort-eligible women had an intact uterus, had at least one ovary, were not currently using exogenous hormones, were either premenopausal or early perimenopausal, and self-identified as one of the study's designated racial/ethnic groups. Data from the baseline interview and six annual follow-up visits are reported. Outcomes are self-reported ratings of importance of sex; frequency of sexual desire, arousal, masturbation, sexual intercourse, and pain during intercourse; and degree of emotional satisfaction and physical pleasure. RESULTS: With adjustment for baseline age, chronological aging, and relevant social, health, and psychological parameters, the odds of reporting vaginal or pelvic pain increased and desire decreased by late perimenopause. Masturbation increased at early perimenopause but declined during postmenopause. The menopausal transition was unrelated to other outcomes. Health, psychological functioning, and importance of sex were related to all sexual function outcomes. Age, race/ethnicity, marital status, change in relationship, and vaginal dryness were also associated with

sexual functioning. CONCLUSIONS: Pain during sexual intercourse increases and sexual desire decreases over the menopausal transition. Masturbation increases during the early transition, but then declines in postmenopause. With adjustment for other factors, the menopausal transition was not independently associated with reports of the importance of sex, sexual arousal, frequency of sexual intercourse, emotional satisfaction with partner, or physical pleasure.

The effects of oestrogen on urogenital health.
Lachowsky M, Nappi R
Maturitas. 2009 Apr 30. [Epub ahead of print]

The decline in sex hormone levels that accompanies the menopause has substantial effects on the tissues of the urogenital system, leading to atrophic changes. These changes can have negative effects on sexual and urinary function, leading to dyspareunia and incontinence. Treatment of urogenital atrophy with systemic or local oestrogens can improve the adverse effects of loss of oestrogen on both sexual and urinary functions. In some cases, treatment with oestrogen alone may not be sufficient to address sexual problems in menopausal women and androgen addition is required. Because of the complexity of sexual problems in menopausal women, assessment and therapy should address both the physical and other factors that play a role in the condition.

Clinical spectrum of vulva metastatic crohn's disease.
Leu S, Sun PK, Collyer J, Smidt A, Stika CS, Schlosser B, Mirowski GW, Vanagunas A, Buchman AL
Dig Dis Sci. 2009 May 7. [Epub ahead of print]

Crohn's disease is a chronic granulomatous disorder that may involve any segment of the gastrointestinal tract. Extraintestinal manifestations of Crohn's disease such as erythema nodosum and pyoderma gangrenosum are well recognized and appreciated. However, metastatic Crohn's disease (MCD), defined as the same granulomatous inflammation seen in Crohn's disease but at a skin site distant to the gastrointestinal tract, is less well recognized. We report three cases of MCD involving the perianal and vulvar skin that initially presented with vulvar pain.

A rare case of vulvar endometriosis in an adolescent girl.
Eyvazzadeh AD, Smith YR, Lieberman R, Quint EH
Fertil Steril. 2009 Mar;91(3):929.e9-11.

OBJECTIVE: To describe a case of vulvar endometriosis in a teenager after a history of vulvar ulcers in the same location. DESIGN: Case report. SETTING: University medical center. PATIENT(S): A 13-year-old girl with a history of vulvar ulcers. MAIN OUTCOME MEASURE(S): None RESULT(S): A 13-yr-old female presented with painful, open vulvar ulcerations on the inner side of her labia minora. Biopsy revealed dermatitis with ulceration. One year later she noted an ulcer and blood in her undergarments. Biopsy results were consistent with endometriosis. Five years later, the lesions persisted and bled during menses. A bilateral labial excision was performed. Pathology again revealed endometriosis. CONCLUSION(S): Vulvar endometriosis is extremely unusual. This rare case of vulvar endometriosis in the same location as a previous vulvar ulcer is most likely due to ectopic transplantation of endometrial cells during a menstrual cycle. Excision is considered definitive treatment.

Candida albicans internalization by host cells is mediated by a clathrin-dependent mechanism.
Moreno-Ruiz E, Galan-Diez M, Zhu W, Fernandez-Ruiz E, d'Enfert C, Filler SG, Cossart P, Veiga E.
Cell Microbiol. 2009 Mar 31. [Epub ahead of print]

ABSTRACT Candida albicans is a major cause of oropharyngeal, vulvovaginal and hematogenously disseminated candidiasis. Endocytosis of C. albicans hyphae by host cells is a prerequisite for tissue invasion. This internalization involves interactions between the fungal invasin Als3 and host E- or N-

cadherin. Als3 shares some structural similarity with InlA, a major invasion protein of the bacterium Listeria monocytogenes. InlA mediates entry of L. monocytogenes into host cells through binding to E-cadherin. A role in internalization, for a non classical stimulation of the clathrin-dependent endocytosis machinery was recently highlighted. Based on the similarities between the C. albicans and L. monocytogenes invasion proteins, we studied the role of clathrin in the internalization of C. albicans. Using live-cell imaging and indirect immunofluorescence of epithelial cells infected with C. albicans, we observed that host E-cadherin, clathrin, dynamin and cortactin accumulated at sites of C. albicans internalization. Similarly, in endothelial cells, host N-cadherin, clathrin and cortactin accumulated at sites of fungal endocytosis. Furthermore, clathrin, dynamin or cortactin depletion strongly inhibited C. albicans internalization by epithelial cells. Finally, beads coated with Als3 were internalized in a clathrin-dependent manner. These data indicate that C. albicans, like L. monocytogenes, hijacks the clathrin-dependent endocytic machinery to invade host cells.

Validation of an immunologic diagnostic kit for infectious vaginitis by trichomonas vaginalis, candida spp., and gardnerella vaginalis.
Bravo AB, Miranda LS, Lima OF, Cambas AV, Hernandez ML, Alvarez JM
Diagn Microbiol Infect Dis. 2009 Mar;63(3):257-60.

FemPure is a kit for the rapid diagnosis of vaginitis by Trichomonas vaginalis, Candida spp., and Gardnerella vaginalis, based on aggregation of latex particles joined to specific antibodies. The validation of the method involved the parameters specificity, detection limit, robustness, clinical sensitivity, and clinical specificity. Also, samples analyzed in parallel by the validated test and other recognized tests conducted by external laboratory were included. The method was specific for the 3 infectious agents, and no cross-reaction with other microorganisms usually present in vaginal exudates. The detection limit > or =1 x 10(6) CFU/mL for Candida albicans and G. vaginalis avoids the detection of concentrations considered normal flora, whereas T. vaginalis was detected until 1 x 10(5) cells/mL. Values of clinical sensitivity > or =80% and clinical specificity > or =90% and concordance > or =90% were found between samples evaluated in parallel by different methods. Robustness showed that the test can be used in laboratories with different management systems; its simple implementation without equipment allows the use in primary health care areas.

Association between group A beta-haemolytic streptococci and vulvovaginitis in adult women: a case-control study.
Bruins MJ, Damoiseaux RA, Ruijs GJ
Eur J Clin Microbiol Infect Dis. 2009 Apr 3. [Epub ahead of print]

Guidelines for the management of vaginal discharge mention Candida albicans, Trichomonas vaginalis, bacterial vaginosis, Chlamydia trachomatis and Neisseria gonorrhoeae as causes and do not recommend full microbiological culture. The role of non-group B beta-haemolytic streptococci in vaginal cultures is unclear, except for group A streptococci that are known to cause vulvovaginitis in children. In a case-control study, we investigated the association between non-group B beta-haemolytic streptococci and vulvovaginitis in adult women. Cases were women with recurrent vaginal discharge from whom a sample was cultured. Controls were asymptomatic women who consented to submitting a vaginal swab. Group A streptococci were isolated from 49 (4.9%) of 1,010 cases and not from the 206 controls ($P < 0.01$). Isolation rates of group C, F and G streptococci were low and did not differ statistically between cases and controls. Group A beta-haemolytic streptococci are associated with vaginal discharge in adult women. The other non-group B streptococci require more study. For the adequate management of vaginal discharge, culturing is necessary if initial treatment fails. Guidelines should be amended according to these results.

Langerhans cells in lichen sclerosus of the vulva and lichen sclerosus evolving in vulvar squamous cell carcinoma.
Raspollini MR, Baroni G, Taddei GL
Histol Histopathol. 2009 Mar;24(3):331-6.

Vulvar lichen sclerosus (LS) represents a benign chronic inflammatory skin lesion that carries a risk for development of vulvar squamous cell carcinoma (SCC). We aimed at determining whether premalignant changes in vulvar LS, a multifactorial disease, presenting a welter of evidence implicating the immune system in its pathogenesis, could be identified by analysing the Langerhans' cells (LCs), the primary cell responsible for antigen recognition and presentation. The relationship existing between inflammation and cancer due to chronic infection, and demonstrated in many solid tumors, led us to study LCs in eight cases of vulvar LS, which showed an evolution to carcinoma of the vulva and in ten cases of unchanged vulvar LS in matched patients by immunohistochemistry for antibodies CD1a and S100. We did not find a statistically significantly different number of LCs counted either in S100 stained specimens, nor in CD1a stained specimens of LS epithelium in unchanged or evolving cases. The data emerging in our study do not support the hypothesis that the variation in the number of LCs may be related to the development of SCC in late stage LS cases.

The expanding spectrum of cutaneous borreliosis.
Eisendle K, Zelger B
G Ital Dermatol Venereol. 2009 Apr;144(2):157-71.

The known spectrum of skin manifestations in cutaneous Lyme disease is continuously expanding and can not be regarded as completed. Besides the classical manifestations of cutaneous borreliosis like erythema (chronicum) migrans, borrelial lymphocytoma and acrodermatitis chronica atrophicans evidence is growing that at least in part also other skin manifestations, especially morphea, lichen sclerosus and cases of cutaneous B-cell lymphoma are causally related to infections with Borrelia. Also granuloma annulare and interstitial granulomatous dermatitis might be partly caused by Borrelia burgdorferi or similar strains. There are also single reports of other skin manifestations to be associated with borrelial infections like cutaneous sarcoidosis, necrobiosis lipoidica and necrobiotic xanthogranuloma. In addition, as the modern chameleon of dermatology, cutaneous borreliosis, especially borrelial lymphocytoma, mimics other skin conditions, as has been shown for erythema anulare centrifugum or lymphocytic infiltration (Jessner Kanof) of the skin.

Melanocytic proliferations associated with lichen sclerosus in adolescence.
Bussen SS.
Arch Gynecol Obstet. 2009 Mar 28. [Epub ahead of print]

Lichen sclerosus is found in children with an estimated prevalence of at least 1 in 900. Pigmentation in lichen sclerosus is infrequent and melanocytic proliferations in lichen sclerosis are rare and difficult to interpret. In this report, we describe the case of a prepubertal girl presenting with a junctional melanocytic nevus of the labia minora superimposed by lichen sclerosus. The lesion was completely excised and free margins confirmed by histological examination. After a 3 months course of topical clobetasol treatment the girl remained asymptomatic. No local recurrence was notified with a follow-up time of 12 months.

Vulvar cancer and the need for awareness of precursor lesions.
Maclean AB, Jones RW, Scurry J, Neill S
J Low Genit Tract Dis. 2009 Apr;13(2):115-7.

Vulvar cancer continues to rise in incidence. In the absence of screening, attempts to reduce this cancer must focus on recognizing precursor lesions, namely, lichen sclerosus and vulvar intraepithelial neoplasia (VIN). The steep rise in human papillomavirus-repeated VIN will fall after the introduction of vaccination against human papillomavirus; in the meantime, those patients with VIN must be treated and then

reviewed carefully and frequently. Lichen sclerosus has a 3% to 5% risk of progressing to vulvar cancer. Recommendations about which patients require referral to and follow-up by specialists/specialist clinics are given.

Response of vulval lichen sclerosus and squamous hyperplasia to photodynamic treatment using sustained topical delivery of aminolevulinic acid from a novel bioadhesive patch system.
Zawislak AA, McCluggage WG, Donnelly RF, Maxwell P, Price JH, Dobbs SP, McClelland HR, Woolfson AD, Mccarron PA
Photodermatol Photoimmunol Photomed. 2009 Apr;25(2):111-3.

This study evaluated the clinical and histopathological responses of vulval lichen sclerosus (LS) and squamous hyperplasia (SH) to photodynamic therapy (PDT). A novel bioadhesive patch containing aminolevulinic acid (ALA) at a dose of (38 mg/cm(2)) was used to treat 10 patients before irradiation with light of 630 nm. Clinical, histopathological and pathological responses to treatment were assessed at 6 weeks post-treatment. After 17 cycles of PDT, six patients reported significant symptomatic relief and no cutaneous photosensitivity. Histopathological differences were not demonstrated, but statistically significant induction of apoptosis was seen. It can be concluded that ALA-PDT patch-based formulation is pragmatic and primarily offers symptomatic management of vulval LS and SH.

Basic Science

Surgical and anatomical landmarks for the perineal branch of the posterior femoral cutaneous nerve: implications in perineal pain syndromes.
Tubbs RS, Miller J, Loukas M, Shoja MM, Shokouhi G, Cohen-Gadol AA
J Neurosurg. 2009 Apr 10. [Epub ahead of print]

Object: The perineal branch of the posterior femoral cutaneous nerve (PBPFCN) has received little attention in the literature. Because perineal pain syndromes can be disabling and pudendal nerve surgical decompression/block is often not efficacious, an anatomical study of this cutaneous nerve of the perineum seemed warranted. Methods The authors dissected 20 adult cadavers (40 sides) to identify the branching pattern and landmarks for the PBPFCN. Results This branch arose directly from the posterior femoral cutaneous nerve in 55% of sides and from the inferior cluneal nerve in 30% of sides. It was absent in 15% of sides. On average, the nerve coursed 4 cm inferior to the termination of the sacrotuberous ligament onto the ischial tuberosity. No PBPFCN was found to pierce the sacrotuberous ligament. The PBPFCN provided 2-3 branches to the medial thigh that continued on to the scrotum and labia major. In general, 2 small ascending branches were identified. In males, one ascending branch traveled inferior to the corpora cavernosum and anterior to the spermatic cord to cross the midline. The other ascending branch traveled to skin at the junction of the perineum and adductor tendon. A single descending branch, approximately 2 mm in diameter, traveled to the inferior scrotum anterior to the testicle in the male specimens and the lower labia majora in the female specimens. Communications between the PBPFCN and the perineal branch of the pudendal nerve were common. Conclusions Entrapment of the PBPFCN may be the cause of some forms of the perineal pain syndrome. Specific knowledge of the PBPFCN may assist surgeons in releasing and anesthetizing this cutaneous nerve of the perineum.

Differential islet-1 expression among lumbosacral spinal motor neurons in prenatal mouse.
Han DY, Kobayashi M, Nakano M, Atobe Y, Kadota T, Funakoshi K
Brain Res. 2009 Apr 10;1265:30-6.

Onuf's nucleus in the lumbosacral spinal cord, comprising somatic motoneurons that innervate the pelvic floor muscles via the pudendal nerve, shares some characteristics with the autonomic preganglionic

neurons and functions in coordination with the autonomic nervous system. In mouse, neurons projecting to the urethral sphincter and ischiocavernosus muscles form the dorsolateral (DL) nucleus at the caudal lumbar levels, whereas neurons projecting to the limb and hip joint muscles comprise the retrodorsolateral and ventral nucleus, as well as the DL nucleus at the rostral lumbar levels. The results of the present study in mouse revealed that the expression pattern of a LIM homeodomein protein Islet-1, an embryonic marker for motoneurons in the spinal cord, was different among motoneuronal groups at the prenatal stage (embryonic days 13.5-15.5); the highest expression was observed in the DL at the caudal lumbar cord, whereas there was little expression in the lateral part of the rostral DL. Islet-1 expression was also observed in the parasympathetic preganglionic neurons at the sacral spinal cord. These findings provide evidence that the DL neurons at the caudal lumbar cord, corresponding to Onuf's nucleus, are chemically distinct among the motoneuronal groups at the prenatal stages. This differential Islet-1 expression among the motoneuronal groups suggests that Islet-1 not only leads to a motoneuronal lineage, but also to the differentiation of motoneuronal subsets in the lumbosacral spinal cord.

Reactive oxygen species in rats with chronic post-ischemia pain.
Kwak KH, Han CG, Lee SH, Jeon Y, Park SS, Kim SO, Baek WY, Hong JG, Lim DG
Acta Anaesthesiol Scand. 2009 May;53(5):648-56.

BACKGROUND: An emerging theme in the study of the pathophysiology of persistent pain is the role of reactive oxygen species (ROS). In the present study, we examined the hypothesis that the exogenous supply of antioxidant drugs during peri-reperfusion would attenuate pain induced by ischemia/reperfusion (IR) injury. We investigated the analgesic effects of three antioxidants administered during peri-reperfusion using an animal model of complex regional pain syndrome-type I consisting of chronic post-ischemia pain (CPIP) of the hind paw. METHODS: Application of a tight-fitting tourniquet for a period of 3 h produced CPIP in male Sprague-Dawley rats. Low-dose allopurinol (4 mg/kg), high-dose allopurinol (40 mg/kg), superoxide dismutase (SOD, 4000 U/kg), N-nitro-L-arginine methyl ester (L-NAME, 10 mg/kg), or SOD (4000 U/kg)+L-NAME (10 mg/kg) was administered intraperitoneally just after tourniquet application and at 1 and 2 days after reperfusion for 3 days. The effects of antioxidants in rats were investigated using mechanical and cold stimuli. Each group consisted of seven rats. RESULTS: Allopurinol caused significant alleviation in mechanical and cold allodynia for a period of 4 weeks in rats with CPIP. Both SOD and L-NAME, which were used to investigate the roles of superoxide (O2(-)) and nitric oxide (NO) in pain, also attenuated neuropathic-like pain symptoms in rats for 4 weeks. CONCLUSIONS: Our findings suggest that O2(-) and NO mediate IR injury-induced chronic pain, and that ROS scavengers administered during the peri-reperfusion period have long-term analgesic effects.

Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study.
Keskin N, Teksen YA, Ongun EG, Ozay Y, Saygili H
Arch Gynecol Obstet. 2009 Mar 20. [Epub ahead of print]

OBJECTIVE: In several studies, the prolonged exposure to talc has been associated with development of ovarian cancer. However, some studies have advocated contrary views. The present study aims to investigate histopathological changes and whether long-term talc exposure is associated with potential carcinogenic effects on the female genital organs of rats. MATERIALS AND METHODS: The present study was conducted at Dumlupinar University Medical Faculty and a total of 28 Sprague-Dawley rats were included. The experimental animals were allocated into four groups having seven rats each. Groups 1 and 2 served as controls, where the rats in Group 1 did not receive any intervention and Group 2 received intravaginal saline. Groups 3 and 4 received intravaginal or perineal talc application, respectively. Talc was applied for 3 months on a daily basis. Histopathological changes in the peritoneum and female genital system were evaluated. For statistical analyses, Fisher's exact test was carried out using SPSS. FINDINGS: In both the groups exposed to talc (Groups 3 and 4), evidence of foreign body reaction and infection, along with an increase in inflammatory cells, were found in all the genital tissues. Genital infection was observed in 12 rats in the study group and 2 rats in the control group. Neoplastic change was not found. However, there was an increase in the number of follicles in animals exposed to talc. No peritoneal change was observed. In the groups not exposed to talc, similar infectious findings

were found, but there was a statistically significant difference between the groups (Groups 1 and 2 vs. Groups 3 and 4, $P > 0.05$). Neoplastic change was also not observed in these groups. Four groups were compared in terms of neoplastic effects and infections. In Groups 1, 5 rats were normal, two developed vulvovaginitis and endometritis with overinfection (in both ovaries), and one developed salpingitis (in both fallopian tubes), that is, infection was found in a total of two rats. In Group 2, only one experimental animal had endometritis. All the animals in Groups 3 and 4 developed infections. CONCLUSIONS: Talc has unfavorable effects on the female genital system. However, this effect is in the form of foreign body reaction and infection, rather than being neoplastic.