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Vulvodynia/Pain

Urogenital infections in relation to the occurrence of vulvodynia.
Nguyen RH, Swanson D, Harlow BL
J Reprod Med. 2009 Jun;54(6):385-92

OBJECTIVE: To determine whether antecedent urogenital infections and their frequency are associated with the development of vulvodynia. STUDY DESIGN: Data were obtained from a case-control study of 191 case and 171 control women in the Boston area from 2000 to 2005. Using questionnaire data, we examined self-reported urogenital infections occurring before onset of vulvar pain (cases) and reference age (controls), using unconditional logistic regression accounting for matched variables (current age and residence). RESULTS: Analysis was restricted to women reporting intercourse before first vulvar pain (cases) or reference age (controls). After adjusting for race, age at first intercourse, coital frequency and number of sex partners, a history of genital warts (adjusted odds ratio [OR] = 3.4, 95% CI 1.3-8.8), trichomoniasis (OR = 5.7, 95% CI 1.1-29, urinary tract infection (OR = 2.0, 95% CI 1.3-3.1) or yeast infection (OR = 2.1, 95% CI 1.3-3.3) were associated with increased estimated risk for vulvodynia. With an increasing number of types of antecedent infections (1, 2 or 3+), ORs = 1.3, 2.6 or 8.3, respectively, were observed. CONCLUSION: Our data suggest that diverse urogenital infections may precede onset of vulvodynia, with multiple assaults significantly compounding risk. However, prospective studies documenting urogenital infections and treatment are warranted.

Prevalence of vulvar and vaginal symptoms during pregnancy and the puerperium.
Kennedy CM, Turcea AM, Bradley CS
Int J Gynaecol Obstet. 2009 Jun;105(3):236-9

OBJECTIVE: To identify the prevalence of vulvar and vaginal symptoms during pregnancy and at 3 months post partum. METHODS: A prospective, longitudinal, descriptive study of 103 pregnant women was undertaken in which a self-administered questionnaire was completed at each trimester and 3 months post partum. Retrospective data was collected from 122 women, queried using similar tools, who comprised a nonpregnant control group. Descriptive and comparative statistics were employed. RESULTS: The prevalence of vulvar burning, itching, pain, and vaginal discharge generally increased during pregnancy, and improved postpartum. Dyspareunia increased during pregnancy, but remained elevated post partum. Compared with the historical nonpregnant group (adjusted for age, marital status, education, and smoking), dyspareunia was reported less often in the first trimester (P=0.03) and more often post partum (P<0.01). Furthermore, reports of vulvar pain and vaginal discharge were significantly greater during the second and third trimesters. CONCLUSIONS: Vulvar and vaginal symptoms are common during pregnancy, and the prevalence of some, but not all, increase during gestation and decrease post partum.

Dyspareunia in Puerto Rican middle-aged women.
Avellanet YR, Ortiz AP, Pando JR, Romaguera J
Menopause. 2009 Jul-Aug;16(4):742-7

OBJECTIVE: Dyspareunia is a common sexual dysfunction. There is a lack of studies that address female sexual dysfunction in Puerto Rico. The present cross-sectional study characterized dyspareunia in a sample of Puerto Rican women aged 40 to 59 years and evaluated the relationship between reported dyspareunia with demographic, lifestyle, and health factors. METHODS: Nine hundred twenty Puerto Rican women participated in health fairs conducted in 22 municipalities between May 2000 and November 2001 where they filled out a questionnaire. Contingency table and chi statistics were used to evaluate the bivariate associations of dyspareunia with demographic, lifestyle, and health factors. Crude and multivariate logistic regression models were used to estimate the magnitude of the association between dyspareunia and demographic, lifestyle, and health factors. RESULTS: The overall prevalence of dyspareunia in this population was 18%. Dyspareunia was somewhat lower among women aged 40 to 49 years (17%) than among those aged 50 to 59 years (21%), not reaching statistical significance. Dyspareunia was associated with educational attainment, employment status, menopause status, current hormone therapy use, genitourinary symptoms, and loss of libido ($P < 0.05$). Current cigarette smoking, body mass index, physical activity, alcohol use, parity, and ever use of oral contraceptives were not associated with dyspareunia in bivariate analysis ($P > 0.05$). In the multivariate analysis, incontinence (prevalence odds ratio [POR], 1.67; 95% CI, 1.02-2.73), vaginal dryness (POR, 3.97; 95% CI, 2.49-6.31), vaginal itching (POR, 2.44; 95% CI, 1.55-3.83), loss of libido (POR, 3.08; 95% CI, 1.92-4.94), and partnership (POR, 2.22; 95% CI, 1.29-3.82) remained associated with dyspareunia. CONCLUSIONS: Our results agree with previous studies regarding the potential association between health and lifestyle factors and dyspareunia. Additional studies of female sexual dysfunction in Puerto Rican women are highly warranted.

Self-reported vulvar pain characteristics and their association with clinically confirmed vestibulodynia.
Harlow BL, Vazquez G, Maclehose RF, Erickson DJ, Oakes JM, Duval SJ
J Womens Health (Larchmt) 2009 Aug 24. [Epub ahead of print]

Abstract Objective: We evaluated a series of questions pertaining to vulvar pain symptoms to determine their association with a localized vulvodynia (vestibulodynia) diagnosis in women from the general population. Methods: A sample of 12,435 women completed a self-administered screening questionnaire for the presence of specific types and characteristics of vulvar pain lasting 3 months or longer. Sensitivity, specificity, and predictive values were calculated for each cross-classification of vulvar pain type and characteristic, using as the gold standard 121 subjects with a clinically confirmed vestibulodynia diagnosis. Results: Relative to women with clinically confirmed vestibulodynia, 83% reported >10 episodes of pain on contact at the time of tampon insertion, intercourse, or pelvic examination, and 83% also reported pain on contact that limited or prevented sexual intercourse. These strong associations with a vestibulodynia diagnosis were not observed with respect to women who reported vulvar pain symptoms of burning or knifelike pain, or vulvar pain characteristics of continuous versus intermittent pain, or provoked versus spontaneous pain. Conclusions: Our findings suggest that a small number of symptoms may be suitable for identifying a large proportion of women suffering from vestibulodynia which may be ideal for the development of an effective screening test in the future. However, we also recognize that a large proportion of women experiencing vulvar pain symptoms will not meet the diagnostic criteria for vestibulodynia. Thus, implementing such a screening procedure as part of a routine examination or testing would require a subsequent pelvic examination to confirm a vestibulodynia diagnosis and to rule out other known explanations for vulvar pain.

A retrospective study of relevant diagnostic procedures in vulvodynia.
Petersen CD, Kristensen E, Lundvall L, Giraldi A
J Reprod Med. 2009 May;54(5):281-7

OBJECTIVE: To identify objective clinical signs of vulvodynia and determine specific diagnostic tests for vulvodynia in women referred to a vulvar outpatient clinic for vulval complaints. STUDY DESIGN: A retrospective study was performed of the medical records of 201 consecutive Danish patients suspected of suffering from vulvodynia who were referred to a vulvar outpatient clinic (Department of Gynecology, Rigshospitalet University Hospital) between October 2003 and January 2006. RESULTS: Of 201 women, 117 were diagnosed with vulvodynia and 84 had other diagnoses. Of the women diagnosed with vulvodynia in the vulvar clinic, 88.9% were correctly diagnosed before referral. The women with vulvodynia were more likely to report dyspareunia (chi2 = 7.89, p = 0.005) and stinging pain (chi2 = 3.74, p = 0.05). The nonvulvodynia group was more likely to report a tendency toward fissures (chi2 = 5.94, p < 0.05). CONCLUSION: Self-reported dyspareunia and stinging pain are strongly associated with vulvodynia. Self-reported pruritus and a tendency toward fissures are not likely to be associated with vulvodynia. Whether vulvar biopsies should be performed regularly when redness and pain is present must be explored further in prospective studies.

The relationship of interstitial cystitis/painful bladder syndrome to vulvodynia.
Carrico DJ, Sherer KL, Peters KM
Urol Nurs. 2009 Jul-Aug;29(4):233-8.

INTRODUCTION: Many patients have interstitial cystitis/painful bladder syndrome (IC/PBS), a condition of frequency, urgency, and pain affecting more than 1 million women in the United States. The vulva, not the urethra or bladder, may actually be the site of some of the reported pain in women with IC/PBS. PURPOSE: The purpose of this study was to identify the presence of vulvodynia in women diagnosed with IC/PBS. METHOD: A mailed survey was used to identify women with IC/PBS who also reported vulvar pain. The survey also identified related factors, such as menstrual/hormonal status, sexual function, abuse, and sequence of vulvar and bladder pain from adolescence to adulthood. RESULTS: Four-hundred-sixteen women with a documented diagnosis of IC/PBS were mailed a survey. The response rate was 49.6%, with 197 completed surveys returned. Results include vulvar pain in adolescence reported by 10.9% of the respondents, while vulvar pain in adulthood was reported by 48.4% of the women. During the last year, 62.7% of the respondents reported vulvar pain. Ninety-five percent (95%) of the women reported having been sexually active in adulthood, but one-third were not currently sexually active; 27% reported fear of pain as the reason. An abuse history was reported by 28.5% of the women. Of the women who were postmenopausal (two-thirds of the group), 38% used hormone replacement therapy. Birth history showed no correlation to vulvar pain. CONCLUSIONS: The chronic pain that IC/PBS patients feel may not be totally related to their bladder, but instead, may be vulvar pain. The incidence of abuse, past pelvic surgeries, pelvic floor dysfunction, and the chronologic sequence of co-morbid symptoms should be further assessed.

Interstitial cystitis is an etiology of chronic pelvic pain in young women.
Rackow BW, Novi JM, Arya LA, Pfeifer SM
J Pediatr Adolesc Gynecol. 2009 Jun;22(3):181-5

STUDY OBJECTIVE: The prevalence of interstitial cystitis (IC) in young women, especially in those 18 years old or younger, is not well defined. This case series was performed to investigate IC as a cause of chronic pelvic pain (CPP) in young women. DESIGN: Case series. SETTING: University medical center. PARTICIPANTS: Twenty-eight women with CPP, ages 13 to 25, who underwent concomitant laparoscopy and cystoscopy. INTERVENTIONS: All subjects underwent concomitant diagnostic laparoscopy and cystoscopy with hydrodistension for evaluation of CPP. Charts were reviewed to discern preoperative symptoms, operative findings, and postoperative diagnoses. MAIN OUTCOME MEASURE: Diagnosis of IC based on symptoms and cystoscopic findings. RESULTS: All 28 women had CPP, 23 (82%) had dysmenorrhea, and 12 of 25 (48%) sexually active subjects had dyspareunia. Twenty-six subjects (93%)

had urinary symptoms including frequency (75%), nocturia (32%), urgency (25%), and dysuria (18%). Eleven (39%) subjects were diagnosed with IC and 18 (64%) with endometriosis, including 7 (25%) subjects with both IC and endometriosis. Laparoscopic findings were normal in 6 (21%) subjects. Of the 26 subjects with urinary symptoms, 21 (81%) had findings on laparoscopy or cystoscopy. In this cohort of young women with chronic pelvic pain, urinary frequency and dyspareunia were significantly associated with the diagnosis of IC. CONCLUSIONS: The results of this study suggest that interstitial cystitis is an etiology of CPP in young women. Evaluation of the bladder as an origin of pelvic pain is warranted in young women with CPP and urinary frequency or dyspareunia.

Abdominal myofascial pain syndrome must be considered in the differential diagnosis of chronic pelvic pain.

Montenegro ML, Gomide LB, Mateus-Vasconcelos EL, Rosa-E-Silva JC, Candido-Dos-Reis FJ, Nogueira AA, Poli-Neto OB

Eur J Obstet Gynecol Reprod Biol. 2009 Jul 21. [Epub ahead of print]

Chronic pelvic pain is lower abdominal pain lasting at least 6 months, occurring continuously or intermittently and not associated exclusively with menstruation or intercourse. The involvement of the musculoskeletal system in chronic pelvic pain has been increasingly demonstrated. However, few studies exclusively examining abdominal myofascial pain syndrome as a cause of chronic pelvic pain in women are available. Therefore the objective of this manuscript is to describe the association between abdominal myofascial pain syndrome and chronic pelvic pain in women, and comment on methods for diagnosis and therapeutic options. There is evidence that the musculoskeletal system is compromised in some way in most women with chronic pelvic pain and that in 15% of these cases chronic pelvic pain is associated with abdominal myofascial pain syndrome but the scarcity of published data impairs the definition of protocols for the diagnosis and treatment of this disease. Abdominal myofascial pain syndrome is a highly prevalent disease associated with CPP, and because of this physicians should get used to make a precise and early diagnosis in order to avoid additional and unnecessary investigation.

Botulinum toxin type A-A novel treatment for provoked vestibulodynia? Results from a randomized, placebo controlled, double blinded study.

Petersen CD, Giraldi A, Lundvall L, Kristensen E

J Sex Med. 2009 Jul 10. [Epub ahead of print]

ABSTRACT Introduction. Vestibulodynia is an increasingly recognized problem among women and is often difficult to treat. Aim. This randomized, double blinded, placebo-controlled study aimed to evaluate the efficacy of Botox in the treatment of vestibulodynia. Methods. Sixty-four women were randomized to receive Botox (N = 32) or saline placebo (N = 32). Botulinum toxin A (20 I.E.) diluted in 0.5 mL saline or 0.5 mL saline was injected in the musculus bulbospongiosus at baseline. Main Outcome Measures. Pain was measured monthly on a visual analog scale (VAS) Likert scale. Sexual function was measured using the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale at baseline and at 3 and 6 months follow up. Quality of life was measured using the 36-item short-form (SF-36). Results. Sixty women (94%) completed the 6 months follow up. Both Botox and placebo produced significantly pain reduction ($P < 0.001$). There was no significant difference in the median VAS score between the groups at 6 months follow up ($P = 0.984$). An improvement on the FSFI full score from baseline until 6 months was not significantly different between the groups ($P = 0.635$). In the placebo group a statistical significant larger reduction in sexual distress was observed from baseline until 6 months follow up compared to the Botox group ($P = 0.044$). No statistical significant differences were observed between the B- and P-groups in regard to the SF-36 scores. Conclusion. Injection of 20 I.E. Botox in the vestibule of women diagnosed with vestibulodynia does not reduce pain, improve sexual functioning, or impact the quality of life compared to placebo and evaluated at 3 and 6 moths follow up. Both the Botox group and the placebo groups experienced a reduction in pain on the VAS Likert scale at 6 months follow up. Women with vestibulodynia have difficulty with sexual function and present with sexual distress, which has to be addressed in conjunction with pain to eliminate the disorder. Petersen CD, Giraldi A, Lundvall L, and Kristensen E. Botulinum toxin Type A-A novel treatment for provoked vestibulodynia? Results from a

randomized, placebo controlled, double blinded study.

Using botulinum toxin for pelvic indications in women.
Rao A, Abbott J
Aust N Z J Obstet Gynaecol. 2009 Aug;49(4):352-7

BACKGROUND: Botulinum toxin (BoNT) is a potent neurotoxin. Its ability to cause muscle paralysis is increasingly being utilised for the management of a number of conditions of interest to the gynaecologist. AIMS: This review aims to give the reader an overview of the use of BoNT for conditions presenting a management challenge for the gynaecologist, such as chronic pelvic pain and idiopathic detrusor overactivity. METHODS: The literature was reviewed regarding the use, side-effects and complications of BoNT in the pelvis, focussing on chronic pelvic pain, provoked vestibulodynia, conditions involving the lower gastrointestinal tract and detrusor overactivity. RESULTS: In terms of pain caused by pelvic floor spasm, daily pelvic pain and dyspareunia are the symptoms most likely to be improved by BoNT. Limited data regarding use for provoked vestibulodynia indicate an improvement in pain scores. In the lower gastrointestinal tract, injection into puborectalis has been showed to objectively improve intravaginal pressures, though there are no randomised controlled trials (class I studies) validating its use in this setting. Class I studies demonstrate a role for BoNT in the management of idiopathic detrusor overactivity, though long-term follow-up data are lacking. Potential problems with BoNT injection include toxin reactions, urinary and faecal incontinence, urinary retention and secondary treatment failure due to antibody production. CONCLUSIONS: A single class I study supports the use of BoNT for refractory pelvic floor spasm; however, further adequately powered class I studies for this indication and for provoked vestibulodynia are warranted.

Sacral neuromodulation in the treatment of vulvar vestibulitis syndrome.
Ramsay LB, Wright J Jr, Fischer JR
J Reprod Med. 2009 Jun;54(6):385-92

BACKGROUND:: Vulvar vestibular syndrome is a chronic pain syndrome that typically results in pain and irritation of the vulvar vestibule and has few effective options for treatment. CASE:: A 42-year-old woman presented with symptoms consistent with chronic vulvar vestibular syndrome that was refractory to multiple attempted therapies. The patient was offered sacral neuromodulation for treatment. She underwent a standard two-phase surgical implantation with good result at 2 years postimplantation. CONCLUSION:: Sacral neuromodulation was shown to be a valid treatment option for this patient and resulted in excellent patient satisfaction at 2-year follow-up. Although the exact mechanism of action is unknown, sacral neuromodulation may be a viable option for the management of chronic pain syndromes of the vulva and vagina.

Does physiotherapy treatment improve the self-reported pain levels and quality of life of women with vulvodynia? A pilot study.
Forth HL, Cramp MC, Drechsler WI
J Obstet Gynaecol. 2009 Jul;29(5):423-9

The study investigated whether a 3-month period of physiotherapy treatment improved the pain levels and quality of life of women with vulvodynia. A quasi-experimental method was used, comprising a within-subjects, pre-test/post-test design in which subjects acted as their own controls. A convenience sample of 14 subjects was recruited from referrals to women's health physiotherapy between May and August 2004. The McGill Pain Questionnaire and Short Form 36 (version 2) were used to assess changes in self-reported pain levels and quality of life, respectively. Subjects completed questionnaires on recruitment to the study, 3 months later (immediately prior to commencing physiotherapy treatment), and after 3 months of treatment. The study investigated whether changes in pain levels and quality of life observed during the 3-month intervention phase differed from those observed during the 3-month control phase. The pain levels of study subjects reduced during the treatment period relative to the control period, and

improvements were also observed in some aspects of quality of life. These results indicate that physiotherapy may offer some benefit in the treatment of vulvodynia. However, none of the findings reached statistical significance due to the small sample size. This study supports the view that physiotherapy provides pain relief for women with vulvodynia. Larger, randomized controlled trials are required to confirm the effectiveness of the treatment.

Current perspectives in vulvodynia.
Damsted-Petersen C, Boyer SC, Pukall CF
Womens Health (Lond Engl) 2009 Jul;5(4):423-36

Vulvodynia, or chronic vulvar pain, is a common but poorly understood condition. Although its etiology is not well understood, it appears to be multifactorial. As such, treatment options are targeted to reduce singular symptoms in a piecemeal fashion. A number of randomized, controlled trials have been conducted and at least one paper on combination therapy has been published; however, further systematic research is needed in order to more fully inform clinical practice.

Development and initial validation of the vaginal penetration cognition questionnaire (VPCQ) in a sample of women with vaginismus and dyspareunia.
Klaassen M, Ter Kuile MM
J Sex Med. 2009 Jun;6(6):1617-27

INTRODUCTION: Although the relevance of cognitions has been implicated in the etiology, explanatory models, and treatment of female sexual pain disorders, an instrument that assesses vaginal penetration cognitions is nonexistent. AIM: The aim of this study was to develop and to investigate the psychometric properties of the Vaginal Penetration Cognition Questionnaire (VPCQ). The VPCQ was explicitly designed to assess cognitions regarding vaginal penetration in women with vaginismus and dyspareunia. METHODS: A sample of 247 Dutch women with a female sexual dysfunction (FSD; 122 women with lifelong vaginismus and 125 women with dyspareunia) and 117 women without sexual complaints completed the questionnaire. Factor analyses were only conducted in the sample of women with FSD. Validation measures were conducted in both women with and without FSD. MAIN OUTCOME MEASURE: All women completed the VPCQ and several additional questions regarding biographic and complaint characteristics. RESULTS: Conduction of factor analyses yielded five subscales regarding cognitions about vaginal penetration: "control cognitions,""catastrophic and pain cognitions,""self-image cognitions,""positive cognitions," and "genital incompatibility cognitions." Reliability of these five VPCQ subscales ranged from 0.70 to 0.83, and the test-retest correlations were satisfactory. The five VPCQ subscales were reasonably stable across demographic variables and demonstrated good discriminant validity. All five subscales were able to detect significant differences between women with and without FSD. Additionally, the four subscales of the VPCQ concerning negative cognitions demonstrated the ability to differentiate between the two samples of women with FSD. Women with lifelong vaginismus reported lower levels of perceived penetration control and higher levels of catastrophic and pain cognitions, negative self-image cognitions, and genital incompatibility cognitions, when compared with women with dyspareunia. CONCLUSIONS: The present study indicates that the VPCQ is a valid and reliable brief self-report measure for assessing cognitions regarding vaginal penetration in women with vaginismus or dyspareunia.

Fear avoidance and self-efficacy in relation to pain and sexual impairment in women with provoked vestibulodynia.
Desrochers G, Bergeron S, Khalifé S, Dupuis MJ, Jodoin M

Clin J Pain. 2009 Jul-Aug;25(6):520-7

BACKGOUND: Provoked vestibulodynia is believed to be the most frequent cause of vulvodynia in women of childbearing age, with prevalence rates of up to 12% in the general population. Despite this high prevalence and the fact that vestibulodynia impacts negatively on quality of life, in particular sexual functioning, there has been a paucity of sound research to elucidate the condition's etiology. More specifically, few studies have focused on the role of psychologic factors in the experience of vulvo-vaginal pain and associated sexual impairment. OBJECTIVES: The present study aimed to determine the extent to which fear avoidance variables (catastrophizing, anxiety, fear of pain, hypervigilance) and self-efficacy differentially influenced changes in levels of induced and intercourse pain and also associated sexual dysfunction in these women. METHODS: Data were obtained from 75 vestibulodynia participants who completed a gynecologic examination, structured interview, and standardized questionnaires. RESULTS: The results of regression analyses revealed that higher catastrophizing, fear of pain, and hypervigilance in addition to lower self-efficacy together accounted for 15% of the variation in increased intercourse pain intensity. Among these, only catastrophizing contributed unique variance to intercourse pain. Results also showed that higher state anxiety and fear of pain (escape/avoidance) and also lower self-efficacy explained 22% of the variation in women's sexual impairment. However, only self-efficacy was found to be an independent correlate of sexual impairment. CONCLUSION: Findings support a theoretical model of vestibulodynia as a pain disorder influenced among others by cognitive and affective factors.

Effects of appraisal of sexual stimuli on sexual arousal in women with and without superficial dyspareunia.
Brauer M, Ter Kuile MM, Laan E
Arch Sex Behav. 2009 Aug;38(4):476-85

This study examined the effects of appraisal of sexual stimuli on sexual arousal in women with superficial dyspareunia (n = 50) and sexually functional women (n = 25). To elicit different appraisals of an erotic film fragment, participants received an instruction prior to viewing it, with a focus on genital pain or on sexual enjoyment. A neutral instruction served as a control condition. Assignment to instruction condition was randomized. Genital arousal (vaginal pulse amplitude) and self-report ratings of affect and genital sensations were obtained in response to the erotic stimulus. As predicted, appraisal of the erotic stimulus affected genital responding, albeit marginally significant. Follow-up tests indicated that women who received the genital pain instruction responded with marginally significant lower genital arousal levels than women who received the sexual enjoyment instruction (d = 0.67). A significant instruction effect for negative affect was found, signifying that negative affect ratings were highest after the genital pain instruction and lowest after the sexual enjoyment instruction (d = 0.80). A marginally significant group by instruction interaction effect was observed for positive affect, indicating that women with dyspareunia reported significantly less positive affect than controls after the sexual enjoyment instruction (d = 1.48). Whereas women with dyspareunia reported overall marginally significant more negative affect than controls (d = 0.48), there were no differences in genital responsiveness between groups. These results provided preliminary evidence for the modulatory effects of appraisal of sexual stimuli on subsequent genital responding and affect in women with and without sexual complaints.

Automatic and deliberate affective associations with sexual stimuli in women with superficial dyspareunia.
Brauer M, de Jong PJ, Huijding J, Laan E, Ter Kuile MM
Arch Sex Behav. 2009 Aug;38(4):486-97.

Current views suggest that in women with superficial dyspareunia the prospect of penile-vaginal intercourse automatically activates fear-related associations. The automatic activation of negative associations is assumed to interfere with the development of sexual arousal. In turn, this may further aggravate the dyspareunia-related complaints. To assess whether automatic negative associations are involved in this sexual pain disorder, women with superficial dyspareunia (n = 35) and a control group (n

= 35) completed a modified pictorial Affective Simon Task (AST). Questioning the role of dysfunctional automatic associations in superficial dyspareunia, the AST indicated that symptomatic women displayed relatively positive rather than negative automatic associations with sexual stimuli. At the self-report level, however, affective associations with sex cues were significantly more negative for women with dyspareunia than for controls. This discrepancy between "reflective" and "reflexive" affective associations with sexual stimuli in women with dyspareunia points to the relevance of conscious appraisal and deliberate rather than automatic processes in the onset and maintenance of dyspareunia.

Neuromodulators and therapeutic targets in neuropathic pain: from molecules to man.
Bermejo PE, Anciones B
CNS Neurol Disord Drug Targets. 2009 Jun;8(3):175-83

Neuropathic pain is a phenomenon characterized by a high population prevalence by possessing several etiologies. In contrast to nociceptive pain, painful signals in neuropathic pain are originated in the nervous system, present poor responses to conventional treatments and may worsen the quality of life. Antiepileptic drugs are increasingly used for different purposes including migraine, neuropathic pain, tremor or psychiatric disorders and they have started to be called neuromodulators. These drugs may act on very different targets such as sodium, potassium or calcium channels, purinergic, GABAergic, glutamatergic or vanilloid receptors and different cytokines including IL-6 or TNF, each if which may be important in managing some aspects of neuropathic pain. Antiepileptic drugs have demonstrated effectiveness in the treatment of this pathology, and owing to the important development of these drugs in the last years, they may become a very effective tool. On the other hand, the increasing knowledge of the pathophysiology of nociception is leading to new channels and receptors as potential targets for treatment. In this paper we try to review the different potential therapeutic targets and role of antiepileptic drugs in the treatment of this pathology.

Myofascial referred-pain data provide physiologic evidence of acupuncture meridians.
Dorsher PT
J Pain. 2009 Jul;10(7):723-31.

Recently published data suggest substantial anatomic, clinical, and physiologic (referred pain to meridian) overlap of myofascial trigger points and acupuncture points, particularly in the treatment of pain disorders. This qualitative study examines whether myofascial referred-pain data from the Trigger Point Manual can provide independent physiologic evidence of acupuncture meridians. Trigger point regions were subdivided from prior, validated trigger point region-classical acupuncture point correspondence results into subsets according to the 12 acupuncture Organs of their anatomically corresponding acupuncture points (Bladder, Gallbladder, Heart, Kidney, Large Intestine, Liver, Lung, Pericardium, Small Intestine, Spleen, Stomach, and Triple Energizer). The referred-pain patterns for each subset of trigger point regions were graphically applied to a virtual human model along with the subset's corresponding acupuncture Principal meridian. All 12 meridian distributions were compared qualitatively with the summed referred-pain distributions of their anatomically corresponding trigger point regions. For all 12 subsets of trigger point regions, their summed referred-pain patterns accurately predicted the distributions of their corresponding acupuncture meridians, particularly in the extremities. The myofascial referred-pain data from the Trigger Point Manual provides independent physiologic evidence of acupuncture meridians. Understanding these meridians may enhance treatment of both pain and non-pain conditions. PERSPECTIVE: This article demonstrates that myofascial referred-pain data provide independent physiologic evidence of acupuncture meridians. The acupuncture tradition provides pain practitioners with millennia of accumulated clinical experience treating pain (and visceral) disorders and offers the potential for novel pain treatment approaches and understanding of pain neurophysiology.

Visceral organ cross-sensitization - An integrated perspective.
Brumovsky PR, Gebhart GF
Auton Neurosci. 2009 Aug 11. [Epub ahead of print]

Viscero-somatic referral and sensitization has been well documented clinically and widely investigated, whereas viscero-visceral referral and sensitization (termed cross-organ sensitization) has only recently received attention as important to visceral disease states. Because second order neurons in the CNS have been extensively shown to receive convergent input from different visceral organs, it has been assumed that cross-organ sensitization arises by the same convergence-projection mechanism as advanced for viscero-somatic referral and sensitization. However, increasing evidence also suggests participation of peripheral mechanisms to explain referral and sensitization. We briefly summarize behavioral, morphological and physiological support of and focus on potential mechanisms underlying cross-organ sensitization.

Visceral afferents: what role in post-inflammatory pain?
Vergnolle N
Auton Neurosci. 2009 Aug 8. [Epub ahead of print]

Several weeks to several months after a bout of inflammation or an infectious event in a visceral organ, while inflammation or infection has resolved, defective nociceptive functions are sometimes still present, characterized by chronic pain symptoms, visceral hyperalgesia and allodynia. Visceral afferents which convey nociceptive messages have been shown to be hyperexcitable in inflammatory states. Only recently, studies have addressed visceral afferent electrical properties and neuroplastic changes in post-inflammatory situations. This review tries to appraise in post-inflammatory hypersensitive states, the most recent advances in the knowledge of visceral afferent inputs, together with in vivo recordings of visceral hyperalgesia and allodynia.

Sex Differences in Pain

Sex-related differences in pain.
Cairns BE, Gazerani P
Maturitas. 2009 Aug 20;63(4):292-6

This article provides an overview of sex-related differences in musculoskeletal pain and the role sex hormones and response to analgesic drugs may play in these differences. Some common pain conditions that include temporomandibular disorders, rheumatoid arthritis, fibromyalgia syndrome and tension-type and migraine headaches, show fairly marked sex-related differences in their occurrence, however, with the exception of rheumatoid arthritis, these pain conditions are also characterized by a lack of understanding of their basic underlying pathophysiology. The association of pain symptoms of these musculoskeletal pain conditions with the reproductive cycle of women is strongly suggestive of a role of the estrogens and/or progesterones, the main female sex hormones, in sex-related differences in pain. Nevertheless, an alternative suggestion that testosterone, the major male sex hormone, protects men from these chronic musculoskeletal pain conditions, has also been made. Indeed, emerging evidence suggests that both male and female sex hormones may contribute to the marked sex-related differences in the occurrence of certain musculoskeletal pain conditions. Men and women also appear to differ in response to pain treatment with certain analgesic drugs. The mechanistic basis for these sex-related differences is not entirely understood but sex hormones are thought to be one of the influencing factors. An improved understanding of mechanisms which underlie sex-related differences in musculoskeletal pain and response to analgesic drugs should permit improved pain management strategies for male and female musculoskeletal pain patients in the clinical setting.

Evidence for a key role of steroids in the modulation of pain.
Mensah-Nyagan AG, Meyer L, Schaeffer V, Kibaly C, Patte-Mensah C
Psychoneuroendocrinology. 2009 Jul 3. [Epub ahead of print]

Neurotransmitters such as glutamate, substance P, serotonin and gamma-aminobutyric acid pivotally control pain mechanisms. It is also well known that inflammatory and/or neuropathic pain may depend on the action of diverse cytokines and other molecules including eicosanoids, endorphins, calcitonin-gene related peptide, free radicals and transcription factors. Because steroids control the development, activities and plasticity of the nervous system, these compounds are of particular interest in the modulation of pain. The paper discusses various data supporting the existence of key regulatory effects of steroids in the control of pain. In particular, we analyzed three categories of observations which historically contributed to demonstrate that endogenous and synthetic steroids play a crucial role in the regulation of neurobiological processes involved in pain sensation. The first series of data, which present the chemical characteristics enabling steroids to act on several tissues, also summarize pertinent results supporting the modulation of pain sensation by steroidal compounds. The second category of data evokes psychosocial, fundamental and clinical results suggesting the existence of sex steroid-based differences in pain perception. Finally, we discuss recent evidence showing the endogenous production of neurosteroids and their effects in the spinal cord which crucially controls pain transmission. Taken together, the data reviewed herein suggest that future investigations aiming to develop effective steroid-based strategies against chronic pain must integrate in a complementary manner anti-inflammatory properties of steroids, sex steroid-induced dimorphism in pain perception and regulatory effects exerted by endogenous neurosteroids in pain neural circuits.

Excitatory and inhibitory pain mechanisms during the menstrual cycle in healthy women.
Tousignant-Laflamme Y, Marchand S
Pain. 2009 Jul 8. [Epub ahead of print]

Sex differences in pain perception have been clearly documented in the literature during the last decades and it has been shown that women perceived more pain than men. Sex hormones (SHs) are thought to be one of the main mechanisms which explain sex differences in pain. Pain is a dynamic phenomenon involving both excitatory and inhibitory mechanisms. Previous studies have verified the effect of SH on excitatory mechanisms but not on endogenous pain inhibitory mechanisms. The main objective of this study was to establish if pain perception and diffuse noxious inhibitory control (DNIC) vary across the menstrual cycle (MC). Thirty-two healthy women with a regular MC were tested three times across their MC (days 1-3, days 12-14 and days 19-23). Experimental pain consisted of two tonic heat pain stimulations (thermode) separated by a 2-min cold pressor test (CPT) (conditioning stimulus activating DNIC). Pain ratings were measured with a visual analogue scale. Heat pain threshold, pain tolerance and mean pain intensity during both the 2-min thermode test and CPT did not vary throughout the MC. However, we found significantly more pain inhibition (DNIC effectiveness) during the ovulatory phase compared to the menstrual and luteal phases ($p=0.05$). The main finding of this study is the observation that only inhibitory mechanisms (DNIC analgesia) and not excitatory pain mechanisms vary throughout the MC, where women have greater DNIC in the ovulatory phase. The higher occurrence of pain and lower pain threshold previously reported during the MC could be related to a reduction in endogenous pain control mechanisms.

Women experience greater heat pain adaptation and habituation than men.
Hashmi JA, Davis KD
Pain. 2009 Jul 24. [Epub ahead of print]

It is not clear how males and females cope with pain over time and how sensory and emotional qualities fluctuate from moment to moment, although studies of pain at discrete time points suggest that women are more pain sensitive than men. Therefore, we developed a new broader-based pain model that incorporates a temporally continuous assessment of multiple pain dimensions across sensory and affective dimensions, and normalized peak pain intensity to unmask sex differences that may otherwise be confounded by inter-individual variability in pain sensitivity. We obtained continuous ratings of pain, burning, sharp, stinging, cutting, and annoyance evoked by repeated prolonged noxious heat stimuli in 32

subjects. Strikingly, females reported more pain than males at the outset of the first exposure to pain, but then experienced less pain and annoyance than males as a painful stimulus was sustained and with repeated stimulation. Patterns of pain and annoyance attenuation in women resembled the attenuation of sharp, stinging and cutting sensations, whereas patterns of pain and annoyance in men resembled burning sensations. Taken together, these data demonstrate a prominent sex difference in the time course of pain. Notably only females demonstrate adaptation and habituation that allow them to experience less pain over time. These findings suggest a sexual dichotomy in mechanisms underlying pain intensity and annoyance that could involve specific quality-linked mechanisms. Importantly, temporal processing of pain differs between males and females when adjusted for sex differences in pain sensitivity. Our findings provide insight into sex differences in tonic and possibly chronic pains.

Sex differences in inflammation evoked by noxious chemical, heat and electrical stimulation.
Carmichael NM, Charlton MP, Dostrovsky JO
Brain Res. 2009 Jun 18;1276:103-11. Epub 2009 Apr 15

Neurogenic inflammation (NI) is a feature of several inflammatory pain conditions in which females are overrepresented. Therefore, we asked if there are sex differences in the inflammatory response evoked by well known neurogenic stimuli. We compared the amount of plasma extravasation (PE), a measure of inflammation, in the hindpaw skin of male and female rats caused by subcutaneous injection of capsaicin, application of noxious heat (51 degrees C water bath) or electrical stimulation of the saphenous nerve. We also compared the amount of PE in males and females evoked by substance P (SP), the principal neurogenic mediator of PE. PE was quantified using a video camera and digital image analysis to measure changes in reflectance (pixel intensity, PI) of skin due to accumulation of extravasated Evans blue (EB) dye. The increase in PI induced by capsaicin was significantly greater in females compared to males ($p<0.001$) and in estrus, diestrus, and metestrus females compared to proestrus females. The time to reach maximal capsaicin-induced PE was two times longer in estrus, diestrus, and metestrus females compared to males ($p<0.05$). PE induced by heat was also significantly greater in females compared to males ($p<0.001$), however, there was no sex-related difference in PE induced by electrical stimulation or by injection of SP. These findings show that females have a greater inflammatory response when inflammation is induced by capsaicin and noxious heat suggesting possible sex-related changes in TRPV-1 receptor mediated mechanisms. These results add to the growing list of sex difference responses to noxious somatic stimulation.

Autonomic reactivity to pain throughout the menstrual cycle in healthy women.
Tousignant-Laflamme Y, Marchand S
Clin Auton Res. 2009 Jun;19(3):167-73

INTRODUCTION: We previously demonstrated that only men showed a significant correlation between heart rate (HR) and pain. Other authors also found sex differences in the autonomic and cardiovascular reactivity to pain, and sex hormones have been proposed to be partly responsible for these differences. However, no previous studies were done to examine if the autonomic and cardiovascular reactivity to pain vary across the menstrual cycle (MC). METHODS: Thirty-two healthy women were randomly tested 3 times across their MC (days 1-3, days 12-14 and days 19-23). The painful stimulus consisted of a 2 min cold pressor test (CPT) (immersion of the arm in cold noxious water at 12 degrees C). HR and blood pressure were recorded before and during the immersion using an ECG which also allowed us to measure heart rate variability (HRV). RESULTS: Pain ratings during the CPT did not vary across the MC ($P = 0.14$). HRV (sympathetic and parasympathetic indicators) and blood pressure (systolic and diastolic) analysis showed that women had similar cardiovascular reactivity to pain throughout their MC. However, we found that the correlation between HR and pain ratings during the CPT varied across the MC, where there was a significant positive relationship between HR and pain ($r = 0.36$, $P < 0.05$) only during the menstrual phase. INTERPRETATION: These results add to our previous finding but tend to show that sex hormones have minimal influence on autonomic reactivity. Moreover, the great variability in intra- and inter-subject reactivity to pain does not allow us to predict the autonomic and cardiovascular reactivity to pain women will show throughout the MC.

Estrogen-dependent changes in visceral afferent sensitivity.
Sanoja R, Cervero F
Auton Neurosci. 2009 Jul 22. [Epub ahead of print]

Many forms of chronic pain are more prevalent in women and this is interpreted as the consequence of a direct role of estrogens in the modulation of pain perception. Some functional pain states, i.e. those without a clear and demonstrable pathology, are also more prevalent in women and the pain in these conditions is also modulated by hormonal variations during the menstrual cycle. Increased pain sensitivity is commonly interpreted as the consequence of peripheral or central hyperexcitability of nociceptive pathways. Therefore a role has been suggested for estrogen in the modulation of the excitability of nociceptive afferents and central neurons. The literature on the sign of this modulation is not uniform, with reports pointing to estrogen as either pro- or anti-nociceptive. In our hands, a permanent reduction in the levels of estrogen, such as that induced by surgical ovariectomy (OVX) generates a hyperalgesic state of slow onset and long duration that can be prevented or reversed by exogenous administration of estrogen. The hyperalgesia is characterized by mechanical and thermal hyperalgesia in the abdominal and pelvic regions as well as by visceral hypersensitivity. The possible role of estrogen in the prevention of chronic painful states is discussed.

Effects of 17{beta}-estradiol on responses of viscerosomatic convergent thalamic neurons in the ovariectomized female rat.
Reed WR, Chadha HK, Hubscher CH
J Neurophysiol. 2009 Aug;102(2):1062-74

Ovarian hormones have been shown to exert multiple effects on CNS function and viscerosomatic convergent activity. Ovariectomized (OVX) female rats were used in the present study to examine the long-term effects of proestrus levels of 17beta-estradiol (EB) delivered by a 60-day time-released subcutaneous pellet on the response properties of viscerosomatic convergent thalamic neurons. In addition, avoidance thresholds to mechanical stimulation for one of the convergent somatic territories, the trunk, was assessed using an electro-von Frey anesthesiometer before and at the end of the 6-wk post-OVX/implant period prior to the terminal electrophysiological experiments, which were done under urethane anesthesia. Rats implanted with an EB-containing pellet, relative to placebo controls, demonstrated 1) altered thalamic response frequencies and thresholds for cervix and vaginal but not colon stimulation; 2) some response variations for just the lateral group of thalamic subnuclei; and 3) altered thalamic response frequencies and thresholds for trunk stimulation. Thalamic response thresholds for trunk pressure in EB versus placebo rats were consistent with the avoidance thresholds obtained from the same groups. In addition, EB replacement affected visceral and somatic thresholds in opposite ways (i.e., reproductive-related structures were less sensitive to pressure, whereas somatic regions showed increased sensitivity). These results have obvious reproductive advantages (i.e., decreased reproductive organ sensitivity for copulation and increased trunk sensitivity for lordosis posturing), as well as possible clinical implications in women suffering from chronic pelvic pain syndromes and/or neuropathic pain.

Other Vulvovaginal Disorders

Prevalence and impact of vaginal symptoms among postmenopausal women.
Santoro N, Komi J
J Sex Med. 2009 Aug;6(8):2133-42

INTRODUCTION: Vulvovaginal atrophy (VVA) is reported by one-quarter to one-half of postmenopausal women. AIM: We evaluated the prevalence, inconvenience of, and issues surrounding hormone use for

VVA symptoms in women who were current, past, and never users of menopausal hormone therapy (MHT), along with the relationship of sexual activity to VVA symptoms. METHODS: An online survey was sent to 3,471 women >or=45 years old participating in a panel of approximately 43,000 U.S. adults maintained by Knowledge Networks. Respondents were stratified by MHT use (current, past, and never) and sexual activity (sexually active and not sexually active). Final respondent data underwent a poststratification process and Chi-square analysis of hormone use and VVA by sexual activity. Main Outcome Measures. Percent, calculated as the ratio of response over total responding for each survey question for all and stratified respondents. RESULTS: Forty-five percent (1,038/2,290) of respondents (age range 45-89 years; mean 60.7 years) were postmenopausal and currently or previously experienced VVA. Approximately 60% of past or never users of MHT reported vaginal symptoms; >90% found them bothersome. In comparison, 82% of current users reported VVA symptoms prior to use. 85% of all respondents were aware of safety issues associated with MHT. The prevalence and perceived severity of VVA symptoms were substantial but less frequent in nonsexually active women. Analysis of MHT use by past or current hormone use indicated a trend away from oral dosing and towards patch or vaginal hormones. CONCLUSIONS: Postmenopausal women have a high rate of VVA symptoms. Those who use MHT do so for multiple reasons-hot flashes, VVA, bone protection, dyspareunia-and most have concerns about long-term safety, despite the fact that the majority of MHT use was for >5 years. Safety concerns and lack of physician recommendation were major reasons for not using or discontinuing MHT.

Vaginal dryness: a comparison of prevalence and interventions in 11 countries.
Leiblum SR, Hayes RD, Wanser RA, Nelson JS
J Sex Med. 2009 Jul 13. [Epub ahead of print]

Introduction. There is limited research comparing cross-cultural differences in women's experiences of vaginal dryness. Aim. To examine international differences in the prevalence of vaginal dryness, the degree to which it is experienced as problematic or bothersome, the use of lubricants to alleviate it, and women's discussion of this problem with physicians. Main Outcome Measures. Questionnaire measuring the level of vaginal dryness and degree to which it is perceived as bothersome. Methods. The Global Survey of Sexual Attitudes and Practices was administered to 6,725 women from 11 countries: UK, Germany, Japan, Australia, Canada, Spain, Italy, Mexico, Argentina, Brazil and Thailand. Results. Prevalence of self-reported vaginal dryness varied from a minimum of 5.8% in Italy to a maximum of 19.7% in Brazil. The proportion of women with self-reported vaginal dryness who found it very bothersome varied as well (e.g., 5.6% UK, 26.4% Germany). Pain during intercourse ranged from a reported low of 3.6% in Australia to 18.6% in Brazil. Older women (50-65 years) as compared with younger women (18-34 years) reported significantly more vaginal dryness in the UK, Australia, Canada, Italy, Spain, Argentina, and Thailand (P values <0.02). The majority of women under 50 attributed vaginal dryness to inadequate sexual arousal while women over 50 believed it was because of aging or menopause. Cross-culturally, women differed substantially in the likelihood of discussing their sexual life/concerns with a physician. Conclusion. Women from different countries differ substantially in their experiences, concerns, and reports of vaginal dryness/sexual pain, as well as their familiarity with personal lubricants as a treatment. Researchers should assess the prevalence and degree of the bother of vaginal dryness in order to make international comparisons of the burden of this condition.

Efficacy and tolerability of local estrogen therapy for urogenital atrophy.
Archer DF
Menopause. 2009 Jul 13. [Epub ahead of print]

OBJECTIVE: This study aimed to identify vaginal discomfort in the form of dryness, itching, burning, and dyspareunia, which remains an inadequately addressed clinical problem for many postmenopausal women, and to describe the age or menopause-related dysfunction of the female urethral tract, which is prevalent. METHODS: Medical literature on the incidence and treatment of vulvovaginal symptoms in postmenopausal women was reviewed. RESULTS: Urogenital atrophy should not be considered an

inevitable consequence of menopause because various hormonal and nonhormonal products are available to relieve symptoms. Estrogen deficiency is the primary cause of atrophic urogenital changes, and postmenopausal estrogen therapy is the most logical choice for treatment. All available low-dose local estrogen formulations are effective, but the optimal dose and preferred mode of estrogen administration to achieve symptom relief can vary from woman to woman. Individualization of therapy is the key to balancing the desired local effects of topical vaginal estrogens with potential systemic effects, which may or may not be desired. CONCLUSIONS: This article reviews the use of products for the management of urogenital atrophy in terms of their efficacy, safety, and other characteristics that may influence prescribing and woman's preference.

Effect of intravaginal dehydroepiandrosterone (prasterone) on libido and sexual dysfunction in postmenopausal women.
Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez JL, Girard G, Baron M, Ayotte N, Moreau M, Dubé R, Côté I, Labrie C, Lavoie L, Berger L, Gilbert L, Martel C, Balser J
Menopause. 2009 Aug 5 [Epub ahead of print]

OBJECTIVE: The objective of this study was to provide evidence that the transformation of DHEA into both androgens and/or estrogens locally in cells of the three layers of the vagina (epithelium, lamina propria, and muscularis) would have effects of greater impact, including effects on sexual function, than only effects on superficial epithelial cells as achieved with estrogens. METHODS: This prospective, randomized, double-blind, and placebo-controlled phase III clinical trial has evaluated the effect of daily local intravaginal application of Prasterone (dehydroepiandrosterone; DHEA) for 12 weeks on the domains of sexual dysfunction, namely, desire/interest, arousal, orgasm, and pain at sexual activity, in 216 postmenopausal women with moderate to severe symptoms of vaginal atrophy. RESULTS: A time- and dose-dependent improvement of the four domains of sexual function was observed. At the 12-week time interval, the 1.0% DHEA dose led, compared with placebo, to 49% (P = 0.0061) and 23% (P = 0.0257) improvements of the desire domains in the Menopause Specific Quality of Life and Abbreviated Sex Function questionnaires, respectively. Compared with placebo, the Abbreviated Sex Function arousal/sensation domain was improved by 68% (P = 0.006), the arousal/lubrication domain by 39% (P = 0.0014), orgasm by 75% (P = 0.047), and dryness during intercourse by 57% (P = 0.0001). CONCLUSIONS: By a local action in the vagina, DHEA applied daily at doses at which serum steroids remain well within normal postmenopausal values exerts relatively potent beneficial effects on all four aspects of sexual dysfunction. Such data indicate that combined androgenic/estrogenic stimulation in the three layers of the vagina exerts important beneficial effects on sexual function in women without systemic action on the brain and other extravaginal tissues.

Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy.
Freedman M, Kaunitz AM, Reape KZ, Hait H, Shu H
Menopause. 2009 Jul-Aug;16(4):735-41

OBJECTIVE: The aim of this study was to evaluate low-dose synthetic conjugated estrogens A (SCE-A) cream administered twice weekly for the treatment of moderate to severe vulvovaginal atrophy (VVA) in a symptomatic postmenopausal population. METHODS: In a multicenter, double-blind, randomized, placebo-controlled study, 305 women with symptoms of VVA were treated with either 1 g SCE-A cream (n = 150) or matching placebo (n = 155) for a period of up to 12 weeks. Participants had to have a vaginal pH of greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and at least one of five symptoms of VVA (dryness, soreness, irritation, pain with intercourse, and bleeding after intercourse) that was moderate or severe in intensity. Women had to select one moderate or severe symptom as the most bothersome. RESULTS: Efficacy was assessed at 2, 3, 4, 8, and 12 weeks and included the change from baseline in the severity of the most bothersome symptom (MBS), maturation index, and pH. Most women identified vaginal dryness as the MBS (48%) followed by pain with intercourse (31.3%). A statistically significant increase in the maturation index and significant decreases in pH and severity of the MBS were observed for those treated with SCE-A vaginal cream compared with placebo. CONCLUSIONS: A low dose (1 g = 0.625 mg) of SCE-A vaginal cream administered twice weekly was shown to be effective

compared with placebo in treating VVA in postmenopausal women for the three coprimary efficacy measures of maturation index, pH, and severity of the MBS.

Monthly itraconazole versus classic homeopathy for the treatment of recurrent vulvovaginal candidiasis: a randomised trial.
Witt A, Kaufmann U, Bitschnau M, Tempfer C, Ozbal A, Haytouglu E, Gregor H, Kiss H
BJOG 2009; DOI: 10.1111/j.1471-0528.2009.02262.x

Objective Antimycotics effectively treat sporadic and recurrent vulvovaginal candidiasis (RVVC). Classic homeopathy (CH) is also used to treat this condition. We compared the efficacy of CH and itraconazole in reducing the frequency of RVVC episodes. Design Single-centre, prospective, randomised trial. Sample One hundred-and-fifty patients with a history of RVVC and an acute episode of VVC. Methods Women were randomised into 3 groups: itraconazole with lactobacilli (group 1), itraconazole without lactobacilli (group 2) and CH (group 3). Itraconazole treatment of acute infection was followed by a 6-month maintenance regimen with monthly single-day itraconazole (200 mg bid). Women in group 1 were given additional vaginal lactobacilli for 6 days per month throughout the maintenance regimen Thereafter, patients were followed without treatment for 6 months. CH treatment was performed for 12 months. Results Women in groups 1 and 2 reached a culture-free status significantly earlier than women in group 3 (log-rank test; $P < 0.0001$). Specifically, before the start of the maintenance regimen, 44 of 49 women (89.8%) in group 1 and 40 of 47 women (85%) in group 2 were free of Candida detectable by culture, 22 of 46 (47%) women in group 3 reached a culture-free status after the first visit, but had a recurrence significantly earlier compared with women in groups 1 and 2 (log-rank test; $P = 0.002$). After 12 months, 19 of 25 (76%) women in group 1, 18 of 23 (78%) women in group 2 and 9 of 23 (39%) women in group 3 were free of culture-detectable Candida. Assessment of RVVC-associated complaints by VAS score showed that women in group 3 had a significantly higher level of discomfort (36.8, 25.1 and 27.7 respectively; $P < 0.001$) and were significantly less satisfied (59.2, 68.2 and 71.7 respectively; $P < 0.001$) than patients in groups 1 and 2. Conclusions Monthly cycle-dependent itraconazole is more effective than CH in the treatment of RVVC. Lactobacilli do not confer an added benefit.

The role of lactobacillus probiotics in the treatment or prevention of urogenital infections--a systematic review.
Abad CL, Safdar N
J Chemother. 2009 Jun;21(3):243-52

Probiotics are increasingly being used to treat and prevent urogenital infections. However, a critical assessment of their efficacy in major urogenital infections is lacking. We report the results of a systematic review to determine the efficacy of probiotics for prevention or treatment of three major urogenital infections: bacterial vaginosis, vulvovaginal candidiasis, and urinary tract infection. Using multiple computerized databases, we extracted data from clinical trials using a lactobacillus-containing preparation to either prevent or treat a urogenital infection. Of 25 included studies, 18 studies used lactobacillus preparations for treatment or prevention of urogenital infections and seven studies focused solely on vaginal colonization. Four studies included patients with vaginal candidiasis, five included patients with urinary tract infections, and eight included patients with bacterial vaginosis. One included several types of genitourinary infections. Overall, lactobacilli were beneficial for the treatment of patients with bacterial vaginosis. No clear benefit was seen for candidiasis or urinary tract infection. Studies were heterogeneous, with some limited by a small population size. In conclusion, the use of certain lactobacillus strains such as L. rhamnosus GR-1 and L. reuteri for prevention and treatment of recurrent urogenital infection is promising, especially for recurrent bacterial vaginosis. Scant data on the use of probiotics for urinary tract infection and vulvovaginal candidiasis precludes definitive recommendations. Further research and larger studies on types of lactobacilli strains, dosage of lactobacilli, optimal route and vehicle of administration are needed.

Susceptibility profile of vaginal isolates of candida albicans prior to and following fluconazole introduction - impact of two decades.
Bulik CC, Sobel JD, Nailor MD
Mycoses. 2009 Jun 26 [Epub ahead of print]

Current treatment options for vulvovaginal candidiasis due to Candida albicans include over-the-counter and prescription antifungal agents. Fluconazole has been used extensively with an unknown impact on susceptibility. To investigate antifungal susceptibility trends in clinical vaginal isolates of C. albicans from 1986 to 2008, microdilution susceptibility was performed on randomly selected single isolates. Minimum inhibitory concentrations (MICs) were determined for: fluconazole, clotrimazole, miconazole, ketoconazole, itraconazole, voriconazole, flucytosine and amphotericin B. The MIC(90) for each drug was then calculated for the time periods: 1986-1989, 1992-1996 and 2005-2007. A total of 250 C. albicans vaginal isolates were included. The MIC(90) (mcg ml(-1)) for fluconazole was 0.25, 0.5 and 0.5 mcg ml(-1) for each grouping, respectively. The corresponding MIC(90) for flucytosine was 1, 2 and 8 mcg ml(-1), respectively. The MIC(90) for the remaining agents remained unchanged across time periods mentioned. Of note, the percentage of isolates with MIC >/=1 and >/=2 mcg ml(-1) for fluconazole increased from 3% to 9% over the study period. Although the C. albicans MIC(90) to fluconazole in vaginal isolates has not shown a clinically significant increase since 1986, there is an increasing number of isolates with elevated MICs. The implications of this increase are unknown, but given the achievable vaginal concentrations of fluconazole, reduced susceptibility may have clinical relevance.

Vaginal microbiota of women with frequent vulvovaginal candidiasis.
Zhou X, Westman R, Hickey R, Hansmann MA, Kennedy C, Osborn TW, Forney LJ
Infect Immun. 2009 Sep;77(9):4130-5

Vulvovaginal candidiasis (VVC) is an insidious infection that afflicts a large proportion of women of all ages, and 5 to 8% of affected women experience recurrent VVC (RVVC). The aim of this study was to explore the possible importance of vaginal bacterial communities in reducing the risk of RVVC. The species composition and diversity of microbial communities were evaluated for 42 women with and without frequent VVC based on profiles of terminal restriction fragment polymorphisms of 16S rRNA genes and phylogenetic analysis of cloned 16S rRNA gene sequences from the numerically dominant microbial populations. The data showed that there were no significant differences between the vaginal microbial communities of women in the two groups (likelihood score, 5.948; bootstrap P value, 0.26). Moreover, no novel bacteria were found in the communities of women with frequent VVC. The vaginal communities of most women in both groups (38/42; 90%) were dominated by species of Lactobacillus. The results of this study failed to provide evidence for the existence of altered or unusual vaginal bacterial communities in women who have frequent VVC compared to women who do not have frequent VVC. The findings suggest that commensal vaginal bacterial species may not be able to prevent VVC.

Reduced fluconazole susceptibility of candida albicans isolates in women with recurrent vulvovaginal candidiasis: effects of long-term fluconazole therapy.
Shahid Z, Sobel JD
Diagn Microbiol Infect Dis. 2009 Jul;64(3):354-6

Fluconazole resistance and resultant failure to control Candida vaginitis (vulvovaginal candidiasis) remains extremely uncommon; however, long-term clinically relevant decrease in fluconazole susceptibility undoubtedly occurs and accompanies prolonged fluconazole chemoprophylaxis. Accordingly, in patients with refractory vaginitis or breakthrough infections due to Candida albicans, in vitro susceptibility testing is essential to optimally manage vaginitis.

Prospective study of vaginal bacterial flora and other risk factors for vulvovaginal candidiasis.

McClelland RS, Richardson BA, Hassan WM, Graham SM, Kiarie J, Baeten JM, Mandaliya K, Jaoko W, Ndinya-Achola JO, Holmes KK
J Infect Dis. 2009 Jun 15;199(12):1883-90

BACKGROUND: It has been suggested that vaginal colonization with lactobacilli may reduce the risk of vulvovaginal candidiasis (VVC), but supporting data are limited. Our objective was to determine the relationship between vaginal bacterial flora and VVC. METHODS: We conducted a prospective cohort analysis that involved 151 Kenyan sex workers. At monthly follow-up visits, VVC was defined as the presence of yeast buds, pseudohyphae, or both on a wet preparation (including potassium hydroxide preparation) of vaginal secretions. Generalized estimating equations were used to identify correlates of VVC. RESULTS: Participants returned for a median of 12 visits (interquartile range, 11-12 visits). VVC was identified at 162 visits, including 26 involving symptomatic VVC. Bacterial vaginosis was associated with fewer episodes of VVC (adjusted odds ratio [aOR], 0.29 [95% confidence interval {CI}, 0.16-0.50]). After excluding women with concurrent bacterial vaginosis, another possible cause of vaginal symptoms, the likelihood of symptomatic VVC was higher among those who had had yeast identified on wet preparation of vaginal secretions during the past 60 days (aOR, 4.06 [95% CI, 1.12-14.74]) and those with concurrent vaginal Lactobacillus colonization (aOR, 3.75 [95% CI, 1.30-10.83]). CONCLUSIONS: Contrary to the commonly posited hypothesis that vaginal Lactobacillus colonization has a protective effect, we found that such colonization was associated with a nearly 4-fold increase in the likelihood of symptomatic VVC.

Hyaluronan in vaginal secretions: association with recurrent vulvovaginal candidiasis.
Lev-Sagie A, Nyirjesy P, Tarangelo N, Bongiovanni AM, Bayer C, Linhares IM, Giraldo PC, Ledger WJ, Witkin SS
Am J Obstet Gynecol. 2009 Aug;201(2):206.e1-5

OBJECTIVE: We evaluated whether vaginal concentrations of hyaluronan were altered in women with recurrent vulvovaginal candidiasis (RVVC). STUDY DESIGN: Lavage samples from 17 women with acute RVVC, 27 women who were receiving a maintenance antifungal regimen, and 24 control women were tested for hyaluronan and interleukin (IL)-6, IL-12, and IL-23 by enzyme-linked immunosorbent assay. RESULTS: Median vaginal hyaluronan concentrations were 33.8 ng/mL (range, 21.6-66.3 ng/mL) in women with acute RVVC, 15.0 ng/mL (range, 11.2-50.6 ng/mL) in women who were receiving maintenance therapy, and 4.2 ng/mL (range, 3.6-12.0 ng/mL) in control subjects (P </= .02). The vaginal hyaluronan concentration was 27.4 ng/mL (range, 15.4-37.7 ng/mL) when Candida was detected by microscopy and 9.5 ng/mL (range, 7.7-14.6 ng/mL) in microscopy-negative cases (P = .0354). Elevated hyaluronan levels were associated with itching plus burning (40.7 ng/mL) or itching plus discharge (42.1 ng/mL), as opposed to itching only (6.2 ng/mL; P = .0152). Hyaluronan and IL-6 levels were correlated (P = .0009). CONCLUSION: Hyaluronan release is a component of the host response to a candidal infection and may contribute to symptoms.

Rapid detection of vaginal candida by newly developed immunochromatography.
Matsui H, Hanaki H, Takahashi K, Yokoyama A, Nakae T, Sunakawa K, Omura S
Clin Vaccine Immunol. 2009 Aug 5 [Epub ahead of print]

For the diagnosis of vulvovaginal candidiasis, we developed a simple immunochromatographic method that enables the detection of vaginal Candida within about 30 min. Overall, the sensitivity, specificity, positive predictive value and negative predictive value of this method appeared to be 80.3, 99.3, 98.0 and 92.0 %, respectively.

Topical calcineurin inhibitors for the treatment of vulvar dermatoses.
Goldstein AT, Thaçi D, Luger T

Eur J Obstet Gynecol Reprod Biol. 2009 Sep;146(1):22-9.

Repeated courses of potent topical corticosteroids and maintenance therapy with moderately potent topical corticosteroids are frequently needed to treat various forms of vulvar dermatoses, which are often characterized by an abnormal proliferation or activation of T lymphocytes. Because such therapeutic regimen is associated with an increased risk of potential side effects, particularly skin atrophy, an anti-inflammatory alternative to topical corticosteroids is desirable. The two non-steroid topical calcineurin inhibitors pimecrolimus and tacrolimus are immunomodulators that block the release of inflammatory cytokines from T lymphocytes in the skin while promoting cutaneous innate host defences. They are currently approved in Europe and in the United States of America as second-line anti-inflammatory agents for the treatment of atopic dermatitis. We provide a comprehensive summary of existing case reports, series of cases, and open-label prospective studies concerning the use of topical pimecrolimus and tacrolimus for the treatment of anogenital lichen sclerosus, genital lichen planus, vulvar lichen simplex chronicus and related pruritic vulvar dermatoses (chronic vulvar pruritus and allergic contact dermatitis of the vulva). The available data suggest that both topical calcineurin inhibitors may be effective and well tolerated in these vulvar dermatoses, although topical pimecrolimus may exhibit a better long-term tolerability profile. Being devoid of steroid-related side effects, they may represent a useful second-line therapeutic option for patients who are intolerant of, or resistant to topical corticosteroids. Controlled clinical trials and comparative studies are warranted to substantiate the promising findings summarized in this review.

T cells reactive with the NC16A domain of BP180 are present in vulval lichen sclerosus and lichen planus.

Baldo M, Bailey A, Bhogal B, Groves RW, Ogg G, Wojnarowska F

J Eur Acad Dermatol Venereol. 2009 Aug 14 [Epub ahead of print]

Background: Lichen sclerosus (LS) is a chronic inflammatory skin condition. The recent demonstration of circulating autoantibodies to extracellular matrix protein 1 and to basement membrane zone (BMZ) components, chiefly BP180, suggests that autoimmunity to these components might contribute to pathogenesis. However, there is no binding of autoantibodies in vivo and as LS is characterized by a lymphocytic infiltrate, it seems likely that LS is mediated, in part, by antigen-specific lymphocytes. Similar mechanisms may apply to vulval lichen planus (LP), an interface dermatitis, with clinical and immunological overlap with LS. Objectives This study aims to test the hypothesis that T cells reactive with the NC16A domain of BP180 are present in the peripheral blood of patients with vulval LS and LP. Methods Isolated peripheral blood mononuclear cells from 14 patients with vulval LS, 5 with vulval LP and 4 healthy controls were grown in vitro. We examined for immunogenicity of overlapping peptides spanning the NC16A domain of BP180 using interferon-gamma enzyme-linked immunospot assay (ELIspot) on the cultured T-cell lines. BMZ antibodies were assayed, HLA type determined and clinical parameters noted. Results Significant interferon-gamma production was observed in response to the NC16A peptides in 6 of the 14 vulval LS and 2 of the 5 LP patients, but not in the control subjects. There was an associated autoantibody response to BP180 in 3 LS and 1 LP patient with T-cell responses. These data suggest that in some vulval LS and LP patients, NC16A domain-specific T cells circulate at sufficiently high frequency to be detectable in vitro and show rapid effector function. There was no association with HLA type or clinical parameters. Conclusion We have demonstrated that in > 40% of our vulval LS and LP patients, the NC16A domain of BP180 is a target for circulating T cells, and in vulval LS and LP there are associated autoantibodies to BP180.

Altered p53 and Bcl-2 expression in keratinocytes of vulvar lichen sclerosus during pimecrolimus treatment.

Nissi R, Kotila V, Knuuti E, Väre PO, Kauppila S

Br J Dermatol. 2009 Jul 31 [Epub ahead of print]

No abstract available.

The period prevalence of oral lichen planus in a cohort of patients with vulvar lichen sclerosus.
J Saunders H, Buchanan J, Cooper S, Hollowood K, Sherman V, Wojnarowska F
Eur Acad Dermatol Venereol. 2009 Jun 8 [Epub ahead of print]

Background: Lichen sclerosus and lichen planus are chronic inflammatory mucocutaneous disorders that may coexist. Objective The aim of this study was to estimate the period prevalence of oral lichen planus in a cohort of patients with vulvar lichen sclerosus and to document their clinical characteristics. Methods: We report a series of cases of vulvar lichen sclerosus presenting to two dermatologist-led vulvar clinics in Oxfordshire, England between 1997 and 2007 with coexistent clinical signs of oral lichen planus. Results: Thirteen cases with coexistent vulvar lichen sclerosus and oral lichen planus were identified, of which five had oral biopsies. Four oral biopsies showed histological features consistent with lichen planus. One oral biopsy was not diagnostic but compatible with oral lichen planus. No cases of oral lichen sclerosus were identified. The period prevalence of oral lichen planus was 6 per 1000 cases of vulvar lichen sclerosus. Conclusion: The period prevalence of oral lichen planus in women with vulvar lichen sclerosus (0.6%) is similar to that reported for oral lichen planus in the general population (1-2%).

Histopathological work-up and interpretation of sentinel lymph nodes removed for vulvar squamous cell carcinoma.
Regauer S
Histopathology. 2009 Aug;55(2):174-81

AIMS: To evaluate the work-up of sentinel lymph nodes (SLNs) removed for vulvar pT1-pT2 squamous cell carcinoma (SCC). Inguinal lymphadenectomy yields metastases in only 30% of cases. Patients with missed inguinal disease, however, have a risk of dying from systemic disease. SLN dissections reduce morbidity, but work-up should reliably identify metastatic disease. METHODS AND RESULTS: All SLNs removed from 38 patients with pT1-pT2 SCC and clinically negative inguinal lymph nodes were submitted for frozen section analysis. When negative, SLN were formalin-fixed, sectioned entirely at 330-microm intervals to produce three slides per millimetre [two haematoxylin and eosin (H&E) stained slides; one slide for immunohistochemistry]. If screening of H&E-stained sections was negative, all remaining slides were subjected to immunohistochemistry with an antibody to cytokeratin. Twenty-five of 38 patients (66%) were pN0, 7/38 (18%) had metastases on frozen sections/H&E stains. Immunohistochemistry detected micrometastases in two patients and single tumour cells and anucleate cell structures in four patients. In 12/13 patients the SLN metastases, including all single-cell deposits, were from lichen sclerosus (LS)-associated SCC. Twelve of 13 patients with metastases had a pT2 SCC. CONCLUSIONS: Micrometastases and single tumour cell deposits in SLNs are typical of LS-associated vulvar SCC. Single tumour cell deposits in SNLs should be regarded as 'positive'. Identification requires serial sectioning and immunohistochemical analysis of all removed SLNs.

Anatomy / Basic Science

Surgical anatomy of the extrapelvic part of the pudendal nerve and its applications for clinical practice.
Pirro N, Sielezneff I, Le Corroller T, Ouaissi M, Sastre B, Champsaur P
Surg Radiol Anat. 2009 Jun 3 [Epub ahead of print]

PURPOSE: This study aims to report the topography of the extrapelvic part of the pudendal nerve

(EPPN) and its relationship with the sacrospinous ligament and the pudendal artery. METHODS: The pudendal nerve (PN) was dissected by a gluteal approach in 40 cases. The morphology of the EPPN, its topography and the relationship between the PN on the one hand, and the pudendal artery and the tip of the ischial spine on the other hand were reported. RESULTS: The length and the diameter of the EPPN were identical on the right and on the left side. The PN was a single trunk in 3/4 of cases. The PN was medial to the pudendal artery in 32 cases and crossed the sacrospinous ligament in 32 cases and the ischial spine in 6 cases. CONCLUSIONS: The topographic variations of the EPPN are large and complicate its surgical and radiological approach.

The somatosensory representation of the human clitoris: An fMRI study.
Michels L, Mehnert U, Boy S, Schurch B, Kollias S
Neuroimage. 2009 Jul 23 [Epub ahead of print]

We studied the central representation of pudendal afferents arising from the clitoral nerves in 15 healthy adult female subjects using electrical dorsal clitoral nerve stimulation and fMRI. As a control body region, we electrically stimulated the right hallux in eight subjects. In a block design experiment, we applied bilateral clitoral stimulation and unilateral (right) hallux stimulation. Activation maps were calculated for the contrasts 'electrical dorsal clitoral nerve stimulation versus rest' and 'electrical hallux stimulation versus rest'. A random-effect group analysis for the clitoral stimulation showed significant activations bilateral in the superior and inferior frontal gyri, insulae and putamen and in the postcentral, precentral and inferior parietal gyri (including the primary and secondary somatosensory cortices). No activation was found on the mesial surface of the postcentral gyrus. For the hallux, activations occurred in a similar neuronal network but the activation in the primary somatosensory cortex was localized in the inter-hemispheric fissure. The results of this study demonstrate that the central representation of pudendal afferents arising from the clitoral nerves and sensory inputs from the hallux can be studied and distinguished from each other by fMRI. From the somatotopic order described in the somatosensory homunculus one would expect for electrical clitoral nerve stimulation activation of the mesial wall of the postcentral gyrus. In contrast, we found activations on the lateral surface of the postcentral gyrus.