Vulvodynia

Symptom-associated alterations in functional connectivity in primary and secondary provoked vestibulodynia
Talia C Oughourlian, Guistinna Tun, Kevin M Antony, Arpana Gupta, Vickie M Mays, Emeran A Mayer, Andrea J Rapkin, Jennifer S Labus

Primary provoked vestibulodynia (PVD) is marked by the onset of symptoms at first provoking vulvar contact, whereas secondary PVD refers to symptom onset after some period of painless vulvar contact. Different pathophysiological processes are believed to be involved in the development and maintenance of primary PVD and secondary PVD. The primary aim of this study was to test the hypotheses that the resting state functional connectivity of the brain and brain stem regions differs between these subtypes. Deep clinical phenotyping and resting state brain imaging were obtained in a large sample of a women with primary PVD (n = 46), those with secondary PVD (n = 68), and healthy control women (n = 94). The general linear model was used to test for differences in region-to-region resting state functional connectivity and psychosocial and symptom assessments. Direct statistical comparisons by onset type indicated that women with secondary PVD have increased dorsal attention-somatomotor network connectivity, whereas women with primary PVD predominantly show increased intrinsic resting state connectivity within the brain stem and the default mode network. Furthermore, compared with women with primary PVD, those with secondary PVD reported greater incidence of early life sexual abuse, greater pain catastrophizing, greater 24-hour symptom unpleasantness, and less sexual satisfaction. The findings suggest that women with secondary PVD have alterations in brain stem circuitry responsible for the processing and modulation of ascending and descending peripheral signals.
**Characterizing the innervation of the vulvar vestibule and the immunohistochemical features of neuroproliferative vestibulodynia**

Diane Tomalty, Olivia Giovannetti, Stephen Magliocchetti, Andre Williams, Johanna Hannan, Barry Komisaruk, Sue Goldstein, Irwin Goldstein, Michael A Adams


**Background:** Provoked vestibulodynia (PVD) is a chronic pain condition characterized by allodynia localized to the vulvar vestibule. The finding of increased densities of nerve fibers in the vestibular mucosa of patients with PVD has led to the identification of a neuroproliferative subtype. The etiology of PVD, including neuroproliferative vestibulodynia (NPV), is not fully understood. The gross and microscopic innervation of the vulvar vestibule remains incompletely described, despite the preliminary data supporting the role of peripheral innervation in PVD. **Aim:** To characterize the gross anatomic and microscopic innervation of the vulvar vestibule through cadaveric dissection and immunohistochemistry.

**Methods:** The pudendal nerve and inferior hypogastric plexus (IHP) were dissected using 6 cadaveric donors. Histology and immunohistochemistry were used to confirm patterns of innervation identified gross anatomically. Immunohistochemistry was performed on vestibulectomy specimens obtained from 6 patients diagnosed with NPV and compared with cadaveric vestibular tissues. **Outcomes:** Outcomes included (1) dissection of pelvic innervation and (2) immunohistochemical localization of markers for the following: general innervation protein gene product 9.5 (PGP9.5), sensory innervation (calcitonin gene-related peptide), autonomic innervation (vasoactive intestinal polypeptide, tyrosine hydroxylase), neuroproliferation (nerve growth factor [NGF]), and immune activation (C-kit). **Results:** Perineal (pudendal) nerve branches were traced to the external wall of the vulvar vestibule. Some anatomic heterogeneity was observed in perineal nerve-branching patterns. Fibers from the IHP were identified in close proximity to the vulvar vestibule. Autonomic and sensory nerve fibers were identified in both patient and cadaveric vulvar vestibule samples. Patient samples were characterized by the proliferation of PGP9.5-positive nerve fibers and C-kit-positive mast cells, which were in proximity to nerve bundles and showed coexpression with putative NGF-positive cells. NGF expression was localized to a subset of nerves, including those that demonstrated coexpression of sensory and autonomic nerve markers. Increased densities of autonomic fibers positive for vasoactive intestinal polypeptide and tyrosine hydroxylase were observed in 1 patient sample. **Clinical translation:** Heterogeneity in gross and microscopic patterns of innervation could explain variability in clinical response to treatment and should be used to inform future therapeutic interventions. **Strengths and limitations:** This study used a combination of approaches to elucidate the innervation of the vulvar vestibule, including in NPV. The small sample size is a limitation. **Conclusion:** The vulvar vestibule contains both sensory and autonomic innervation, which may originate from the pudendal nerve and IHP. Our results support the existence of a neuroproliferative subtype that is characterized by the proliferation of sensory and autonomic nerve fibers and neuroimmune interactions.

**The Association Between Immune-Related Conditions Across the Life-Course and Provoked Vulvodynia**

Bernard L Harlow, Chad M Coleman, Hanna Mühlrad, Jacinth Yan, Evelina Linnros, Donghao Lu, Matthew P Fox, Nina Bohm-Starke


Vulvodynia, impacts up to 8% of women by age 40, and is hypothesized to manifest through an altered immune-inflammatory response. To test this hypothesis, we identified all women born in Sweden between 1973 and 1996 diagnosed with localized provoked vulvodynia (N76.3) and/or vaginismus (N94.2 or F52.5) between 2001 and 2018. We matched each case to two women from the same birth year with no vulvar pain ICD codes. As a proxy for immune dysfunction, we used Swedish Registry data to capture 1) immunodeficiencies, 2) single organ and multiorgan autoimmune conditions, 3) allergy and atopies, and 4) malignancies involving immune cells across the life course. Women with vulvodynia, vaginismus or both were more likely to experience immune deficiencies (OR 1.8, 95% CI, 1.2-2.8), single organ (OR 1.4, 95% CI, 1.2-1.6) and/or multi-organ (OR 1.6, 95% CI, 1.3-1.9) immune disorders, and allergy/atopy conditions (OR 1.7, 95% CI, 1.6-1.8) compared to controls. We observed greater risk with increasing numbers of unique immune related conditions (1 code: OR = 1.6, 95% CI, 1.5-1.7; 2 codes: OR = 2.4, 95% CI, 2.1-2.9; 3 or more codes: OR = 2.9, 1.6-5.4). These findings suggest that women with vulvodynia may have a more compromised immune system either at birth or at points across the life course than women with no vulvar pain history. PERSPECTIVE: Women with vulvodynia are substantially more likely to experience a spectrum of immune related conditions across the life course. These findings lend support to the hypothesis that chronic inflammation initiates the hyperinnervation that causes the debilitating pain in women with vulvodynia.

Treatment of Provoked Vulvodynia: A Systematic Review
Nina Bohm-Starke, Karin Wilbe Ramsay, Per Lytsy, Birgitta Nordgren, Inga Sjöberg, Klas Moberg, Ida Flink

Background: Treatment recommendations for provoked vulvodynia (PVD) are based on clinical experiences and there is a need for systematically summarizing the controlled trials in this field. Aim: To provide an overview of randomized controlled trials and non-randomized studies of intervention for PVD, and to assess the certainty of the scientific evidence, in order to advance treatment guidelines. Data sources: The search was conducted in CINAHL (EBSCO), Cochrane Library, Embase (Embase.com), Ovid MEDLINE, PsycINFO (EBSCO) and Scopus. Databases were searched from January 1, 1990 to January 29, 2021. Study eligibility criteria: Population: Premenopausal women with PVD. Interventions: Pharmacological, surgical, psychosocial and physiotherapy, either alone or as combined/team-based interventions. Control: No treatment, waiting-list, placebo or other defined treatment. Outcomes: Pain during intercourse, pain upon pressure or touch of the vaginal opening, sexual function/satisfaction, quality of life, psychological distress, adverse events and complications. Study design: Randomized controlled trials and non-randomized studies of interventions with a control group. Study appraisal and synthesis methods: 2 reviewers independently screened citations for eligibility and assessed relevant studies for risk of bias using established tools. The results from each intervention were summarized. Studies were synthesized using a narrative approach, as meta-analyses were not considered appropriate. For each outcome, we assessed the certainty of evidence using grading of recommendations assessment, development, and evaluation (GRADE). Results: Most results of the evaluated studies in this systematic review were found to have very low certainty of evidence, which means that we are unable to draw any conclusions about effects of the interventions. Multimodal physiotherapy compared with lidocaine treatment was the only intervention with some evidential support (low certainty of evidence for significant treatment effects favoring physiotherapy). It was not possible to perform meta-analyses due to a heterogeneity in interventions and comparisons. In addition, there was a heterogeneity in outcome measures, which underlines the need to establish joint core outcome sets. Clinical implications: Our result underscores the need of stringent trials and defined core
outcome sets for PVD. **Strength and limitations:** Standard procedures for systematic reviews and the Population Intervention Comparison Outcome model for clinical questions were used. The strict eligibility criteria resulted in limited number of studies which might have resulted in a loss of important information. **Conclusion:** This systematic review underlines the need for more methodologically stringent trials on interventions for PVD, particularly for multimodal treatments approaches. For future research, there is a demand for joint core outcome sets.

**Health economic evaluation of a randomized controlled trial (EMBLA study), an internet-based treatment for provoked vulvodynia**
A Hess Engström, N Bohm-Starke, M Buhrman, U Högberg, A Skalkidou, S Lagenskiöld

Internet-based treatment (IBT) for provoked vulvodynia (PVD) may reduce pain during intercourse and increases pain acceptance. However, there is still a knowledge gap regarding the cost-effectiveness of IBT for PVD. The aim of this study was to perform a health economic evaluation of guided internet-based intervention for PVD as an addition to standard treatment. The sample consisted of 99 women with a PVD diagnosis. Healthcare related costs, health-related quality of life, and quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratio (ICER) were analyzed. After the IBT, the intervention group had fewer visits to a midwife than the control group (p = 0.03), but no between-group differences were found for visits to other professionals, treatment length, health-related quality of life, QALYs, and costs for treatment. It was estimated a cost of 260.77 € for a clinical meaningful change in pain acceptance. Internet-based treatment as add-on to clinical treatment may lower number of visits to a healthcare.

**Vulvodynia: A practical guide in treatment strategies**

Vulvodynia is a debilitating condition characterized by chronic vulvar pain, with a detrimental impact on the patient’s overall quality of life. Its etiology is multifactorial, but still in the process of being clearly outlined. Vulvodynia is not a single entity. It is a heterogeneous condition characterized by multiple triggers, making it challenging to define a reference standard for its treatment. In this manuscript we selected all articles including the following key criteria: "vulvodynia". The primary outcomes observed included the resolution of chronic pelvic pain, dyspareunia and sexual satisfaction, psychological well-being, and overall quality of life. Most pharmacologic treatments require further evidence to be recommended. On the other hand, non-pharmacologic approaches such as psychotherapy, physical therapy, and surgery have received stronger support. This review summarizes pros and cons of adopting available treatments. Multimodal approaches should be introduced to improve patient outcomes. Further investigations are warranted to improve patients' quality of life.
Improving communication between women with vulvodynia and their romantic partners: insights and recommendations for practitioners
Elizabeth A Hintz

Background: Interactions among female patients with vulvodynia, their romantic partners, and clinicians are key to promoting positive health outcomes. Previous studies have investigated how the content of romantic partners’ responses to expressions of pain are related to these outcomes. Yet, the content of patients’ conversations and the appraisals of their difficulty remain unknown. Aim: This study offers guidance to clinicians counseling patients with vulvodynia by explicating the frequency and difficulty of various salient conversational topics. Methods: Thirty-four women with vulvodynia completed a screener survey indicating the frequency and difficulty of conversational topics. Follow-up in-depth interviews were conducted with 26 women. A dominant partner response type was identified for each participant. Results: Topics most often discussed, such as sex, were rated as among the least difficult to discuss. Most participants reported experiencing the facilitative partner response type, which promotes adaptive coping. Conclusion: Determining patients' perceived conversational difficulty and frequency is necessary to provide quality and efficient counseling to women with vulvodynia and their partners. Patients also experience partner response types. Therefore, clinicians must solicit subjective assessments of conversational difficulty when advising patients and their romantic partners.

Moderators of the Relationship Between Pain and Pain-Related Sexual Disability in Women with Provoked Vestibulodynia Symptoms
Larah Maunder, Emma Dargie, Caroline F Pukall

Background: Previous studies have demonstrated the deleterious effects of pain anxiety (ie, the degree to which one fears pain), stress, and solicitous partner responses (ie, expressions of sympathy and attention to one's partner’s pain) on pain and pain-related disability, but little is known about whether these variables moderate the robust pain-pain-related disability relationship in individuals with provoked vestibulodynia (PVD). Aim: We investigated whether pain anxiety, stress, and solicitous partner responses moderated the relationship between penetrative pain and pain-related sexual disability in women with PVD symptoms. Methods: Participants with PVD symptoms (N = 65, age range = 18-73 years) completed an online survey assessing pain anxiety (Pain Anxiety Symptoms Scale-20), perceived stress (Perceived Stress Scale), solicitous partner responses (WHYMPI Solicitous Responses Scale), penetrative pain (Female Sexual Function Index), and pain-related sexual disability (Pain Disability Index). Moderated regression analyses were performed using pain anxiety, stress, and solicitous partner responses as moderators of the relationship between penetrative pain, and pain-related sexual disability. Outcomes: Outcomes in the current study included the moderating effect of pain anxiety, perceived stress, and solicitous partner responses on the relationship between penetrative genital pain and pain-related disability in sexual behavior. Results: Higher genital pain from penetrative intercourse and higher pain anxiety significantly predicted higher pain-related sexual disability, but perceived stress was not significantly related to sexual disability. Solicitous partner responses were significantly positively correlated with pain-related sexual disability. None of the moderators significantly moderated the pain-pain-related sexual disability relationship. Clinical implications: For women with PVD, pain anxiety and solicitous partner responses to their pain may exacerbate their pain-related sexual disability, signifying
that pain anxiety and solicitous partner responses represent important targets of therapeutic intervention for women with PVD. **Strengths and limitations:** The present study extended past research on the relationships between psychological and behavioral factors and pain in women with PVD symptoms by demonstrating the deleterious relationship between pain anxiety, solicitous responses, and pain-related sexual disability. However, the study was correlational in nature, which precludes conclusions about the effect of pain anxiety, and solicitous partner responses on pain-related sexual disability. **Conclusion:** High pain anxiety and frequent solicitous partner responses to an individual's pain predicted higher pain-related sexual disability, suggesting that it may be possible to improve the quality of life of PVD sufferers through interventions that aim to decrease pain anxiety, and solicitous partner responses, in addition to interventions that aim to decrease pain per se.

**A scoping review: the psychosocial barriers that exist for people with vulvodynia**

Jenny Niedenfuehr, Mary Edwards, Lindsey M King


**Background:** Vulvodynia, including generalized vulvodynia and vestibulodynia, affects at least 8% to 16% of people with a vulva and may have a negative impact on one's quality of life, psychological health, interpersonal relationships, and individual behaviors. **Aim:** The aim of this scoping review is to synthesize and analyze the emerging literature of vulvodynia research while determining what psychosocial barriers exist for people with vulvodynia. **Methods:** A rigorous literature search was completed in 6 databases: PubMed, CINAHL, Embase, Web of Science, APA PsycInfo, and Academic Search Premier. Key terms and subject headings, including Medical Subject Headings, were used to systematically search these databases. Two reviewers were utilized to assess the reference list and reduce bias. **Outcomes:** A total of 671 articles were discovered during the search, which was narrowed down to 73 that included at least 1 psychosocial barrier that patients experience in the United States and Canada. **Results:** The findings of the literature search revealed the various psychosocial barriers that patients commonly face: pain, anxiety, depression, catastrophization, fear, lack of self-efficacy, low desire and arousal, negative body image, stigma, distress, posttraumatic stress disorder, child maltreatment and abuse, mistrust, invalidation and isolation, low levels of self-compassion, negative partner support, low relationship satisfaction, lack of physical affection, emotional regulation, and avoidance and lack of approach goals. In addition to psychosocial barriers, structural determinants and environmental barriers-such as delayed diagnosis, low health literacy, cost, transportation, and racial disparities-adversely affected individuals with vulvodynia. **Clinical implications:** This review should serve as a guide for researchers, medical providers, and program developers to understand all the barriers that patients may face. **Strengths and limitations:** This review comprehensively highlights existing psychological barriers while promoting structural and environmental barriers that people with vulvodynia face. More research and greater emphasis on the underlying physical conditions that contribute to vulvodynia are needed to effectively educate providers and patients on vulvar pain conditions. **Conclusions:** This scoping review highlights the numerous barriers faced by patients with vulvodynia and serves to improve education for patients and providers to achieve earlier diagnoses and better patient outcomes.
Quality-of-life impact of interstitial cystitis and other pelvic pain syndromes
Andrew R Cunningham, Lin Gu, Alexandra Dubinskaya, Amanda M De Hoedt, Kamil E Barbour, Jayoung Kim, Stephen J Freedland, Jennifer T Anger

Objective: To compare health-related quality of life (HRQOL) and pelvic pain levels over time in patients with interstitial cystitis/bladder pain syndrome (IC/BPS) and those with other pelvic pain conditions (OPPC) including chronic prostatitis, dyspareunia, vaginismus, vulvodynia, and vulvar vestibulitis.

Methods: We prospectively enrolled male and female patients from any Veterans Health Administration (VHA) center in the US. They completed the Genitourinary Pain Index (GUPI) quantifying urologic HRQOL and the 12-Item Short Form Survey version 2 (SF-12) quantifying general HRQOL at enrollment and 1 year later. Participants were classified by ICD diagnosis codes and confirmed by chart review to be IC/BPS or OPPC (308 and 85 patients respectively).

Results: At baseline and follow-up, IC/BPS patients, on average, had worse urologic and general HRQOL than OPPC patients. IC/BPS patients demonstrated improvement in urologic HRQOL measures over the study but demonstrated no significant change in any general HRQOL measure suggesting a condition-specific impact. Patients with OPPC demonstrated similar improvements in urologic HRQOL but had deteriorating mental health and general HRQOL at follow-up suggesting a wider general HRQOL impact for these diseases.

Conclusions: We found that patients with IC/BPS had worse urologic HRQOL compared to other pelvic conditions. Despite this, IC/BPS showed stable general HRQOL over time, suggesting a more condition-specific impact on HRQOL. OPPC patients showed deteriorating general HRQOL, suggesting more widespread pain symptoms in these conditions.

Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review
Beth Pollack, Emelia von Saltza, Lisa McCorkell, Lucia Santos, Ashley Hultman, Alison K Cohen, Letícia Soares

Long COVID disproportionately affects premenopausal women, but relatively few studies have examined Long COVID's impact on female reproductive health. We conduct a review of the literature documenting the female reproductive health impacts of Long COVID which may include disruptions to the menstrual cycle, gonadal function, ovarian sufficiency, menopause, and fertility, as well as symptom exacerbation around menstruation. Given limited research, we also review the reproductive health impacts of overlapping and associated illnesses including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), connective tissue disorders like Ehlers-Danlos syndrome (EDS), and endometriosis, as these illnesses may help to elucidate reproductive health conditions in Long COVID. These associated illnesses, whose patients are 70%-80% women, have increased rates of dysmenorrhea, amenorrhea, oligomenorrhea, dyspareunia, endometriosis, infertility, vulvodynia, intermenstrual bleeding, ovarian cysts, uterine fibroids and bleeding, pelvic congestion syndrome, gynecological surgeries, and adverse pregnancy complications such as preeclampsia, maternal mortality, and premature birth. Additionally, in Long COVID and associated illnesses,
symptoms can be impacted by the menstrual cycle, pregnancy, and menopause. We propose priorities for future research and reproductive healthcare in Long COVID based on a review of the literature. These include screening Long COVID patients for comorbid and associated conditions; studying the impacts of the menstrual cycle, pregnancy, and menopause on symptoms and illness progression; uncovering the role of sex differences and sex hormones in Long COVID and associated illnesses; and addressing historical research and healthcare inequities that have contributed to detrimental knowledge gaps for this patient population.

**Persistent Genital Arousal Disorder**

**Persistent genital arousal disorder - the present knowledge**

Natalia Ewa Kapuśniak, Magdalena Piegza

Persistent genital arousal disorder (PGAD) is a relatively recently described sexual disorder, characterized by symptoms of spontaneous genital arousal which persist in the absence of sexual desire and may affect women and men. Epidemiological studies conducted so far indicate that the prevalence of PGAD in the population may reach 1-4%. The etiology of PGAD remains unclear and complex, hypothesized causes include vascular, neurological, hormonal, psychological, pharmacologic, dietary, mechanical factors or a combination of these factors. Proposed methods of treatment include pharmacotherapy, psychotherapy, electroconvulsive therapy, hypnotherapy, injection of botulinum toxin, pelvic floor physical therapy, application of anesthetizing agents, reduction of identifiable factors exacerbating the symptoms, and transcutaneous electrical nerve stimulation. There is no standardized treatment algorithm for PGAD due to lack of clinical trials (evidence-based medicine). The classification of PGAD is under discussion: it could be classified as a separate sexual disorder, a subtype of vulvodynia or a disorder with pathogenesis similar to overactive bladder (OAB) and restless legs syndrome (RLS). Due to specificity of symptoms, patients may feel shame and discomfort during the examination or even delay reporting symptoms to the specialist. Thus, it is crucial to spread knowledge about this disorder, which would allow doctors to diagnose and help PGAD patients sooner.

**Psychological Treatment of Persistent Genital Arousal Disorder/Genitopelvic Dysesthesia Using an Integrative Approach**

Kathleen E Merwin, Lori A Brotto

Persistent genital arousal disorder/genitopelvic dysesthesia (PGAD/GPD) is characterized by persistent, unwanted physiological genital arousal (i.e., sensitivity, fullness, and/or swelling) in the absence of sexual excitement or desire which can persist for hours to days and causes significant impairment in psychosocial well-being (e.g., distress) and daily functioning. The etiology and course of PGAD/GPD is still relatively unknown and, unsurprisingly, there are not yet clear evidence-based treatment recommendations for those suffering from PGAD/GPD. We present the case of a 58-year-old woman with acquired persistent genital arousal disorder, which began in March 2020; she believed she
developed PGAD/GPD due to a period of significant distress and anxiety related to the COVID-19 pandemic. After seeking medical diagnosis and treatment from multiple healthcare providers and trying a combination of pharmacological and medical treatment modalities, she presented for psychological treatment. An integrative therapy approach (3 assessment sessions, 11 treatment sessions), which included cognitive behavior therapy, distress tolerance and emotion regulation skills from dialectical behavior therapy, and mindfulness practice, was utilized. The patient reported improvements anecdotally (e.g., decreased impact on occupational and social functioning, greater self-compassion, less frequent and shorter duration of PGAD/GPD flare-ups, improved ability to cope with PGAD/GPD symptoms, and decreased need for sleeping medication) and on self-report measures (e.g., lower PGAD/GPD catastrophizing, lower anxiety and depression, and greater overall quality of life). We report the use of an integrative (i.e., psychoeducational, cognitive behavioral, dialectical behavioral, and mindfulness-based) intervention, which may be an effective psychological treatment for PGAD/GPD.

**Pudendal Neuralgia**

*First case-series of robot-assisted pudendal nerve release: technique and outcomes*
Carlo Giulioni, Anastasios D Asimakopoulos, Filippo Annino, Giulia Garelli, Julien Riviere, Julie Piechaud-Kressmann, Nam-Son Vuong, Laurent Hugo Lopez, Jean-Baptiste Roche, Jean Rouffilange, Jean-Luc Hoepffner, Andrea Benedetto Galosi, Richard Pierre Gaston, Thierry Piechaud, Grégory Pierquet

**Objective:** Pudendal Nerve Entrapment (PNE) may determine chronic pelvic pain associated with symptoms related to its innervation area. This study aimed to present the technique and report the outcomes of the first series of robot-assisted pudendal nerve release (RPNR). **Patients and methods:** 32 patients, who were treated with RPNR in our centre between January 2016 and July 2021, were recruited. Following the medial umbilical ligament identification, the space between this ligament and the ipsilateral external iliac pedicle is progressively dissected to identify the obturator nerve. The dissection medial to this nerve identifies the obturator vein and the arcus tendinous of the levator ani, which is cranially inserted into the ischial spine. Following the cold incision of the coccygeous muscle at the level of the spine, the sacrospinous ligament is identified and incised. The pudendal trunk (vessels and nerve) is visualized, freed from the ischial spine and medially transposed. **Results:** The Median duration of symptoms was 7 (5, 5-9) years. The median operative time was 74 (65-83) minutes. The median length of stay was 1 (1-2) days. There was only a minor complication. At 3 and 6 months after surgery, a statistically significant pain reduction has been encountered. Furthermore, the Pearson correlation coefficient reported a negative relationship between the duration of pain and the improvement in NPRS score, - 0.81 (p = 0.01). **Conclusions:** RPNR is a safe and effective approach for the pain resolution caused by PNE. Timely nerve decompression is suggested to enhance outcomes.
**Randomized clinical trial with fractional CO\textsubscript{2} laser and Clobetasol in the treatment of Vulvar Lichen Sclerosus: a clinic study of feasibility**

Hakayna Calegaro Salgado, Denise Gasparetti Drumond, Gabriel Duque Pannain, Louise Gracielle de Melo E Costa, Fernanda Souza Sampaio, Isabel Cristina Gonçalves Leite


**Objectives:** The main objective of the study was to describe and compare the feasibility of using fractional CO\textsubscript{2} laser to the usual treatment with Clobetasol. Randomized clinical trials brought together 20 women from a Brazilian university hospital, 9 of them were submitted to Clobetasol treatment and 11 to laser therapy. Sociodemographic data were obtained and quality of life parameters, vulvar anatomy, self-perception and histopathological analysis of vulvar biopsies were evaluated. Evaluations were made before the beginning of the treatment, during its implementation, right after its completion (3 months), and 12 months after. The SPSS 14.0 software was used, obtaining descriptive measurements. The level of significance adopted was 5%. **Results:** The clinical/anatomical characteristics of the vulva did not differ between the treatment groups, as much before as after its performance. There was no statistically significant difference between the treatments performed regarding the impact on the life quality of the patients. A higher satisfaction degree with the treatment was obtained with the patients in the Laser group in the third month of evaluation. Laser therapy also revealed higher occurrence of telangiectasia after treatment completion. Fractional CO\textsubscript{2} laser has proven to be well accepted and is a promising therapeutic option. Registration number and name of trial registry The institutional review board status was approved by the Research Ethics Committee of HU/ UFJF under advisory number 2881073 and registered in the Brazilian Clinical Trials, with consent under registration RBR-4p9s5y. Access link: https://ensaiosclinicos.gov.br/rg/RBR-4p9s5y.

**Nd:YAG/Er:YAG dual laser vs. topical steroid to treat vulvar lichen sclerosus: study protocol of a randomized controlled trial**

Volker Viereck, Marianne Gamper, Sigrid Regauer, Claudia Walser, Irena Zivanovic


**Purpose:** Vulvar lichen sclerosus (LS) is a chronic debilitating inflammatory skin disease. Today, the gold standard is a life-long topical steroid treatment. Alternative options are highly desired. We present a study protocol of a prospective, randomized, active-controlled, investigator-initiated clinical trial comparing a novel non-invasive dual Nd:YAG/Er:YAG laser therapy with the gold standard for the management of LS. **Methods:** We recruited 66 patients, 44 in the laser arm and 22 in the steroid arm. Patients with a physician-administered clinical LS score ≥ 4 were included. Participants received either four laser treatments 1-2 months apart, or 6 months of topical steroid application. Follow-ups were planned at 6, 12, and 24 months. The primary outcome looks at the efficacy of the laser treatment at the 6-month follow-up. Secondary outcomes look at comparisons between baseline and follow-ups within the laser or the steroid arm, and comparisons between laser vs. steroid arm. Objective (LS score, histopathology, photo documentation) and subjective (Vulvovaginal Symptoms Questionnaire, symptom VAS score, patient satisfaction) measurements, tolerability, and adverse events are evaluated.
Conclusion: The findings of this trial have the potential to offer a novel treatment option for LS. The standardized Nd:YAG/Er:YAG laser settings and the treatment regime are presented in this paper.

Dermatoscopy and Optical Coherence Tomography in Vulvar High-Grade Squamous Intraepithelial Lesions and Lichen Sclerosis: A Prospective Observational Trial

Objective: This study aimed to examine potential discriminatory characteristics of dermatoscopy and dynamic optical coherence tomography (D-OCT) on vulvar high-grade squamous intraepithelial lesions (vHSIL) and lichen sclerosus (LS) compared with healthy vulvar skin. Methods: A prospective observational clinical trial was performed in 10 healthy volunteers, 5 vHSIL and 10 LS patients. Noninvasive imaging measurements using dermatoscopy and D-OCT were obtained at several time points, including lesional and nonlesional vulvar skin. Morphologic features of vHSIL and LS were compared with healthy controls. Epidermal thickness and blood flow were determined using D-OCT. Patients reported tolerability of each study procedure, including reference vulvar biopsies. The main outcome measures were feasibility and tolerability of imaging modalities, dermatoscopy and OCT characteristics, OCT epidermal thickness and D-OCT dermal blood flow. Results: The application of dermatoscopy and D-OCT is feasible and tolerable. In vHSIL, dermatoscopic warty structures were present. In LS, sclerotic areas and arborizing vessels were observed. Structural OCT in the vulvar area aligned with histology for hyperkeratosis and dermal-epidermal junction visualization. Currently, the OCT algorithm is unable to calculate the epidermal thickness of the uneven vulvar area. Dynamic optical coherence tomography showed statistically significant increased blood flow in LS patients (mean ± SD, 0.053 ± 0.029) to healthy controls (0.040 ± 0.012; p = .0024). Conclusions: The application of dermatoscopy and D-OCT is feasible and tolerable in vHSIL and LS patients. Using dermatoscopy and D-OCT, we describe potential characteristics to aid differentiation of diseased from healthy vulvar skin, which could complement clinical assessments.

Comorbidity of Urogynecological and Gastrointestinal Disorders in Female Patients With Lichen Sclerosis
Jenni M Söderlund, Niina K Hietan, Samu H Kurki, Katri J Orte, Päivi Polo-Kantola, Sakari H Hietanen, Marjut A M Haataja

Objective: Lichen sclerosus (LS) is a chronic inflammatory disease with a significant impact on quality of life. The aim of this cross-sectional case-control study was to characterize concomitant urogynecological and gastrointestinal disorders in female patients with LS. Methods: A medical records search between 2004 and 2012 yielded 455 women and girls (mean age 64 years) with LS. The study cohort was compared with a 10-fold age- and sex-matched control cohort. Gynecological cancers and their precursors; gynecological, urinary, and gastrointestinal disorders; and pain syndromes were evaluated. Results: The well-known association between LS and increased risk of vulvar cancer and its precursors...
was also found in our study (relative risk [RR] = 100.0; p < .001 and high-grade squamous intraepithelial lesions RR = 110.0; p < .001, respectively), but we also found an increased risk for cervical cancer (RR = 6.0; p = .005) and endometrial cancer (RR = 2.9; p < .001). Gynecological pain syndromes such as dyspareunia (RR = 20.0; p < .001) and interstitial cystitis (RR = 5.0; p < .001) and urinary incontinence (RR = 4.8; p < .001) were also increased. Among gastrointestinal disorders, we found increased risk for celiac disease (RR = 6.8; p < .001), diverticular intestine diseases (RR = 1.9; p < .001), functional intestinal disorders (RR = 2.3; p = .003), and anal and rectal fissures (RR = 2.4; p = .046). **Conclusions:** We found that female patients with LS have an increased risk for gynecological cancers as well as for several urogynecological and gastrointestinal disorders. Increased awareness is required to identify and treat these concomitant disorders.

**The Efficacy and Safety of 5-Aminolevulinic Acid Photodynamic Therapy for Lichen Sclerosus: A Meta Analysis**

Chun Qing, Xiaoyong Mao, Gaoqing Liu, Yibin Deng, Xiaokun Yang


**Background:** Lichen sclerosus (LS) is a chronic inflammatory dermatosis that occurs mainly in the anogenital area and causes itching, soreness, atrophy and scarring, which may result in burying of the clitoris in females and phimosis in males. Photodynamic therapy (PDT) has been suggested during the past years as an alternative non-invasive treatment for LS, but there is still no meta-analysis to evaluate its efficacy and safety. **Aims:** To assess the efficacy and safety of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) for treatment of LS. **Methods:** We undertook a meta-analysis using the methodology of the Cochrane Collaboration and the guideline of PRISMA. A systematic literature search was carried out in PubMed, EMBASE, The Cochrane Library, WanFang Data, CBM and CNKI up to 30 June 2020. Randomized controlled trials (RCTs) were compared with ALA-PDT, corticosteroids or tacrolimus ointments for treating LS. The risk of bias for each trial was rated according to the Cochrane Handbook. Risk ratios (RR) with 95% confidence intervals (CI) were utilized to express the comparative outcomes. **Results:** We included 4 RCTs with a total of 184 participants. The meta-analysis showed ALA-PDT was better than topical ointments in treating LS (total effective rate: RR 1.38 [95% CI 1.19-1.60]). **Conclusions:** The current limited evidence supports the efficacy and safety of ALA-PDT in treating LS. The adverse reactions included pain, swelling, redness and exfoliation which would decrease with the continuing sessions of treatment. Further high-qualified RCTs of large samples are necessarily needed.

**Genital and extragenital oncological risk in women with vulvar lichen sclerosus: A multi-center Italian study**

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Vulvar lichen sclerosus is a chronic inflammatory disease involving vulvar skin. The risk of developing invasive vulvar cancer for women with LS is reported in the literature, but the risk of extra-vulvar tumors has been under-investigated. This multicentric study aims to estimate the risk of developing cancers in a cohort of women with a diagnosis of vulvar lichen sclerosus. **Methods:** A cohort of women diagnosed
with and treated for vulvar lichen sclerosus in three Italian gynecological and dermatological clinics (Turin, Florence, and Ferrara) was retrospectively reviewed. Patient data were linked to cancer registries of the respective regions. The risk of subsequent cancer was estimated by dividing the number of observed and expected cases by the standardized incidence ratio. **Results:** Among 3414 women with a diagnosis of vulvar lichen sclerosus corresponding to 38,210 person-years of follow-up (mean 11.2 years) we identified 229 cancers (excluding skin cancers and tumors present at the time of diagnosis). We found an increased risk of vulvar cancer (standardized incidence ratio = 17.4; 95% CL 13.4-22.7), vaginal cancer (standardized incidence ratio = 2.7; 95% CL 0.32-9.771), and oropharyngeal cancer (standardized incidence ratio = 2.5; 95% CL 1.1-5.0), and a reduced risk of other gynecological tumors (cervical, endometrial, ovarian) and breast cancer. **Conclusions:** Patients with vulvar lichen sclerosis should undergo annual gynecological check-up with careful evaluation of the vulva and vagina. The increased risk of oropharyngeal cancer also suggests the need to investigate oropharyngeal cavity symptoms and lesions in patients with vulvar lichen sclerosis.

**Alpha, Beta and Gamma Human Papillomaviruses in Genital Lichen Sclerosis: A Retrospective Cross-Sectional Study**
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**Background:** Lichen sclerosis (LS) is an inflammatory disease mostly arising at the genital level. It is unclear whether human papillomaviruses (HPVs) have an etiological significance in LS, and data on their prevalence in patients with LS are controversial. **Objectives:** We assessed alpha, beta, and gamma HPV prevalence in patients with genital LS. The association of HPV positivity with demographic and clinical factors was also investigated. **Methods:** One hundred thirty-two formalin-fixed, paraffin-embedded LS samples (2016-2020) were retrieved from the archives of a pathology department. Alpha HPVs were genotyped with the INNO-LiPA HPV Genotyping Extra II kit. Beta and gamma HPVs were searched by multiplex Polymerase Chain Reaction. Immunostaining for p16INK4a was performed on high-risk HPV-positive samples. **Results:** Patients had a median age of 61 years, were mostly women (n = 73, 55.3%), and with an early disease stage (n = 79, 59.8%). Alpha HPVs were detected in 12/132 cases (9.1%). Among the 5 high-risk HPV-positive cases, only 2 displayed a strong and diffuse p16INK4a staining. Beta genus was the most prevalent (35/132, 26.5%) and HPV5 was the most frequent beta genotype (25/132, 18.9%). There were 3 gamma HPV-positive cases among those with a valid result (3/131, 2.3%). Multiple infections with genotypes belonging to different genera were infrequent (3/131, 2.3%). No significant differences in the prevalence of the individual genera were observed according to sex and disease stage. **Conclusions:** Of the 3 HPV genera, beta genus showed the highest prevalence. Further research is needed to clarify whether the presence of beta HPVs in genital LS has a clinical significance.

**Clitoral adhesions: a review of the literature**
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Introduction: Clitoral adhesions occur when the prepuce adheres to the glans. These adhesions have been found in up to 22% of women seeking evaluation for sexual dysfunction. The etiology of clitoral adhesions remains largely unclear. Studies published to date on the presentation and management of clitoral adhesions are relatively recent and raise questions for future research. Objectives: We sought to provide a background of existing knowledge on the prevalence, presentation, etiology, associated conditions, and management of clitoral adhesions and to identify areas for future research. Methods: A review of literature was performed for studies that investigate clitoral adhesions. Results: Conditions associated with chronic clitoral scarring appear to have a role in the development of clitoral adhesions. Symptoms include clitoral pain (clitorodynia), discomfort, hypersensitivity, hyposensitivity, difficulty with arousal, and muted or absent orgasm. Complications include inflammation, infection, and the development of keratin pearls and smegmatic pseudocysts. There are surgical and nonsurgical interventions to manage clitoral adhesions. Additionally, topical agents can be included in conservative and/or postprocedural management. Although many studies on clitoral adhesions are limited to patients with lichen sclerosus (LS), clitoral adhesions are not confined to this population. Conclusion: Areas for future research include etiologies of clitoral adhesion; such knowledge is imperative to improve prevention and management. Also, in previous studies, patients were instructed to apply various topical agents and manually retract the prepuce for conservative management or postlysis care. However, the efficacy of these interventions has not been investigated. Surgical and nonsurgical lysis procedures have been described for the management of pain and difficulties with arousal and orgasm that are causes of the sexual dysfunction associated with clitoral adhesion. Although previous studies have assessed efficacy and patient satisfaction, many of these studies were limited to small sample sizes and focused solely on patients with LS. Future studies are needed to inform a standard of care for the management of clitoral adhesions.

Clinical practice gaps in patients with extragenital lichen sclerosus: A retrospective review
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To the Editor: Lichen sclerosus (LS) is a chronic inflammatory skin disorder characterized by progressive epidermal atrophy and hypopigmentation, usually of the anogenital area. Patients may also present with extragenital lesions, though only 6% of LS cases are isolated on extragenital skin.

For patients first presenting with extragenital lichen sclerosus (EGLS), a thorough history and examination of both the extragenital and genital skin can prevent diagnostic delays and improve patient outcomes by identifying concomitant genital lesions.

In this study, we conducted a retrospective analysis to investigate whether dermatologists performed a detailed history and physical examination to determine genital involvement in patients initially presenting with EGLS.
A prospective pilot study to assess for histologic changes on vulvar biopsies in postmenopausal women with lichen sclerosus treated with fractionated CO₂ laser therapy
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Objectives: To investigate the histologic characteristics of vulvar tissues before and after completion of fractionated carbon dioxide (CO₂) laser therapy (FxCO₂) for vulvar lichen sclerosus (LS). The secondary objective was to assess subjective improvement in symptoms via the Skindex-16 questionnaire.

Methods: This prospective single-arm study was conducted from April 2021 to August 2022 at one academic medical center. Ten postmenopausal women with biopsy-proven LS planning FxCO₂ laser treatment were enrolled. Exclusion criteria included prior transvaginal mesh for prolapse, topical corticosteroid use within 8 weeks, prior pelvic radiation, malignancy, active genital infection, or pregnancy. The vulvovaginal SmartXide2-V2-LR laser system fractionated CO₂ laser (DEKA) was utilized to treat visually affected areas of vulvar and perianal LS with a single pass. Subjects underwent three treatments 4-6 weeks apart. Subjects completed the Skindex-16 questionnaire and had vulvar biopsy at baseline and at 4 weeks after completion of fractionated CO₂ laser therapy. Blinded histologic slides were scored by one dermatopathologist (Michael A. Cardis) rating from 1 to 5 the degree of dermal sclerosis, inflammation, and epidermal atrophy. Change scores were calculated as the difference between pre- and post-treatment scores for each subject. Results: The 10 subjects enrolled had a mean age of 61 and most were white, privately insured, and had a college/graduate-level education. Post-fractionated CO₂ laser treatment vulvar biopsies showed significant improvement in sclerosis and epidermal atrophy compared with pretreatment baseline biopsy specimens (p < 0.05) with no statistically significant change found in inflammation score. Skindex-16 and FSFI scores showed a trend towards improvement (p > 0.05 for both). A statistically significant correlation was found between change in sclerosis and Skindex-16 symptoms scores with an average change of 21.4 units in Skindex-16 symptoms score for every one-point change in histologic sclerosis score (p = 0.03). Conclusions: In postmenopausal women with vulvar LS undergoing fractionated CO₂ laser, symptomatic improvements correlated with histologic change in degree of sclerosis on vulvar biopsy. These results demonstrate FxCO₂ laser therapy as a promising option for the treatment of LS and suggest that further studies should assess degree of sclerosis on histopathology.

The use of CO₂ laser in vulvar lichen sclerosus treatment - molecular evidence
Adrianna Marzec, Anita Olejek, Kamila Stopinska, Wojciech Cnota, Iwona Gabriel

Vulvar lichen sclerosus is chronic and difficult to treat disorder, which offer is recurrent and leads to multiple complications. The limited efficacy of pharmacologic treatment directed the search for new therapies including use of CO₂ laser. In our study we focused on collagen and elastin gene expression as well as heat shock proteins and p53 expression in two patients with vulvar lichen sclerosus who underwent CO₂ laser therapy. In both patients we observed decreased clinical symptoms observed by an experienced gynecologist as well as significant changes in gene expression before and after laser treatment.
Too much of a good thing? Iatrogenic Cushing syndrome secondary to excessive topical steroid use in lichen sclerosus
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Lichen sclerosus (LS) is a chronic inflammatory disorder mainly affecting the anogenital region. There is overwhelming evidence for the use of the ultra-potent topical steroid clobetasol propionate 0.05% as the first-line treatment for LS. Topical steroids are widely used in dermatological practice and local side-effects can include atrophy, striae and purpura with excessive use. Systemic side-effects of steroid use are rare and mainly occur with oral administration. These include dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis leading to Cushing syndrome.

The influence of lichen sclerosus on women’s sexual health from a biopsychosocial perspective: a mixed methods study
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Background: Women with lichen sclerosus (LS) may suffer sexually because of dyspareunia, fissures, and introital narrowing. However, the literature remains limited on the biopsychosocial aspects of LS and its impact on sexual health. Aim: To examine the biopsychosocial aspects and impact of LS on the sexual health of Danish women with vulvar LS. Methods: The study was conducted with a mixed methods approach, including women with LS from a Danish patient association. The quantitative sample consisted of 172 women who completed a cross-sectional online survey that included 2 validated questionnaires: the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS). The qualitative sample consisted of 5 women with LS who volunteered for audiotaped, individual, semistructured interviews. Outcomes: This mixed methods study combined data from 2 quantitative questionnaires (FSFI and FSDS) with qualitative interviews to achieve a comprehensive insight into the biopsychosocial aspects of sexual health in women living with LS. Results: The sexual function of women with LS was considerably affected, with FSFI scores below the cutoff value of 26.55, indicating a risk of sexual dysfunction. On average, 75% of the women were sexually distressed, with a total FSDS score of 25.47. Furthermore, 68% of the sexually active women were considerably affected in terms of sexual function and sexual distress, thus meeting international criteria for sexual dysfunction. However, a negative impact on sexual function was not always related to sexual distress and vice versa. The qualitative analysis identified 4 overarching themes: (1) decrease in or loss of sexual activity, (2) interference with relationship dynamics, (3) importance of sex and intimacy - loss and restoration, and (4) worries about sexual insufficiency. Clinical implications: Insight into the influence of LS on sexual health is important for health care professionals, including doctors, nurses, sex therapists, and physiotherapists, to provide the best guidance, support, and management for women with LS. Strengths and limitations: The strengths of the study are its use of a mixed methods design and the inclusion of sexual function and sexual distress. A limitation is related to the properties of the FSFI regarding women with no sexual activity. Conclusions: LS has a considerable influence on women’s sexual health in terms of sexual function and sexual distress, as supported by quantitative and qualitative measures. Our understanding of the complex interactions among sexual activity, intimate relations, and causes of psychological distress has been enriched.
Quality of life and treatment adherence in patients with vulvar lichen sclerosus
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Background: Vulvar lichen sclerosus (VLS) is a chronic, relapsing, inflammatory dermatosis that has significant impact on patients' quality of life (QoL). While disease severity and associated QoL impact have been studied, factors associated with treatment adherence and their relation to QoL in VLS remain unexplored. Objective: To describe demographics, clinical characteristics and skin-related QoL in VLS patients, and to assess the relationship between QoL and treatment adherence. Methods: This was a cross-sectional, single institution, electronic survey study. The relationship between adherence, measured using the validated Domains of Subjective Extent of Nonadherence (DOSE-Nonadherence) scale, and skin-related QoL, using the Dermatology Life Quality Index (DLQI) score, was assessed using Spearman correlation. Results: Of 28 survey respondents, 26 provided complete responses. Among 9 patients classified as adherent and 16 classified as non-adherent, mean DLQI total scores were 1.8 and 5.4 respectively. Spearman correlation between summary non-adherence score and DLQI total was 0.31 (95% CI -0.09, 0.63) overall, and 0.54 (95% CI 0.15-0.79) when patients who reported missing doses due to asymptomatic disease were excluded. Most frequently reported factors preventing treatment adherence included application/treatment time (43.8%) and asymptomatic or well-controlled disease (25%). Conclusions: Though QoL impairment was relatively small in both our adherent and non-adherent groups, we identified important factors preventing treatment adherence, with the most common being application/treatment time. These findings may help dermatologists and other providers generate hypotheses as to how to facilitate better treatment adherence among their patients with VLS, with the goal of optimizing QoL.