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Literature Review

Central Sensitization In Urogynecological Chronic Pelvic Pain: A Systematic Literature Review

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Background: Chronic pelvic pain (CPP) is a complex pain syndrome. Since its pathogenesis is still poorly understood and structural alterations in pain related brain regions may be present, there is a greater acceptance that sensitization of the central nervous system (CNS) plays an important role in the development and maintenance of chronicity.

Objective: The purpose of this study is to systematically review the scientific evidence regarding central sensitization (CS) in female patients with urogynecological CPP.

Study Design: Systematic review of the literature.

Methods: A systematic literature search was conducted in PubMed and Web of Science using different keyword combinations related to urogynecological CPP and central sensitization. Full text clinical reports addressing CS in adult women with urogynecological CPP were included and assessed for methodological quality by 2 independent reviewers.

Results: After screening for the eligibility, a total of 29 full-text articles with low to good methodological quality were retained. All studies were observational, 27 of which were case-control and 2 of which were cohorts. Sensitivity of the CNS was investigated by using a variety of methods. Although different central mechanisms seem to be involved in pain processing, the present evidence suggests hyperexcitability of the CNS in patients with urogynecological CPP. Altered brain morphology and function, generalized hyperalgesia to different type of stimuli, overactive bottom-up nociceptive mechanisms, and autonomic dysregulation were established in patients with urogynecological CPP. Nevertheless, diffuse noxious inhibitory control seemed normal, and therefore the contribution of an impaired endogenous pain inhibition mechanism to CPP requires further study. The same goes for the contribution of psychological factors.

Limitations: The level of evidence of retained studies is low due to the observational study designs and a wide range of diagnoses and assessment methods.

Conclusion: Although the majority of the literature provides evidence for the presence of CS in urogynecological CPP with changes in brain morphology/function and sensory function, it is unclear whether these changes in central pain processing are secondary or primary to CPP, especially since evidence regarding the function of endogenous pain inhibition and the role of psychosocial pain facilitation is scarce. Further studies with good methodological quality are needed in order to clarify exact mechanisms.

Key words: Urogynecological pain, pelvic pain, chronic pelvic pain, hyperalgesia, sensitization, central sensitization, pain processing, pain modulation, pain inhibition, systematic review

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Chronic pelvic pain (CPP) is defined as chronic or persistent pain perceived in structures related to the pelvis for at least 6 months (1). Like many other chronic pain syndromes, CPP is a multifactorial condition with possible sources of pain located in the urogynecological, gastrointestinal, musculoskeletal, and/or in the nervous system, making the differential diagnosing challenging (2).

This multifactorial trait means that CPP mechanisms may include ongoing acute peripheral pain mechanisms involving somatic or visceral tissue, chronic pain mechanisms which especially involve the central nervous system (CNS) and emotional, cognitive, behavioral, and sexual responses and mechanisms (3-6).

Although in the majority of cases of CPP, ongoing tissue trauma, inflammation, or infection are not identifiable (7-11), conditions that cause recurrent trauma, infection, or ongoing inflammation may result in CPP in a small proportion of cases. Activation of acute pain mechanisms by a nociceptive event may sensitize peripheral nociceptive afferents, magnifying the afferent signaling (12,13).

While peripheral sensitization is a local phenomenon, central sensitization (CS) is a central process of the nervous system with the enhanced responsiveness of the central neurons to input from unimodal and polimodal receptors (14-16). This central hypersensitivity could also explain the chronic pain in the absence of peripheral pathology (17) and the discrepancy between the magnitude of tissue damage and magnitude of pain and disability in CPP syndrome (18).

CS indeed encompasses altered sensory processing in the brain (19), malfunctioning of descending pain inhibitory mechanisms (20), increased activity of pain facilitatory pathways, temporal summation of second pain or wind-up (19,21), and long-term potentiation of neuronal synapses in the anterior cingulate cortex (22). Both top-down and bottom-up mechanisms play an important role in the pathophysiology of CS. For example, peripheral injury or other stressors trigger the release of proinflammatory cytokines, with the consequent activation of spinal cord glia with cyclooxygenase-2 and prostaglandin E2 expression in the CNS (23-26). The outcome of these changes within the peripheral nervous system and CNS is a hypersensitive state and amplification of perception of a peripheral stimulus; painful perception of nonpainful stimuli (allodynia) and increased sensitivity for painful stimuli (hyperalgesia) (1,27).

In visceral hyperalgesia, visceral stimuli that are normally sub-threshold may be perceived in the case of CS (28). Of particular importance is that these changes may result in sensory and functional abnormalities not only of the end organ subjected to initiating factors, but also of other organs within the region. This cross-talk between the organs is complicated and can probably happen in any direction (27,29). Cross-sensitization among pelvic structures may contribute to CPP of unknown etiology and involves convergent neural pathways of noxious stimulus transmission from 2 or more organs (viscero-visceral sensitization). Besides the viscera, somatic areas may also be involved. Given enough time, trigger points can develop in peripheral somatic tissue in response to increased nociceptive visceral input (viscero-somatic sensitization) (2,30). Especially increased sensitivity at asymptomatic remote areas, referred to as secondary hyperalgesia, rather than primary hyperalgesia (at asymptomatic places), is suggestive for CS (31). In addition, CS entails much more than generalized hypersensitivity to pain: It is characterized by an increased responsiveness to a variety of stimuli including mechanical pressure (32), chemical substances (33), cold (34), heat (20), electrical stimuli (32,35), stress, emotions, and mental load (15).

In summary, like many chronic disabling pain syndromes, CPP may be the result of an incompletely understood dysfunction in peripheral and/or central neural processing (36). Although, it has already been suggested that many of the mechanisms for the CPP syndromes are based within the CNS (37), there is a need to evaluate and summarize findings of the literature.

To the best of our knowledge, studies evaluating CS in urogynecological CPP have not been reviewed systematically until now. Therefore, the aim of the present study is to systematically review the current evidence regarding central nociceptive processing in women with urogynecological CPP. It is hypothesized that the sensitization of the CNS is responsible for the development and/or maintenance of pain and other symptoms.

Methods

This systematic review is reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines which is an updated reporting guidance addressing the conceptual, methodological, and practical issues of the original Quality of Reporting of Meta-analyses (QUOROM) Statement (38).

Eligibility Criteria

To be included in the present systematic review, papers had to report the results of clinical studies (S) evaluating the clinical, radiologic, and neurophysiologic manifestations of CS (I), assessed by experimental outcome measures (O), in women with urogynecological CPP (P), compared to healthy controls (C).

More specifically, an article had to meet following eligibility criteria: (1) human adult women (> 18 years) suffering from urogynecological CPP were evaluated; (2) central pain processing was assessed; (3) patients were compared to healthy controls; (4) published in English in the last 20 years; and (5) full-text reports, and not abstracts, case-reports, letters, or editorials. The studies not fulfilling any of the 5 inclusion criteria were excluded. The articles assessing only primary hyperalgesia or peripheral sensitization were not included, as these are not supposed to represent CS (31).

Information Sources and Search Strategy

To identify relevant articles regarding CS in urogynecological CPP, PubMed (www.ncbi.nlm.nih.gov/sites/entrez) and Web of Science (http://apps.webofknowledge.com) were searched. The last search was run on November 14, 2012. Two groups of key words were determined related to "urogynecological CPP" and "central sensitization." Key words from group 1 were combined with key words from group 2. The construct of the search strategy is presented in Table 1. Additionally, the reference lists of all included full-text reports were hand searched. Literature search was developed by the first author (SK), who achieved the degree of Master of Science, is experienced in pelvic physiotherapy, and was trained in conducting a systematic review by the last author (MM), who obtained the degree of PhD with a dissertation regarding chronic pain and CS and has published 4 systematic reviews in this domain (39-42).

Table 1. *Search strategy*

Keywords	
Group 1	**Group 2**
pelvic pain OR chronic pelvic pain OR dysmenorrhea OR endometriosis OR adenomyosis OR interstitial cystitis OR painful bladder syndrome OR bladder pain syndrome OR urethral pain syndrome OR genital pain syndrome OR vaginal pain syndrome OR vulvar pain syndrome OR vulvodynia OR vulvar vestibulitis syndrome OR perineal pain syndrome OR vaginismus OR pudendal neuralgia OR pudendal pain syndrome OR pelvic floor muscle pain OR myofascial pelvic floor dysfunction OR myofascial pelvic pain syndrome OR pelvic organ prolapse	sensitization OR (sensitization AND hyperalgesia) OR peripheral sensitization OR central sensitization OR (sensitization AND algometry) OR (pain threshold AND central) OR quantitative sensory testing OR central sensitivity OR central hypersensitivity OR central hyperexcitability OR pain processing OR pain modulation OR neural inhibition OR nociception OR hyperalgesia OR allodynia OR windup OR temporal summation OR spatial summation OR conditioned pain modulation

Data Collection Process

At first, the studies were screened according to the title and abstract with the inclusion and exclusion criteria. As a second step, the remaining papers were screened on a full-text basis.

Data Items

Information was extracted from each included trial on: 1) characteristics of trial participants (including diagnosis, age, and pain duration) and the study's inclusion and exclusion criteria, 2) method of assessment (brain imaging, neurophysiological tests, quantitative sensory tests, subjective pain ratings, psychosocial measures, etc.), 3) type of outcome measure (brain morphology/function, sensation/pain threshold or tolerance, pain ratings, psychosocial scores, etc.) and 4) main results. The first author (SK) extracted the data from included studies and the last author (MM) reviewed the extracted data.

Risk of Bias in Individual Studies

Methodological quality was assessed by 2 independent researchers (SK and LH), who were blinded to each others assessments. The second rater was also trained in assessing methodological quality. In case of uncertainty between these 2 raters, a third decisive opinion was provided by the last author (MM).

Methodological quality was evaluated using Newcastle-Ottawa Scale (NOS). The NOS has been recommended by the Cochrane Non-Randomized Studies Methods Working Group and it is partly validated and primarily used to appraise cohort studies and case-control studies (43,44). The NOS uses a star rating system (range 0 to 9 stars) to judge the quality of a study based on 3 broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively (44).

Level of Evidence

After pooling the results, the overall quality of evidence for each outcome was rated with the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (45).

Grading the evidence was done by 3 researchers (SK, TW, and MM) by means of internal discussion and consensus.

Results

Study Selection and Study Characteristics

The flow-chart in Figure 1 shows the selection process. The initial search resulted in 805 hits. Finally, 29 full-text articles were included in the qualitative synthesis of this review. Of the 29 articles, 27 were case control studies and 2 were cohort studies. The characteristics of the included studies are presented in Table 2.

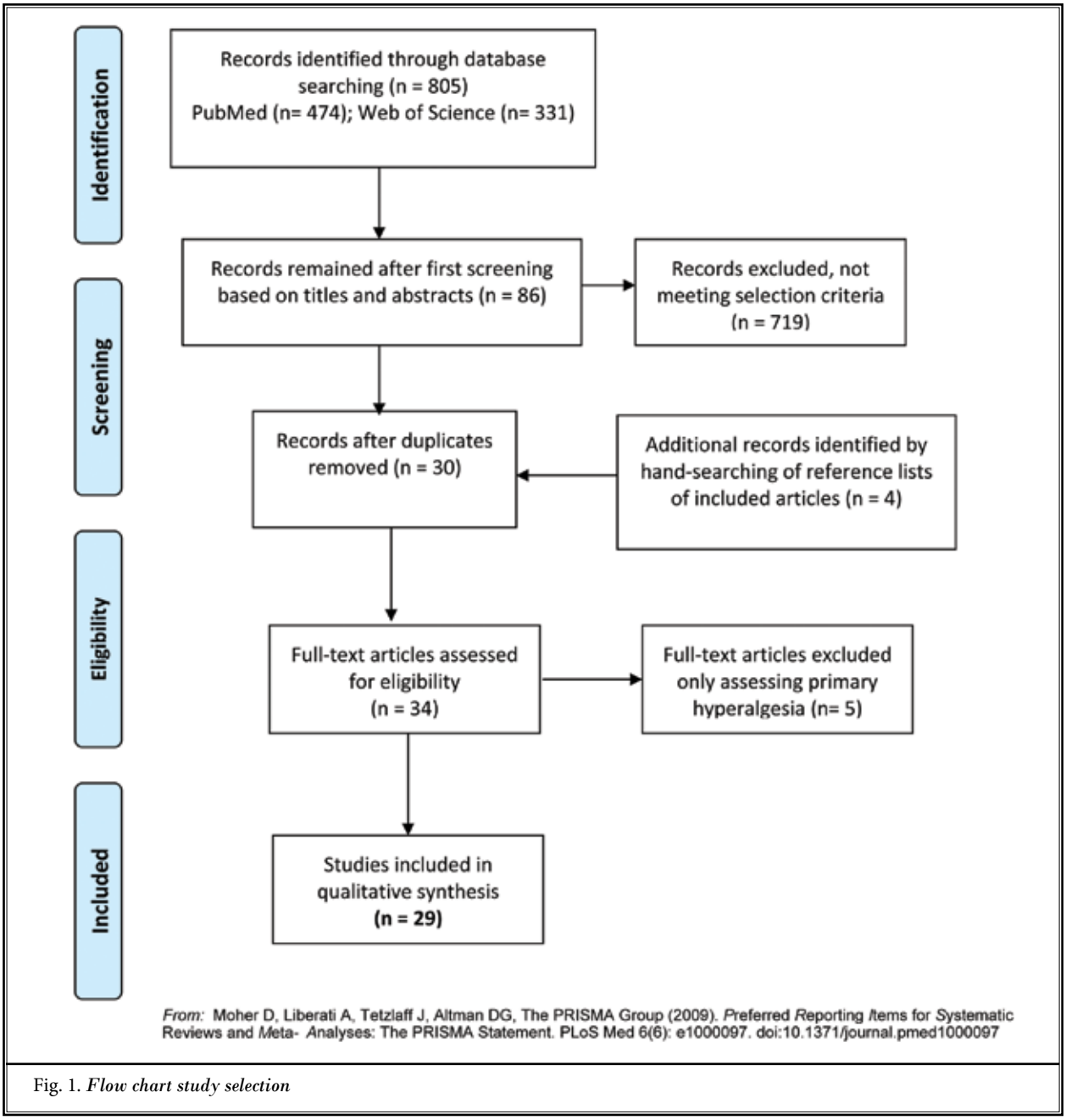

Fig. 1. *Flow chart study selection*

Table 2. *Evidence table*

Studies/ Design/ NOS	Patients (P); Age; Pain Duration	Controls (C)	Outcome Measures	Main Results
Sutton et al (2012) (54)/ Case control/ NOS (5)	Provoked vestibulodynia; 23.78±5.04 (18-36); 3.66 (0.75-10); n= 23	26.52±8.56 (19-44); n= 23	• Pain intensity ratings during gynecological examination • HPT, HP-Tol, ratings for pain tolerance • Peak pain ratings during temporal summation procedure	P↔C • ↑ pain intensity ratings during gynecological examination • ↓ HP-Tol before conditioning stimulus • ↑ magnitude of DNIC responding P = C • HPT • HP-Tol during conditioning stimulus • Ratings for pain tolerance before or during conditioning stimulus • Peak pain ratings before or during conditioning stimulus in the number of DNIC responders
As-Sanie et al (2012) (17)/ Case control/ NOS (7)	1. Endometriosis (+) CPP (+); 26.1±1.5; 5.5 [3.5-9.5]; n= 17 2. Endometriosis (+) CPP (-); 36.8±2.2; 0[0,0]; n= 15 3. Endometriosis (-) CPP (+) ; 24.2±1.9; 3.75[0.90-9.9]; n= 6	25.9±1.6; n=17 36.2±2.6; n= 14 24.8±1.2; n= 12	• Gray matter (GM) volume in regions involved in pain processing • Clinical pain; pain intensity and unpleasantness • Experimental pain testing; pressure- pain values required to elicit faint, mild and slightly intense pain • Measures of mood and function	P1, P3↔C • ↓ GM volume P2↔C • ↑ GM volume
Zhang et al (2011) (56)/ Case control/ NOS (4)	Vulvodynia; n= 12 1. Women with a shorter history of pain 34.6±4.3; 3.4±1.3; n= 5 2. Women with a longer history of pain 35.7±3.2; 9.3±1.4; n= 7	- n= 20	• Vibrotactile detection threshold • Amplitude discrimination capacity • A metric of adaptation (the impact of conditioning stimuli on amplitude discrimination capacity)	P2↔ (P1=C) • ↓ adaptation metric P1=P2=C • Vibrotactile detection threshold • Amplitude discrimination capacity
Vincent et al (2011) (50)/ Case control/ NOS (4)	Dysmenorrhea; 30±7; no years menstruation: 17±6; n= 12	32±10; no years menstruation: 19±10; n= 12	• Behavioral measures * the temperature needed to obtain a pain intensity 5 of 10 * pain intensity and unpleasantness ratings during heat stimulation • Serum cortisol levels • Brain activity with FMRI • Psychological profile and quality of life	P↔C • ↓ temperature • ↓ serum cortisol levels • no deactivation of brain regions during menstrual phase • ↑ brain activity (entorhinal cortex) during nonmenstrual phases • ↓ quality of life P=C • pain intensity and unpleasantness ratings • brain activity during menstrual phase
Neziri et al (2010) (18)/ Case control/ NOS (5)	Endometriosis; 33{30-36}; > 6 month; n= 20	27{24-37}; n= 25	• Reflex receptive fields • Pain and nociceptive withdrawal reflex thresholds after a single and during repeated electrical stimulation • Measures of mood and function	P↔C • ↑ reflex receptive field areas • ↓ thresholds for the subjective feeling of pain /increasing pain sensation and to evoke a nociceptive reflex after a single stimuli and during repeated stimulation
He et al (2010) (70)/ Cohort/ NOS (7)	Endometriosis; 34.4±7.4; 33 (23-52); n= 100; PD Ø	33.4±7.1; 32 (25-51); n= 70	• Dysmenorrhea (DM) severity • Electrical pain test (EPT) sensory and pain threshold • The pain intensity score that matches with patients own DM severity • Ischemic pain test (IPT)	Before surgery P↔C • ↓ EPT pain threshold • ↑ IPT scores P=C • EPT sensory threshold 6 months after surgery P=C • IPT scores • EPT sensory and pain thresholds Post-op 6th month↔Pre-op • ↓ DM severity • ↓ EPT DM matching score

Table 2 (cont.). *Evidence table*

Studies/ Design/ NOS	Patients (P); Age; Pain Duration	Controls (C)	Outcome Measures	Main Results
Tu et al (2010) (46)/ Case control NOS (7)	Primary dysmenorrhea; 23.84±2.99; 10.19±3.25; n=32	23.81±2.80; n=32;	• Psychological measures • Total and regional gray matter (GM) volume	P = C • psychological measures • total GM volume P↔C • ↓ GM volume in regions involved in pain transmission, higher level sensory processing, and affect regulation • ↑ GM volume in regions involved in pain modulation and regulation function of endocrine
Sutton et al (2009) (53)/ Case control/ NOS (6)	Provoked vestibulodynia; 26.08±8.34; 3.77±2.93 (0.8-10.0); n= 20	23.72±4.90; n= 25	• Pain intensity ratings during gynecological examination • QST (PPT, HD, HPT, HP-Tol), pain/sensory intensity and unpleasantness during QST • Psychosocial measures	P↔C • ↑ pain intensity ratings during gynecological examination • ↓ vulvar PPTs, HPTs, HP-Tols • ↑ self-report ratings for HD • ↑ somatization, catastrophization • ↓ sexual self-efficacy, sexual functioning P = C • PPTs, self-report ratings during pressure testing, thermal thresholds and self-report ratings at the forearm for thermal stimuli • vulvar HD • self-report ratings for vulvar HPT, HP-Tol
Tu et al (2009) (49)/ Case control/ NOS (5)	Primary dysmenorrhea; 23.1±3.03 (19-29); 9.17±3.06 (4-16); n= 17	21.7±2.6; n= 16	• Psychological assessment • Regional brain metabolism/ activity with PET scan	P↔C comparing pain state with the pain-free state • ↑ regional metabolism in thalamic, prefrontal/ orbitofrontal regions
Twiss et al (2009) (73)/ Case control/ NOS (4)	Interstitial cystitis/painful bladder syndrome; 45.7±3.2; PD Ø; n= 13	37.2±3.0; n=16	• Psychometric measures • Acoustic startle reflex (ASR) • Intensity and unpleasantness ratings of abdominal stimulation	P = C • perceptual ratings of abdominal stimulation • ASR during context threat and imminent threat conditions P↔C • ↑ ASR at baseline, safe and anticipation conditions • ↑ anxiety and depression scores
Lowenstein et al (2009) (55)/ Case control/ NOS (5)	Painful bladder syndrome 50 (22-69); 4 (1-20); n= 11	46 (35-54); n= 10	O'Leary-Sant scale Pain catastrophizing scale Thermal and vibratory sensory thresholds Supra-threshold habituation to thermal stimuli	P↔C • ↑ thermal thresholds at T12 • ↓ habituation to supra-threshold thermal stimuli • ↑ sensation intensity during tonic heat stimulus • ↑ catastrophization P=C • thermal thresholds at all testing sites except T12 • vibratory thresholds at all testing sites
Frasson et al (2009) (68)/ Case control/ NOS (5)	1. Primary idiopathic lifelong vaginismus 34.1±2.2; DD: lifelong; n=10 2. Vulvar vestibulitis syndrome accompanied by vaginismus; 34.6±2.6; DD: 1-12 y; n=10	37.6±5.5; n=10	• Electromyographic activity from pelvic floor muscles • Bulbocavernosus reflex - The first early response (R1) - Second late response (R2) • Pudendal-nerve somatosensory evoked potentials (SEP) • Pudendal-nerve SEP recovery functions	P↔C • ↑ muscular activity at rest and straining • ↑ R2 amplitude and duration • ↑ cortical P40-N50 amplitude at 20 ms interstimulus interval P=C • R1 latency, amplitude, duratıon • R2 latency • Sensory threshold to electrical stimuli on the dorsal nerve • SEP amplitudes and latencies in response to single stimuli
Schweinhardt et al (2008) (47)/ Case control/ NOS (6)	Provoked vestibulodynia; 25.7±5.1 (19-36); > 6 months; SD: 5±2.9 (1-9); n= 14	25.6±6.0; n= 14	TT and PPT at the posterior vulvar vestibule • Pain intensity ratings during Q-tip test • Pain catastrophizing scale • Total gray matter (GM) volume • Regional GM densities	P↔C • ↓ TTs and PPTs • ↑ pain intensity ratings • ↑ non-vulvar pain catastrophizing • ↑ GM density in pain modulatory and stress related areas P = C • Total GM volume

Table 2 (cont.). *Evidence table*

Studies/ Design/ NOS	Patients (P); Age; Pain Duration	Controls (C)	Outcome Measures	Main Results
Johannesson et al (2007) (60)/ Case control/ NOS (5)	Provoked vestibulodynia; 24.9 (20-33); ≥ 6 months; n= 20	COC group 24.4 (18-34) n= 20 non-COC group 23.8 (18-33) n= 20	• PPTs at peripheral sites • Pain intensity ratings • Other measures	P↔C • ↓ score on vitality and general health • ↑ anxiety and depression more bodily pain • Before cold pressor test • ↓ PPTs During cold pressor test • ↓ PPTs P=C • increase in PPTs during cold noxious stimulation • pain ratings before and during cold noxious stimulation
Pukall et al (2006) (63)/ Case control/ NOS (8)	Vulvar vestibulitis syndrome; 27.4 (22-37); > 6 months; SD: 86.1±55.1 month; n=16	26.3 (21-40); n=16	• Body pain questionnaire scores • General Health Problems questionnaire scores • Pain Catastrohizing • Anxiety Score • Pain behavior, Pain intensity and unpleasantness ratings during tender point (TP) examination	P↔C • ↑ magnitude of non-vulvar pain • ↑ pain interference with daily activities • ↑ number of regularly experienced pains and ↑ ratings for the seriousness and interference of these pains and lifetime health problems • ↑ vulvar and non-vulvar pain catastrophizing • ↑ trait anxiety • ↑ number of painful areas during TP examination • ↑ pain intensity and unpleasantness ratings during TP examination P=C • Total number of lifetime health problems • State anxiety
Foster et al (2005) (71)/ Case control/ NOS (7)	Vulvar vestibulitis syndrome; 31.6; ≤ 4 y (for 4 cases), ≥ 10 y (for 6 cases); n= 10	31.9; n=10	• Post-capsaicin pain response • Spontaneous pain level • Surface area of punctate hyperalgesia • Surface area of dynamic allodynia • Cutaneous blood flow • Regional skin temperature • Vital signs	P↔C • ↑ post-injection spontaneous pain • ↑ area of punctate hyperalgesia • ↑area of dynamic allodynia • ↑ resting pulse rate • ↓ resting mean systolic pressure P = C • Cutaneous blood flow • Regional skin temperature
Granot &Lavee (2005) (64)/ Case control/ NOS (5)	Vulvar vestibulitis syndrome; 22.88±2.27; > 6 months; n= 28	24.60±4.11; n= 50	• Thermal pain threshold • The magnitude estimation of phasic suprathreshold pain • The magnitude estimation of tonic pain • Psychological measures	P↔C • ↓ pain threshold at forearm • ↑ magnitude estimation of phasic suprathreshold stimuli • ↑ trait anxiety • ↑ somatization • ↓ body image P = C • Magnitude estimation of tonic stimuli • State anxiety • Experimental pain catastrophizing
Ness et al (2005) (62)/ Case control/ NOS (4)	Interstitial cystitis; 36±8; PD Ø; n=13	33±8; n=13	• Psychological questionnaires • Thermal pain threshold and tolerance • Muscle PPT • Ischemic pain threshold (I-THR) • Ischemic pain tolerance (I-TOL) • The pressure and volume values during bladder filling (cystometrogram) • Pain intensity and unpleasantness ratings during bladder filling	P↔C • ↓ Quality of life • ↑ reactivity and hypervigilance • ↑ catastrophizing • ↓ muscle PPTs • ↓ I-TOL • ↑ bladder sensitivity P = C • Thermal measures • I-THR

Table 2 (cont.). *Evidence table*

Studies/ Design/ NOS	Patients (P); Age; Pain Duration	Controls (C)	Outcome Measures	Main Results
Laursen et al (2005) (57)/ Case control/ NOS (8)	1. Fibromyalgia/Whiplash/ 46 (37-54)/ 53 months/ n=10 2. Endometriosis; 44 (35-61); 96 months; n=10 3. Low back pain; 45 (28-58); 48 months; n=10 4. Rheumatoid arthritis; 43 (28-58); 42 months; n=10	42 (25-61); n=41	• Pain intensity of the habitual pain • PPTs • Quality of life score	P1,2,3,4↔C • ↑ habitual pain intensity • ↓ PPTs P1=P2=P3=P4 • median PPT values P1↔P2,3,4 • ↑ habitual pain intensity
Pukall et al (2005) (48)/ Case control/ NOS (8)	Vulvar vestibulitis syndrome; 25.7 (19-39); > 6 months; n=14	25.7 (19-39); n= 14	• Intensity and unpleasantness ratings during mild and moderate pressure stimulation • Regional brain activity during non-painful and painful stimuli with FMRI	P↔C • ↑ intensity and unpleasantness ratings • ↑ activation of pain-related brain regions
Granot (2005) (65)/ Case control/ NOS (6)	Vulvar vestibulitis syndrome; 24.1±4.1 (18-36); > 6 months; n= 98	23.3±2.4 (18-31) n= 135	• Personality traits - harm avoidance (HA) - novelty seeking (NS) - reward dependence (RD) • Thermal pain threshold • The magnitude estimation of perceived phasic supra-threshold pain (VAS)	P↔C • ↓ Thermal pain thresholds • ↑ VAS scores in response to the supra-threshold painful stimuli • ↑ Scores in HA and RD P = C • Scores in NS • Sig. correlations between pain sensitivity and personality trait variables (HA and RD)
Giesecke et al 2004 (58)/ Case control/ NOS (8)	Vulvodynia; 33.41±9.39 (18-60); PD Ø; n= 17	37.17±11.43; n= 23	• PPTs in the vulvar areas • PPTs at peripheral sites • The pressures required to produce different levels of subjective pain at the thumb	P↔C • ↓ PPTs in the vulvar region • ↓ PPTs at peripheral sites • ↓ pressures required to elicit faint, mild and slightly intense pain at the thumb
Bajaj et al (2003) (52)/ Case control/ NOS (5)	Endometriosis; 37.7±2.9; 15±3.5; n= 10	30.1±2.3; n=10	• Post-saline pain intensity (VAS) • Post-saline pain areas • PPTs and TTs before and after injection	P↔C • ↑Peak pain VAS after injection into the first dorsal interosseus muscle (FDI) of the hand • ↑ Post-saline pain areas after injection into the FDI • ↓ PPTs and before and after injection P = C • Peak pain VAS after injection into the back • Post-saline pain areas after injection to the back • TTs before and after injection
Granot et al (2002) (66)/ Case control/ NOS (5)	Vulvar vestibulitis syndrome; 27.1±7.6; PD Ø; n= 44	25.4±5.2; n= 41	• Anxiety scores • Heat pain intensity and unpleasantness thresholds • The magnitude of perceived intensity and unpleasantness of phasic and tonic supra-threshold stimuli • The cardiovascular parameters	P↔C • ↑ state anxiety, trait anxiety • ↓ heat pain and unpleasantness thresholds • ↑ magnitude estimation of supra-threshold phasic pain and ↑ unpleasantness ratings at 47°C and 48 °C. • ↑ scoring of tonic pain perception and ↑ unpleasantness ratings • ↑ increase in systolic blood pressure during tonic pain stimuli P=C • Magnitude estimation of perceived intensity and unpleasantness at 44°C, 45°C and 46°C • Heart rate
Bajaj et al (2002) (61)/ Case control/ NOS (4)	Dysmenorrhea; 25.5±1.1; PD Ø; n= 20	28±1.9 n= 15	• McGill Pain Questionnaire • PPT, PiPT, HPT, TT	P↔C (menstrual phase) • ↓ HPT at the control sites • ↓ PPT at referral and control sites P = C (menstrual phase) • HPT at referral areas Menstrual phase↔other phases • ↓ HPT and PPT at referral and control areas Menstrual phase↔ovulatory phase • ↓ PiPT

Table 2 (cont.). *Evidence table*

Studies/ Design/ NOS	Patients (P); Age; Pain Duration	Controls (C)	Outcome Measures	Main Results
Pukall et al (2002) (51)/ Cohort/ NOS (8)	Vulvar vestibulitis syndrome; 25.85 (21-44); > 6 months; 50.08±38.37 month; n= 13	26.31 (21-41); n= 13	• Pain ratings during gynecological examination • Tactile and PPTs • Pain and distress ratings during supra-threshold pain and sustained pressure • PP-Tol at peripheral sites • Psychological measures	P↔C • ↑pain ratings during gynecological examination • ↑ catastrophization scores related to intercourse pain • ↓ TT and PPT for the vestibular sites and labium minus • ↓TT, PPT and PP-Tol over the deltoid muscle • ↑ distress ratings for supra-threshold pain and sustained pressure P = C • TT at forearm and tibia • PPT at tibia session 1= session 2 • TTs at vestibular sites, thigh and labium minus session 2↔session 1 • ↑ mean PPTs of vestibular sites
Granot et al (2001) (67)/ Case control/ NOS (4)	Dysmenorrhea; 23.7±2.8; PD Ø; n= 22	24.1±3.1 (19-30); n= 31	• Anxiety scores • Self-reports of pain • HPT • Supra-threshold magnitude of perceived pain (VAS) • Pain-evoked potentials by laser stimuli (latency, amplitude) • VAS score in response to supra-threshold laser	P↔C • ↑ state anxiety • ↑ VAS score for supra-threshold pain • ↑ latency of the laser-evoked potentials • ↑ VAS score in response to supra-threshold laser stimuli P=C • Trait anxiety • HPT • Amplitude of the laser-evoked potentials
Giamberardino et al (1997) (69)/ Case control/ NOS (5)	Dysmenorrhea; 29±5.6; PD Ø; n= 10	28.7±5.9 ; n= 10	• EPT of skin, subcutis and muscle	P↔C • ↓ EPT of subcutis and muscle P=C • EPT of skin
Clauw et al (1997) (59)/ Case control NOS (6)	Fibromyalgia; 43.8; PD Ø; n= 60 Interstitial cystitis; 44; PD Ø; n= 30	45.6; n= 30	• Questionnaire regarding current symptomatology • PPT • PP-Tol	IC↔C • ↓ PPT, PP-Tol at tender and control points FM↔IC • ↓ PPT, PP-Tol at tender points FM = IC • Frequency of current symptoms • PPT, PP-Tol at control points

(COC: Combined Oral Contraceptive, CPP: Chronic Pelvic Pain, DD: Disease Duration, DNIC: Diffuse Noxious Inhibitory Control, EPT: Electrical Pain Threshold, FMRI: Functional Magnetic Resonance Imaging, HD: Heat Detection, HPT: Heat Pain Threshold, HP-Tol: Heat Pain Tolerance, PET: Positron Emission Tomography, QST: Quantitative Sensory Testing, PPT: Pressure Pain Threshold, PP-Tol: Pressure Pain Tolerance, PiPT: Pinch Pain Threshold, PD: Pain Duration, SD: Symptom Duration, TT: Tactile Threshold, VAS: Visual Analog Scale)

Risk of Bias and Level of Evidence

The methodological quality ratings of the reviewed studies are presented in Table 2. In most cases (91.57% or 239 of the 261 items), the 2 researchers agreed. After a second review and a discussion of the 22 differences, the raters reached a consensus for 21 items. The last author (MM) solved the remaining point of difference.

Methodological scores ranged from 4 to 8 points (maximum score 9). The most common flaws for the case control studies were the representativeness of the patients and the comparability of cases and controls.

Since all studies are observational (case-control or cohort) in the present systematic review, the level of evidence for each relevant outcome began as low-quality evidence according to the GRADE system. Then, for most of the outcomes, the quality of evidence was downgraded to low quality or to very low quality due to the limitations of the study design (risk of bias) and inconsistency of the study results.

Evidence for Central Sensitization

In the following section, the results of this review

are categorized according to the neural, neurophysiological, and clinical correlates of CNS alterations.

Alteration in Brain Morphology and Function

Brain Morphology

Using voxel-based morphometry, 3 studies with moderate risk of bias reported changes in regional gray matter (GM) density/volume in patients having CPP with and without endometriosis and in the other CPP conditions including primary dysmenorrhea and provoked vestibulodynia (PVD) (synonym "vulvar vestibulitis syndrome") (17,46,47). Schweinhardt et al (47) reported only regionally increased GM density compared to both GM volume decreases and increases in other studies (17,46). Studies reported greater decreases in GM volume in regions of the pain system including thalamus, cingulate cortex, putamen (17), precuneus, secondary somatosensory cortex, superior temporal gyrus, cerebellum (46), and insular cortex (17,46) and/or those involved in pain modulation (prefrontal cortex) (17,46) in patients compared to controls. Endometriosis patients without CPP and PVD patients showed no evidence of a GM decrease within the pain system (17,47). Regional increase in GM density/volume was found in pain modulatory, stress, and endocrine function related areas including right inferior/middle frontal gyrus, left amygdala (17), cingulate cortex, hypothalamus, precuneus, superior/middle temporal gyrus, cerebellum (46), mesencephalon (17,46), basal ganglia (47), and hippocampus/parahippocampus (46,47).

There is limited evidence suggesting the change in regional brain morphology in patients with urogynecological CPP, but location and direction (increase or decrease) are conflicting (very low level of evidence).

Brain Function

Two different imaging methods were used to examine CNS activity in 3 studies with low (48), moderate (49), or high risk of bias (50). Using fluoro-deoxyglucose positron emission tomography, Tu et al (49) found that cramping menstrual pain is associated with increased activity in prefrontal/orbitofrontal regions and left ventral posterior thalamus and with decreased activity mainly in sensorimotor regions of left hemisphere in patients with primary dysmenorrhea.

Functional magnetic resonance imaging was used to investigate the cerebral response to experimental thermal and tactile stimuli in patients with dysmenorrhea (50) and vulvar vestibulitis syndrome (VVS) (48). Although the differences in brain activity increases during the menstrual phase were not significant between the groups, deactivation of brain regions in response to noxious thermal stimulation of the control site was observed in control women but not in dysmenorrheic women. In response to stimulation of pain referral site, dysmenorrheic women had higher activity in the left entorhinal cortex and inferior/middle temporal gyrus than controls during non-menstrual phases (without background pain) (50). Women with VVS showed higher activation in the right cerebellum during non-painful tactile vestibular stimulation and higher activation in the insular and frontal cortical regions during painful stimulation compared to control subjects (48).

There is a change in brain activity/function in patients with urogynecological CPP (very low level of evidence) but the evidence is too limited to draw conclusions concerning the regions.

Alteration in Sensory Perception

Tactile Stimuli

Three research papers with low (51) and moderate risk of bias (47,52) examined the response to tactile stimuli with von Frey filaments. Although Bajaj et al (52) did not find any significant difference between groups for punctate tactile thresholds at referral and nonreferral areas of menstrual pain, other studies reported lower punctate tactile thresholds at vestibular sites (47,51), labium minus, and over the deltoid muscle but not at other peripheral sites (forearm, tibia) in PVD patients and these results were reliable over time in symptomatic areas (51).

In patients with PVD, higher distress ratings to sustained supra-threshold pain stimuli in the vestibular region (51) and higher pain intensity ratings during cotton-swab test (47,51,53,54) and speculum insertion (53,54) were also established.

The evidence based on the selected articles is limited and too conflicting to draw conclusion for the response to tactile stimuli in patients with urogynecological CPP (very low level of evidence).

Vibratory Stimuli

In response to vibratory stimuli, 2 studies with moderate (55) to high risk of bias (56) did not provide evidence for the hypersensitivity at both local and remote dermatomes in patients with painful bladder syndrome (PBS) (55) and vulvodynia (56).

Evidence regarding the use of vibratory stimuli is too limited, but hypersensitivity to vibratory stimuli does not seem to be present (very low level of evidence).

Pressure Stimuli

Pressure algometry was used as one of the outcome measures in 10 of the 29 studies with low (51,57,58), moderate (47,52,53,59,60), or high risk of bias (61,62). One study with low risk of bias also used manual tender point examination (63).

Schweinhardt et al (47) assessed pain thresholds in response to pressure at only the symptomatic site (vestibular site) in their brain morphometry study and provided evidence for primary hyperalgesia. All remaining studies examined both local and remote (52,53,57-59,61) or remote sites only (51,60,62,63) and all of them except one (53) established widespread pressure hyperalgesia in women with urogynecological CPP (see Table 2 for details).

Pukall et al (51) assessed the genital thresholds also in a second session (3-12 months later) to test the stability of thresholds over time and reported a similar increase in punctate pain thresholds in the PVD and control groups. This increase at the second session can be explained by reduced anxiety focused on the testing because of the familiarity with the test procedure.

There are 2 studies comparing CPP patients with other chronic pain patients (57,59) such as fibromyalgia/whiplash, low-back pain, and rheumatoid arthritis patients. No significant differences were reported in median pressure pain thresholds between endometriosis patients and other chronic pain patients (57). In the other study, compared to fibromyalgia patients, women with interstitial cystitis reported higher pressure pain thresholds at tender points (9 paired areas) but not at control points (59).

The presence of generalized hyperalgesia in response to pressure stimuli is supported by a low level of evidence in women with urogynecological CPP.

Thermal Stimuli

Thermal stimuli were used in 10 studies, with moderate (53-55,64-66) to high risk of bias (50,61,62,67), to evaluate CS in women suffering from urogynecological CPP. All studies examined the response to heat stimuli at both local and remote sites (50,53,55,61) or at remote sites only (54,62,64-67). Five of them (50,61,64-66) provided evidence for widespread thermal hyperalgesia, while 2 others did not (53,62). Besides this, inconsistent results at peripheral sites (54,67) and hypoesthesia at pain-referral area (55) were also reported (see Table 2 for details).

PVD patients showed peripheral hypersensitivity for pain tolerance but not for pain thresholds (54). Even though Granot et al (67) did not report decreased heat pain thresholds at the thenar eminence of the hand of dysmenorrhea patients, the authors reported higher magnitude estimations on a visual analog scale of supra-threshold pain elicited by thermal and water-cooled CO2 laser stimuli to the hand.

Elevated thermal detection thresholds, indicative for the presence of hypoesthesia, were established at the suprapubic area but not at remote dermatomes in patients with painful bladder syndrome (55). In the same study, supra-threshold thermal stimuli were also applied at T12 (suprapubic) and S3 (remote) dermatomes for 60 seconds to assess the habituation to somatic stimuli. The authors found that habituation to suprathreshold stimuli is less common in patients than in controls, suggesting the impaired habituation (55).

There is conflicting evidence regarding the response to thermal stimuli in patients with urogynecological CPP, although the majority suggest widespread thermal hyperalgesia (very low level of evidence).

Electrical Stimuli

There are 4 papers with moderate risk of bias assessing the response to electrical stimuli (18,68-70). No hypersensitivity was reported at local (68) or at asymptomatic sites for electrical detection thresholds (70). Giamberardino et al (69) investigated the electrical pain thresholds (EPT) at 3 stimulus depths: skin, subcutis, and muscle tissue within the uterine visceretome and on the limbs, and reported similar thresholds for skin, and lower thresholds for subcutis and muscle compared to controls. EPTs were also examined in patients with endometriosis before and following excisional surgery for all visible endometriotic lesions (70). Three and 6 months after surgery, it is reported that patients' generalized hyperalgesia to electrical stimuli significantly and progressively improved, along with their dysmenorrhea severity. In another study by Neziri et al (18), EPTs during sural nerve stimulation were significantly lower in patients with endometriosis than in controls, also demonstrating the generalized hyperalgesia.

There is evidence supporting the generalized electrical hyperalgesia in patients with urogynecological CPP (low level of evidence).

Injection of Specific Pain Mediators

In one study with moderate risk of bias, after intradermal injections of capsaicin in the forearms and feet of VVS patients, they reported greater spontaneous pain, area of punctate hyperalgesia, and dynamic allodynia compared with pain-free controls (71). In another study with moderate risk of bias (52), patients with endometriosis reported higher pain intensity and larger pain areas after injection of hypertonic saline to the control site (into the first dorsal interosseus muscle of the hand). These hyperalgesic responses were not observed following the injection to the menstrual pain referral site (the multifidus muscle at the low back).

The limited available evidence suggests the presence of CS in women with urogynecological CPP with increased response to injection of pain mediators (very low level of evidence).

Ischemic Stimuli

The ischemic pain test (IPT) is a tonic pain stimulus involving multiple noxious input (e.g., pressure and ischemia) (70). Two studies with moderate (70) to high risk of bias (62) used a modified procedure and provided conflicting evidence for the presence of generalized hyperalgesia. In the study of He et al (70), endometriosis subjects had significantly higher IPT visual analog scale scores than controls, but after removing ectopic implants with surgery, their IPT scores were significantly and progressively improved. Six months after surgery, there was no difference in IPT scores between patients and controls anymore.

Ness et al (62) showed that the subjects with interstitial cystitis tolerated the ischemic forearm pain (ischemic tolerance) for a shorter duration than normal subjects, while the difference was not statistically significant for the ischemic threshold duration.

The evidence in response to ischemic stimuli in patients with CPP is too limited and conflicting (very low level of evidence).

Distention Stimuli

One study (62) with high risk of bias used cystometrogram to assess bladder sensitivity, and reported that the subjects with interstitial cystitis are more sensitive to bladder distention than healthy subjects, demonstrating the presence of primary hyperalgesia.

There is limited evidence that sensitivity to distention stimuli in CPP patients is increased (very low level of evidence).

Neurophysiological Changes

Overactive Bottom-up Mechanisms

Four studies with moderate (18,68) to high risk of bias (56,67) evaluated excitability and responsiveness of the CNS by using different kinds of neurophysiological tests.

The spinal withdrawal reflex was used to evaluate reflex receptive fields of spinal cord neurons in patients with endometriosis associated CPP. In comparison with pain-free participants, patients showed larger reflex receptive fields on the foot sole, providing evidence for the expansion of nociceptive reflex receptive fields. Lower thresholds to induce subjective feelings of increasing pain sensation and lower nociceptive reflex thresholds by repeated electrical stimulation (temporal summation) of the cutaneous area of the sural nerve were even so reported, indicating generalized spinal cord hypersensitivity and generalized facilitated temporal summation (18).

CNS excitability was also assessed by measuring electromyographic activity of pelvic floor muscles, bulbocavernosus reflex (BCR), and pudendal nerve somatosensory evoked potentials in women with primary idiopathic lifelong vaginismus. In comparison with the healthy controls, the patients had greater electromyographic activity, higher amplitude and duration for the one component of bulbocavernosus reflex, and higher amplitude of cortical P40-N50 in the pudendal nerve somatosensory evoked poatentials recovery cycle. This abnormal excitability suggests concomitant CNS changes in vaginismus (68).

Patients with dysmenorrhea showed longer latencies of pain-evoked potentials and higher pain ratings in response to supra-threshold pain evoked by the laser stimuli to a non-gynecological site (67).

On the other hand, compared with healthy controls and patients with a shorter history of pain, vulvodynia patients with a longer history of pain demonstrated a significantly reduced effect of adaptation on sensory perception, suggesting central hyperexcitability (56).

Available evidence suggests overactivity of bottom-up CNS mechanisms in the pathophysiology of urogynecological CPP (low level of evidence).

Dysfunctional Top-down Mechanisms

Two studies with moderate risk of bias found no evidence of impaired diffuse noxious inhibitory control response in patients with PVD. There was no significant difference in the number of diffuse noxious inhibi-

tory control responders between the groups (54,60). The magnitude of the response (increase in pressure pain threshold) was similar in both patients and controls in one of the studies (60), while the other study (54) reported a higher magnitude of response (increase in heat pain tolerance) in patients with PVD as compared to controls.

Evidence suggests an intact diffuse noxious inhibitory control function in patients with PVD (low level of evidence).

Dysfunction of Hypothalamic-pituitary-adrenal (HPA) Axis

Only one study which has a high risk of bias investigated whether menstrual pain is a sufficient stressor to affect HPA axis function. Women with dysmenorrhea had significantly lower mean cortisol levels than controls. Also, a significant negative correlation was observed between the number of years that dysmenorrhea had been present and the mean serum cortisol levels (50).

There is limited evidence to support the dysfunction of the HPA axis in urogynecological CPP (very low level of evidence).

Alteration in Psychosocial Functioning

Psychological factors such as anxiety, somatization, catastrophizing, and other personality traits are involved in pain processing (64) and enhanced pain facilitation may be caused by cognitive emotional sensitization (72). Eight studies with low (51,63), moderate (47,53,60,64,65), or high risk of bias (73) reported conflicting results regarding the alteration of psychosocial functioning and/or its association with pain perception. In 3 studies, no association was found between higher anxiety scores and pain response in patients with PVD (60,64) or interstitial cystitis/painful bladder syndrome (73). Other components of psychosocial function including somatization and catastrophization were examined in a variety of ways in women with PVD and results have demonstrated that affected women report more somatic and/or catastrophic symptoms in comparison to control women (47,53,63,64), suggesting that a higher tendency to catastrophize about pain may enhance the pain perception and increase emotional distress related to pelvic pain syndromes (63). Two studies reported an association between enhanced pain perception and psychological factors (53) and personality traits (65) in women with VVS. On the other hand, Granot and Lavee (64) found 4 subgroups of VVS women on the basis of high/low anxiety and high/low pain perception, indicating that not all women with VVS have greater pain sensitivity and anxiety levels. What's more, women with VVS were more sensitive to noxious stimuli regardless of their personality traits (65).

Besides certain psychological factors, the role of self-efficacy and body image in the perception of pain was investigated in 2 studies (53,64). The VVS women demonstrated lower body image, lower sexual functioning, and lower sexual self-efficacy than controls associated with higher pain perception at vulvar and peripheral sites.

Twiss et al (73) examined the acoustic startle responses, which is mediated by output from the amygdala complex, to investigate the responsiveness of affective circuits during visceral related threat. The women with interstitial cystitis/painful bladder syndrome showed significantly greater startle magnitudes than controls during non-imminent threat conditions, indicating increased activation of a defensive emotional circuit and so hypersensitivity to visceral stimuli.

As mentioned in the first part of the results section of this review, the brain imaging studies also point to the importance of cognitive emotional sensitization with changes in morphology and activity of brain regions involved in pain modulation, cognition, stress, and emotions (17,46-50).

Although there are changes in psychosocial functioning of women with urogynecological CPP (very low level of evidence), the literature for the association of them with pain perception is too limited and inconclusive.

Autonomic Dysregulation

One study with moderate risk of bias showed that VVS cases had higher heart rates and lower systolic blood pressures in the resting state compared to pain-free controls. Following capsaicin injection, systolic blood pressure and mean arterial blood pressure in VVS patients increased more rapidly compared to controls (71). This autonomic hyperactivity was confirmed by another study with moderate risk of bias, which showed higher increase in systolic pressure during heat pain stimuli in the same patient group (66).

Autonomic dysregulation has been shown in 2 studies in women with urogynecological CPP (very low level of evidence).

Menstrual Phase Variations

There are 4 studies with moderate (69) to high risk of bias (50,61,67) regarding the influence of the

menstrual phase on pain perception in dysmenorrheic women. Studies reported inconsistent results for the pain sensitivity in menstrual pain referral or control sites with different types of stimulation, including pressure, pinch, heat, laser, or electrical. Although Bajaj et al (61) reported higher sensitivity in the menstrual phase, no menstrual cycle effect was observed in the other 2 studies for the heat stimulation (50,67). Lower sensitivity, not for tactile, but for pressure and pinch stimuli, was also demonstrated by Bajaj et al (61) during the menstrual phase. In response to laser stimuli, dysmenorrhea patients had the longest latency and the highest amplitude of pain-evoked potentials (that is higher pain sensitivity) during the follicular phase, whereas the shortest latency and the lowest amplitude were observed in the luteal phase (67). Another study examined the pain response to electrical stimuli at 3 stimulus depths (skin, subcutis, and muscle) and reported higher pain sensitivity during the periovulatory phase for skin and during the perimenstrual phases for muscle and subcutaneous tissue (69).

The available evidence regarding the effect of menstrual cycle phase on pain perception in women with urogynecological CPP is limited and inconclusive.

Discussion

The present study systematically reviewed scientific literature addressing central hypersensitivity in women with urogynecological CPP. The mechanisms contributing to pain amplification and chronicity in urogynecological CPP seems heterogeneous and likely to occur at various levels of the nervous system.

Voxel-based brain morphometry studies appear to agree with changes in regional brain morphology of women with urogynecological CPP, regardless of the direction of change (increases and decreases in gray matter density/volume) (17,46,47). Variability of the results between studies may be attributed to many factors such as the etiology of pain, pain duration, pain occurrence (intermittent vs. persistent), patient characteristics (age, personality traits), and pain medications (17,46,47). The stress on pain processing systems might be less in menstrual or provoked pain than in continuous pain and this might affect the direction of gray matter changes (47). In addition, gray matter changes may be dynamic and may change over time within an individual. The initial increase in gray matter as an acute adaptive mechanism may be followed by a decrease in gray matter depending on the duration and persistence of the nociceptive input (17). Thus, longitudinal studies are required to evaluate possible bi-directional changes of gray matter in the progression of urogynecological CPP.

Besides change in brain morphology, studies also report alteration in brain function in patients suffering from urogynecological CPP. Hypersensitivity associated with urogynecological CPP is reflected in increased activation (48-50) or no deactivation (50) in pain related brain regions. In dysmenorrhea patients, absence of significant deactivations of certain pain related brain regions in response to noxious stimulus in the menstrual phase can be attributed to dysmenorrhea-pain associated maximally deactivated brain regions where deactivation would usually occur during pain experience (74), so further deactivation in response to a noxious heat stimulus is not observed. Alternatively, alterations in resting state activity may be present in women with dysmenorrhea (50). One study also reported regional cerebral hypometabolism in somatic sensorimotor regions as well as hypermetabolism in thalamo-orbitofrontal-prefrontal regions during cramping menstrual pain (49). This hypometabolism may display a compensatory inhibitory mechanism in response to excitatory input and the generalized hyperalgesia in primary dysmenorrhea (67,69). Although existing evidence suggests increased activation in pain-related brain regions in women with urogynecological CPP, further investigation of other observations (lack of deactivation, hypometabolism) in certain brain regions requires further study specifically adressing activity in these regions.

In most of the included studies, different methods were used to establish primary and secondary hyperalgesia. Reflex hypersensitivity at outside of the area of pain in response to repeated electrical stimulation indicates generalized facilitated temporal summation in patients with menstrual pain (18). Enhanced post-capsaicin and post-saline pain responses extending far beyond the anatomic location of the primary complaint may also reflect an expanded field of neural hypersensitivity consistent with the presence of CS in VVS and endometriosis (52,71). Nevertheless, reversibility of generalized hyperalgesia is suggested, given the normalization after surgical removal of peripheral nociceptive sources (70). Therefore, further research is warranted to assess whether the presence of clinical pain and tissue damage is the crucial factor in the manifestation of CS.

One study also reported cutaneous hyposensitivity at the pain referral area in patients with painful blad-

der syndrome (55). This hyposensitivity is thought to reflect either activity of the diffuse noxious inhibitory control system (75) and/or adaptation (69), in which additional stimuli are perceived as relatively mild because they occur against a background of chronic pain (55). Findings of impaired habituation to non-noxious stimuli in local and remote dermatomes in the same patient group may also underlie increased awareness of visceral events and may facilitate chronic pain (55).

In general, findings for the presence of generalized hyperalgesia are inconclusive because of the differences in the nature of these pain syndromes or differences in the methodology of studies. Available evidence seems to suggest generalized hyperalgesia in response to pressure and electrical stimuli and injection of capsaicin and hypertonic saline, but the response to other stimuli such as tactile, vibratory, thermal, ischemic, and distention, definitely deserves further attention.

Neurophysiological studies also proved overactivity of bottom-up mechanisms. Reduced adaptation metrics may indicate increased hyperexcitability in longstanding vulvodynia (56). The generalized hyperexcitability is reported to be associated with an increased number of responsive spinal neurons or with an expansion of the receptive fields of the spinal neurons (18). In patients with vaginismus or VVS accompanied with vaginismus, concomitant CNS changes may be understood from abnormal and excessive functioning of pelvic floor muscles, reduced inhibition of cortical somatosensory evoked potentials, and hyperexcitable bulbocavernosus reflex (68). The increased latency of pain-evoked potentials by laser stimuli to the hand also confirm the systemic phenomenon rather than a regional change in the pelvis of dysmenorrheic women (67). The limited number of studies with a wide variation of assessment methods requires further neurophysiologic research to confirm these results.

The intact diffuse noxious inhibitory control in vulvodynia patients may be explained by provoked or intermittent pain (with pain-free intervals) of this patient group. It is possible that diffuse noxious inhibitory control dysfunction may play less of a role in chronic pain conditions in which the pain is recurrent (54,60). Zhang et al (56) also suggest that women with vulvar pain for a long duration or with unprovoked pain have more CNS involvement or dysregulation. Alternatively, an excess in descending facilitatory mechanisms may provide an explanation for the pain experienced in PVD (60).

Although an altered psychosocial and sexual profile in women with VVS (or PVD) and interstitial cystitis/painful bladder syndrome has been reported in several studies, only 2 studies demonstrated that augmented pain perception is associated with psychological factors (53) and personality traits (65). On the other hand, reported changes in brain morphology and function may be responsible not only for the development and/or maintenance of the chronic pain, but might also contribute to other common comorbid clinical features, such as mood disorders and cognitive impairment (17). Nonetheless, it is clear that more research is warranted to define the precise influence of psychological factors on the central pain processing.

It is reported that the menstrual phase, segmental site, dysmenorrhea status and depth, and modality of pain stimulation all have interacting effects on pain sensitivity (61,67,69). The inconsistent results of menstrual cycle effects may be partly due to the lack of confirmation of ovulation (61). Well-designed future studies are needed in order to more fully explain these interactions on central pain sensitivity.

The same goes for the precise mechanism of autonomic dysregulation and association between pain and blood pressure.

Women with VVS have been shown to have an elevated heart rate and reduced systolic pressure in the resting state (71) and higher increase in systolic blood pressure in response to experimental pain stimuli suggesting an autonomic dysregulation (66,71). In pain-free subjects, reduced blood pressure has also been shown to be associated with increased pain thresholds (76).

Given the inconclusive findings and the low levels of evidence in the present review, due to the observational study designs, definitely more research is warranted to draw conclusions regarding CS in CPP. In most of the studies, there is also a lack of information about particular factors (comorbid chronic pain syndromes, psychiatric conditions, use of analgesic medication before or during study period, menstrual cycle regularity, oral contraceptive use) known to be involved in pain processing. The variation in study results can be attributed to not only these factors, but also different diagnoses of CPP, using a variety of assessment methods, frequency of pain, pain duration, age, and personality characteristics of study participants. The design of included studies does not allow us to state whether altered brain morphology and function, generalized hypersensitivity, or impaired psychosocial functioning arise from the experience of CPP, or whether they predispose a patient to CPP. Without longitudinal studies,

it is not possible to know whether these alterations are a cause or an effect of pain. Based on these methodological issues, further study designs with a sufficient and justified sample size are needed.

The recognition of the possible involvement of CS has important implications for the development of specific therapies and better clinical management of urogynecological CPP. The traditional practice of focusing on peripheral pathology may not be adequate and needs to be analyzed carefully since several CNS dysfunctions are now indicated in women with urogynecological CPP. A multidisciplinary approach is needed to understand pain variability in this chronic pain syndrome, in which cognitive and emotional factors may play a role together with augmented pain sensitivity. But also, these hypotheses should be the subject of future studies.

Up to now, it seems that generalized hyperalgesia is present in response to pressure and electrical stimuli and bottom-up nociceptive mechanisms are overactive, given the enhanced reflex responses and temporal summation. Also, brain function and brain activation changes are revealed in CPP patients, but the direction and the localization deserves further attention.

On the other hand, evidence for impaired top-down mechanisms (pain inhibition or pain facilitation) is inconclusive. The limited evidence for diffuse noxious inhibitory control indicates intact function of this control, and also the role of psychological factors in pain facilitation is not clear and consistent.

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