Phenotyping sexual pain in endometriosis using the Central Sensitization Inventory

Orr, N. L., Wahl, K. J., Noga, H., Allaire, C., Williams, C., Bedaiwy, M. A., Albert, A., Smith, K. B., & Yong, P. J. (2020). Phenotyping sexual pain in endometriosis using the central sensitization inventory. *The Journal of Sexual Medicine*, 17(4), 761-770. doi:10.1016/j.jsxm.2019.12.019

Abstract

Background. Deep dyspareunia, a common symptom in endometriosis, has previously been associated with bladder or pelvic floor tenderness (BPFT), which suggests a role for central nervous system sensitization. The Central Sensitization Inventory (CSI, 0-100) is a validated self-reported scale for patients with central sensitization.

Aim. The objective of this study was to phenotype deep dyspareunia using BPFT and the CSI.

Methods. Cross-sectional analysis from a prospective registry from January 2018 – June 2018 at a tertiary centre for endometriosis (ClinicalTrials.gov #NCT02911090). Included were women aged 18-50 years with endometriosis (previously surgically diagnosed, current visualized endometrioma on ultrasound, or current palpable or visualized nodule on ultrasound), who were newly or re-referred to the centre. Severity of deep dyspareunia was self-reported using an 11-point numeric rating scale (0=no pain; 10=worst pain imaginable), categorized as no/low deep dyspareunia (0-4) and high deep dyspareunia (5-10). We identified the subgroup with high deep dyspareunia and presence of BPFT, where we hypothesized a central component of the sexual pain. This subgroup was compared to two other subgroups: no/low deep dyspareunia; and high deep dyspareunia but no BPFT. The CSI was compared between the groups using ANOVA, followed by post-hoc testing ($p < .05$).

Outcome. CSI score from 0-100.

Results. Data from 163 women with endometriosis were analyzed. The mean age of this cohort was 36.4±6.8 years and the mean CSI score was 41.0±18.6. Thirty-seven percent (61/163) had high deep dyspareunia and BPFT; 29% (47/163) had high deep dyspareunia and no BPFT; and 34% (55/163) had no/low deep dyspareunia. The CSI significantly differed between the three

groups (ANOVA F = 22.4, p < .001). In post-hoc testing, the CSI was higher in women with high deep dyspareunia and BPFT (51.3±16.9), compared to women with no/low deep dyspareunia (30.9±15.4, p < .001) and compared to women with high deep dyspareunia but no BPFT (39.4±17.2, p = .001).

Clinical Implications. The Central Sensitization Inventory could be used to classify and phenotype patients with endometriosis-associated sexual pain.

Strengths & Limitations. Strengths include a prospective registry with integrated pain scores, validated questionnaires, and physical examination findings. Limitations include the lack of quantitative sensory testing for central sensitization.

Conclusions. In women with endometriosis, the subgroup with high deep dyspareunia and bladder/pelvic floor tenderness had a significantly higher score on the Central Sensitization Inventory compared to other subgroups, suggesting that this group may have a central component to their sexual pain.

Key Words. Endometriosis; Deep dyspareunia; Central sensitization; Central Sensitization Inventory; Bladder/pelvic floor tenderness; Painful bladder syndrome.

Introduction

Endometriosis affects 1 in 10 reproductive-aged females and is the presence of uterine endometrial cells at extra-uterine sites such as the pelvic peritoneum and/or organs [1-5]. Various pain symptoms are associated with endometriosis, including dysmenorrhea, chronic pelvic pain, dyschezia, and dyspareunia [6]. Deep dyspareunia is pelvic pain with deep vaginal penetration during sexual intercourse and affects approximately 50% of women with endometriosis leading to a reduced quality-of-life and relationship strain [7, 8]. Endometriosis-associated deep dyspareunia is multifactorial, and therefore in some cases standard surgical or medical therapy may not be successful in treating deep dyspareunia [8-10].

Recently, the origins of deep dyspareunia in endometriosis have been reviewed [10], and include the endometriosis lesions themselves, co-morbid conditions such as painful bladder syndrome or myofascial pelvic pain syndrome, and underlying central nervous system sensitization. Endometriosis-associated deep dyspareunia can be directly due to endometriosis-specific factors such as deep infiltrating endometriosis of the pouch of Douglas or local neurogenesis around endometriosis of the pouch of Douglas. In these circumstances, the affected pouch of Douglas is hit with deep penetration, leading to deep dyspareunia. Deep dyspareunia can also arise from a tender bladder or pelvic floor, even when endometriosis lesions are not present on these structures [11]. We have observed the association between bladder/pelvic floor tenderness and greater severity of deep dyspareunia in both women with anatomically minimal-mild disease (Stage I-II endometriosis) and women with anatomically moderate-severe disease (Stage III-IV endometriosis) [7]. It has been hypothesized that central sensitization of the nervous system, consisting of central amplification of nociceptive pathways, is one cause of bladder/pelvic floor tenderness and therefore deep dyspareunia among some women with endometriosis [10, 12, 13].

It is the subgroup of women with central origins of sexual pain who may not benefit from conventional hormonal or surgical treatment of endometriosis [14].

In central sensitization, peripheral nociceptive signaling (e.g. from endometriosis lesions) can lead to adaptive changes in neurons of the central nervous system, including presynaptic effects (e.g., changes in neurotransmitter release) and postsynaptic effects (e.g., increase in NMDA channels promoting influx of calcium) [15]. This leads to a reduced threshold for central neuronal activation, and therefore pain hypersensitivity and symptoms of allodynia and hyperalgesia [16]. In addition to pain, co-occurring symptoms of central sensitization include fatigue, sensory sensitivity, and depression [17]. Central sensitization is also characterized by expansion of receptive fields, resulting in pain symptoms beyond the original site of pathology [18]. In some women with endometriosis, allodynia, hyperalgesia, psychological comorbidities, and expansion of receptive fields have been demonstrated [19-21]. Neuroimaging studies have identified changes in gray matter volume in those with endometriosis and pelvic pain, further supporting a central component of endometriosis-associated pain in some individuals [22].

The Central Sensitization Inventory (CSI) is a self-reported validated questionnaire that assesses the severity of symptoms characteristic of central sensitization. The CSI has been used to identify patients with central sensitivity syndromes (e.g., fibromyalgia, irritable bowel syndrome, migraines) that are characterized by underlying central sensitization.

In this study, women with endometriosis were phenotyped into subgroups with respect to deep dyspareunia and bladder/pelvic floor tenderness. We identified the subgroup with high levels of deep dyspareunia and the presence of bladder/pelvic floor tenderness, where a central component of the pain is hypothesized. We hypothesized that the CSI would be significantly higher in this

subgroup, compared to the two other subgroups in the sample: those women with no/low deep dyspareunia and those with high levels of deep dyspareunia but no bladder/pelvic floor tenderness.

Materials and Methods

Participants

This study involved a cross-sectional analysis of data from a prospective data registry, the Endometriosis Pelvic Pain Interdisciplinary Cohort (EPPIC, ClinicalTrials.gov #NCT02911090) [23], at a tertiary referral center for pelvic pain and endometriosis. All patients referred or re-referred to the center are approached for inclusion into the registry before their first appointment, of which approximately 87% of patients prospectively consent. Before the first appointment, the participants complete online self-reported baseline questionnaires at home, including pain scores, medical history, demographics, and validated psychological instruments such as the Patient Health Questionnaire-9 (PHQ-9) [24] for depression, Generalized Anxiety Disorder-7 (GAD-7) [25] for anxiety, and the Pain Catastrophizing Scale (PCS) [26]. We began incorporating the Central Sensitization Inventory into the registry baseline questionnaires in January 2018. Then, at the first appointment, the physicians prospectively enter other elements from history, as well as physical exam and ultrasound variables, into the online registry.

From the registry, participants were included in this study if they were 1) 18-50 years; 2) newly or re-referred to the centre between January 1, 2018 and June 30, 2018; 3) diagnosed with endometriosis through a previous surgical diagnosis, current endometrioma on ultrasound, or current deep infiltrating nodule on palpation or ultrasound; 4) Underwent pelvic examination

with digital palpation of the bladder and levator ani for bladder/pelvic floor tenderness; and 5) prospectively consented to EPPIC. Patients were excluded if they were 1) post-menopausal (spontaneous or surgical); 2) never sexually active; 3) missing dyspareunia severity scores; 4) missing pre-operative pelvic exam (e.g., due to severe vaginismus); or 5) missing Central Sensitization Inventory scores (see flow chart in Figure 1). To avoid bias, all consecutive patients meeting the above criteria were included in the study. Eligibility criteria are listed in Table 1.

Based on the inclusion criteria, several types of endometriosis patients were eligible: a) those with previous surgical diagnosis, where the disease could be Stage I, II, III, or IV; b) those with current endometrioma on ultrasound (without previous surgery), in which case Stage is unknown but would be expected to be primarily Stage III-IV; and those with current nodule on palpation or ultrasound (without previous surgery), in which case Stage is unknown but would also be expected to be primarily Stage III-IV. We did not include patients with clinically suspected superficial endometriosis (without previous surgery), due to the limited sensitivity and specificity in clinical diagnosis of this type of endometriosis [27].

Figure 1. Study population flowchart.

[see attached]

Measures

Severity of deep dyspareunia was measured on a self-reported questionnaire at baseline using an 11-point numeric rating scale (0=no pain; 10=worst pain imaginable), and categorized as no/low deep dyspareunia (0-4) and high deep dyspareunia (5-10).

Bladder or pelvic floor tenderness (BPFT) was obtained from the baseline gynecologist assessment, through a unidigital pelvic examination with palpation of the anterior vaginal wall and the levator ani bilaterally at 3 o'clock and 9 o'clock. The presence of at least one tender site was coded as BPFT present (vs. absent).

The Central Sensitization Inventory (CSI) questionnaire was also completed by subjects at baseline (scale from 0-100), which quantifies severity of downstream symptoms associated with central sensitization. Developed by Mayer et al. in 2011, the CSI item pool was created based on literature regarding the downstream symptoms reported by patients with known central sensitivity syndromes (including both somatic and psychological symptomatology). The CSI assesses 25 symptoms, such as feeling tired/unrefreshed in the morning, muscles being stiff and achy, sensitivity to bright lights, pain all over the body, poor sleep, stress making symptoms worse, and difficulty remembering things, with each symptom rated as never, rarely, sometimes, often, or always (0-4). The CSI underwent psychometric validation in a population of chronic pain patients [28]. A comparison of CSI scores between four groups with presumably different levels of central sensitization related symptoms (i.e. fibromyalgia, chronic widespread pain without fibromyalgia, work-related regional chronic low back pain, and healthy controls) confirmed that the group with fibromyalgia had the highest CSI scores and the controls had the lowest scores [28]. As well, the CSI questionnaire has been found to have good [28, 29] and

153 excellent [30, 31] internal consistency. Previous studies have also found that CSI scores were
154 positively correlated with the number of diagnosed central sensitivity syndromes [32, 33], and
155 that the CSI can discriminate between persons with chronic pain and non-pain controls [28, 32].
156 This questionnaire has also shown good sensitivity, construct validity, and test-retest reliability
157 in chronic pain patients [28-32, 34, 35]. A CSI cut-off of ≥ 40 has been shown to distinguish
158 patients with central sensitivity syndromes from controls [32, 34, 36]. Therefore, the CSI is a
159 promising tool for the identification of endometriosis patients with a central component of sexual
160 pain.

161 *Phenotyping*

162 The sample was phenotyped into three subgroups (Table 2). The first subgroup was those
163 women with high deep dyspareunia and the presence of BPFT, who were hypothesized to have a
164 central component of their sexual pain. The second subgroup was those women with high deep
165 dyspareunia but no BPFT, where the sexual pain may be due to other factors including specific
166 to the endometriosis lesions themselves. The third subgroup was those women with no/low deep
167 dyspareunia.

168

Statistical analysis

Analysis of variance (ANOVA) was used to compare mean CSI scores between subgroups, followed by post hoc Tukey's test to examine differences between individual subgroups. In a corollary analysis, we calculated the proportion of cases in each subgroup with a CSI score above the cut-off of 40 (Chi-square test). In addition, in a previous study, we identified an association between depression and BPFT [11]. Therefore, we performed another corollary analysis where the sample was divided into those with no/low deep dyspareunia; those with high deep dyspareunia and no/mild depression symptoms (PHQ-9 < 10); and those with high deep dyspareunia and moderate-to-severe depression symptoms (PHQ-9 (≥ 10).

Statistical significance was $p < .05$. Missing values were excluded. IBM SPSS Statistics 24 was used for the analysis. This was an exploratory analysis of consecutive patients from the first 6 months of incorporating the CSI into the registry, and thus there was no a priori power analysis.

Results

Study Sample

A total of 163 women with endometriosis met the study criteria (Figure 1) and reported a mean CSI score of 41.0±18.6. In the sample, 55 (33.7%) women had no/low deep dyspareunia (0-4 on a 11-point numeric rating scale), and 108 (66.3%) had high deep dyspareunia (5-10 on a numeric rating scale). Additionally, 73 (44.8%) of the sample had bladder and/or pelvic floor tenderness (BPFT), while 90 (55.2%) did not have BPFT. Sample characteristics are shown in Table 3.

The CSI was significantly higher amongst women with high deep dyspareunia compared to women with no/low deep dyspareunia (46.1±18.0 vs. 30.9±15.4, t = -5.4, p < .001). The CSI was also significantly higher amongst women with BPFT compared to women without BPFT (47.9±18.4 vs. 35.4±16.7, t = -4.6, p < .001).

CSI scores amongst subgroups

For the sample phenotyping (Table 2), 61 subjects (37.4%) had high deep dyspareunia and BPFT, 47 subjects (28.8%) had high deep dyspareunia but no BPFT, and 55 subjects (33.7%) had no/low deep dyspareunia (43 without BPFT and 12 with BPFT).

There was a significant difference in mean CSI between the three subgroups (ANOVA F= 22.4, p<.001) (Figure 2). On post-hoc testing, women with high deep dyspareunia and BPFT had a significantly higher CSI score (51.3±16.9) compared to women with high deep dyspareunia and no BPFT (39.4±17.2; Tukey p =.001) and compared to women with low deep dyspareunia (30.9±15.4; Tukey p <.001). Women with high deep dyspareunia and no BPFT also had a significantly higher CSI score compared to women with no/low deep dyspareunia (Tukey p=.028).

In a sensitivity analysis, there was no difference in CSI scores in those with no/low deep dyspareunia, comparing those with or without BPFT (see Supplementary Figure 1).

208 **Figure 2**. CSI scores by subgroup.

209 [see attached]

210 Error bars indicate ±1 standard deviation. All post-hoc pair-wise comparisons statistically

211 significant (Tukey test, $p < 0.05$).

212

213

214 *Corollary analyses*

215 In the corollary analysis, we determined the proportion of individuals in each subgroup with a
216 CSI score above a previously published cut-off (≥ 40) (Figure 3). Seventy-four percent (45/61)
217 of the subgroup with high deep dyspareunia and BPFT had a CSI score above the cut-off,
218 compared to 53% (25/47) of the subgroup with high deep dyspareunia and no bladder/pelvic
219 floor tenderness and 27% (15/55) of the subgroup with low deep dyspareunia (Chi-square=25.1,
220 $p < .001$) (Figure 3).

221

Figure 3. Subgroups with the number of people above and below the CSI cut-off.

[see attached]

Error bars indicate 95% confidence intervals.

In another corollary analysis, we stratified the sample based on the depression symptom questionnaire (PHQ-9). As shown in Supplementary Figure 2, participants with high deep dyspareunia and moderate-to-severe depression (PHQ-9 ≥ 10) had significantly higher CSI scores, compared to those with high deep dyspareunia and no/mild depression (PHQ-9 < 10) and those with no/low deep dyspareunia.

Discussion

In this study, we phenotyped women with endometriosis-associated deep dyspareunia into three subgroups. We identified a subgroup with high levels of deep dyspareunia and bladder/pelvic floor tenderness, which we hypothesize would include women with a central nervous system sensitization component to their sexual pain. We also identified a subgroup with high levels of deep dyspareunia but no bladder/pelvic floor tenderness, in which sexual pain may have other causes (e.g., the endometriosis lesions themselves), as well as a subgroup with no/low deep dyspareunia. We found that the Central Sensitization Inventory (CSI) scores were significantly higher in the first subgroup, suggesting that this group may represent women with sexual pain related to central sensitization. However, it is important to note that these results should be interpreted with caution since the CSI has not yet been validated in the endometriosis population, and additional work is needed before the CSI can be implemented as a clinical tool in this population.

We recently proposed a framework for the pathophysiology, classification, and management of deep dyspareunia in endometriosis [10]. In this framework, we propose that a subgroup of women likely have deep dyspareunia related to tenderness or the bladder/pelvic floor (that may

be contacted with deep penetration), which in turn could be due to amplification of central nervous system pathways. Our finding of increased CSI in this subgroup supports our proposed framework. However, it should be noted that some patients may have bladder/pelvic floor tenderness related primarily to myofascial origin rather than central origin; the inclusion of these subjects in the current study would be expected to dilute the association we observed between CSI scores and this subgroup, yet it was still statistically significant.

We also found the subgroup of women with high deep dyspareunia and no bladder/pelvic floor tenderness had higher CSI scores compared to the subgroup with no or low levels of deep dyspareunia, but lower CSI scores compared to the subgroup with high deep dyspareunia and bladder/pelvic floor tenderness. One explanation for the finding of some patients with elevated CSI scores in this subgroup may be that there are some patients with high deep dyspareunia and no bladder/pelvic floor tenderness who have central sensitivity that manifests as other tender anatomic sites rather than the bladder and pelvic floor. For example, we have found that tenderness of the uterus-cervix is associated with deep dyspareunia [11]. Alternatively, some patients in this subgroup could include those where deep dyspareunia may be directly related to the pelvic endometriosis lesions themselves, who would not be expected to have elevated CSI scores, since their dyspareunia is of peripheral origin. This subgroup may also include those with deep dyspareunia due to other causes separate to central sensitization, such as hypoestrogenism, fibroids/adenomyosis, and pelvic congestion syndrome.

Also of interest are those patients with no/low deep dyspareunia but with bladder/pelvic floor tenderness, who had similar CSI scores to those with no/low deep dyspareunia and no bladder/pelvic floor tenderness. There are several possible explanations. First, all physical exam maneuvers will have a certain false-negative and false-positive rate; therefore, tenderness on

palpation of the bladder/pelvic floor may be a "false-positive" finding in a few cases. Alternatively, some of these patients may actually have deep dyspareunia, but rate their pain lower, perhaps if this pain is not their main concern (e.g. their primary complaint may be severe chronic pelvic pain). As well, physical examination in the clinic does not always correlate to the sexual context; it is possible that a patient may have bladder/pelvic floor tenderness in the clinic, but with their sexual partner there may be appropriate arousal (emotional as well as physiological) that alleviates pain or the couple may employ self management techniques to avoid pain (such as position changes).

In a corollary analysis, we observed that individuals with high deep dyspareunia and moderate-to-severe depression also reported significantly higher CSI scores. We previously found that higher depressive symptoms were significantly associated with bladder/pelvic floor tenderness and greater severity of deep dyspareunia [11], and that depression predicted persistent deep dyspareunia after one year in the same population [36]. It is possible that depression may play a role in the pathophysiology of bladder/pelvic floor tenderness. In a neuroimaging study, it was determined that in an induced depressed mood there is an increased activity in some prefrontal areas responsible for emotional regulation, as well as increased pain unpleasantness [37]. Moreover, another study observed a significant decrease in cold pain threshold and increased wind-up, both characteristic of central sensitization, in people with depressive disorder [38]. Thus, the central sensitization observed in depression could further amplify pain, leading to a tender bladder/pelvic floor that is hit during deep penetration and results in deep dyspareunia.

Phenotyping of endometriosis-associated sexual pain is important, because it may promote individualized management for women seeking treatment. In particular, women with high levels of deep dyspareunia and bladder/pelvic floor tenderness (with increased CSI scores) may require

304 management beyond or instead of conventional hormonal suppression or surgical removal of
305 endometriosis lesions. For example, these women may benefit from a multidisciplinary
306 treatment plan including physiotherapy and cognitive approaches. This theory was borne out in
307 a recent study on women with pelvic pain primarily due to endometriosis, which showed that a
308 cohort of patients who received multidisciplinary care had improved deep dyspareunia and
309 sexual quality-of-life after one year of treatment [39]. Given the association between depression
310 and bladder/pelvic floor tenderness in this study and previous work, assessment and management
311 of depression are a particularly important component of multidisciplinary care for deep
312 dyspareunia. Our results align with earlier research showing that, among women attending a
313 gynecology outpatient clinic, patients with pelvic or vaginal pain had a higher CSI score,
314 although only two patients in the sample had endometriosis [33]. Evidence for the utility of the
315 CSI in identifying central sensitivity syndromes is recognized in the chronic pain literature in
316 which research participants with chronic or recurrent pain have reported significantly higher CSI
317 scores compared to healthy controls [30, 40]. Additionally, in a sample of patients with a chronic
318 occupational musculoskeletal disorder, a CSI≥40 was significantly associated with having one or
319 more central sensitivity syndromes [41], and a study by Neblett et al. found that the CSI score in
320 their sample of patients with chronic pain increased with each additional central sensitivity
321 diagnosis [35]. Therefore, the CSI may have promise to discriminate between sensitized and
322 non-sensitized women with endometriosis in a practical way in the clinical setting, although this
323 requires future research to validate this concept.

324 Importantly, there are some differences and similarities between the endometriosis population
325 and other chronic pain populations. For example, endometriosis lesions are a histological
326 disease often localized to the pelvis that require surgical and pathological diagnosis, while other

chronic pain conditions like fibromyalgia are primarily central in pathophysiology and are diagnosed clinically in the absence of a characteristic peripheral pathological diagnosis. In endometriosis, central sensitization can be initiated and perpetuated by peripheral nociceptive signalling, related to the local inflammation and invasion of the endometriosis lesions in the pelvis, which drives central amplification [17]. For this reason, surgery is a common treatment for endometriosis, whereby removal of the lesions (i.e. peripheral noxious input) may partially or fully resolve the central sensitization, which is seen clinically in some cases of endometriosis-associated pain. In contrast, there is no surgical treatment to remove a peripheral stimulus for conditions like fibromyalgia. Endometriosis does have similarity to fibromyalgia and other chronic pain conditions, in that some women with endometriosis progress from localized symptoms to systemic pain and other symptoms of central sensitization. As well, neuroimaging in patients with endometriosis and pelvic pain, as well as other chronic pain conditions, have identified similar decreases in gray matter volume in regions of pain processing [22, 42]. Similarly, quantitative sensory testing in women with endometriosis-associated chronic pelvic pain show similar findings (e.g. lowered pain-pressure thresholds systemically) compared to women with chronic pain conditions [21]. Due to these similarities and differences, measures of central sensitization would likely be expected to be more variable and heterogeneous in endometriosis, compared to other chronic pain conditions, as endometriosis-associated pain may be mostly peripheral in one patient, mostly central in another, and mixed in others.

Strengths of this study include the sample size and analysis of a prospective registry that included pain scores, physical examination data, and validated questionnaires such as the CSI. The main limitation is that the CSI measures downstream symptoms of central sensitization, and we did not perform quantitative sensory testing or functional MRI studies that are physiological

markers of central nervous system sensitization [21, 22, 43]. For example, Stratton et al. measured sensitization using neuro-musculoskeletal assessment of regional allodynia or regional hyperalgesia, which was more common in the group with pelvic pain [21]. Future research should include objective tests of central sensitization to correlate with our findings using the validated but self-reported CSI questionnaires. Generalizability of the results also needs to be investigated in different clinical settings involving endometriosis patients (e.g. in primary care or community settings). As well, psychometric testing of the CSI should be done in the endometriosis population, similar to studies done in chronic pain populations [28-32]. Furthermore, a limitation of this study was inferring the ≥ 40 cut-off from studies of the CSI in other populations; we are currently expanding the sample size so we can perform a receiver operating curve (ROC) analysis to identify a cut-off point for the CSI in the endometriosis population.

In summary, we propose that the CSI may be a practical tool for clinicians to assist in phenotyping women with endometriosis-associated sexual pain, and thus may help avoid unnecessary treatments and better personalize care. It is important to emphasize that the CSI alone is unlikely to discriminate between all the multifactorial components of sexual pain in endometriosis, such as local invasion of endometriosis lesions, primary myofascial causes, psychological factors, and problems with the sexual response cycle, which each require their own assessment on history, examination, and validated instruments. Ultimately, however, the CSI may be part of a toolkit to help clinicians determine which endometriosis patients may have sexual pain that responds to surgical or hormonal treatments, and which patients where these conventional treatments are unlikely to be effective and even potentially harmful.

References

[1] Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am 2012;39:535-49. Epub 2012/11/28. doi: 10.1016/j.ogc.2012.10.002. PubMed PMID: 23182559; PubMed Central PMCID: PMCPMC3538128.

[2] Gupta S, Harlev A, Agarwal A. Endometriosis: a comprehensive update: Springer; 2015.

[3] Vercellini P, Somigliana E, Buggio L, Barbara G, Frattaruolo MP, Fedele L. "I Can't Get No Satisfaction": deep dyspareunia and sexual functioning in women with rectovaginal endometriosis. Fertil Steril 2012;98:1503-11. e1.

[4] Olive DL, Pritts EA. Treatment of endometriosis. N Engl J Med 2001;345:266-75.

[5] Johnston JL, Reid H, Hunter D. Diagnosing endometriosis in primary care: clinical update. Br J Gen Pract 2015;65:101-2. Epub 2015/01/28. doi: 10.3399/bjgp15X683665. PubMed PMID: 25624305; PubMed Central PMCID: PMCPMC4325443.

[6] Howard FM. Endometriosis and mechanisms of pelvic pain. J Minim Invasive Gynecol 2009;16:540-50. doi: 10.1016/j.jmig.2009.06.017. PubMed PMID: 19835795.

[7] Orr NL, Noga H, Williams C, Allaire C, Bedaiwy MA, Lisonkova S, Smith KB, Yong PJ. Deep Dyspareunia in Endometriosis: Role of the Bladder and Pelvic Floor. J Sex Med 2018;15:1158-66.

[8] Ferrero S, Esposito F, Abbamonte LH, Anserini P, Remorgida V, Ragni N. Quality of sex life in women with endometriosis and deep dyspareunia. Fertil Steril 2005;83:573-9. doi: 10.1016/j.fertnstert.2004.07.973. PubMed PMID: 15749483.

[9] Williams C, Hoang L, Yosef A, Alotaibi F, Allaire C, Brotto L, Fraser IS, Bedaiwy MA, Ng TL, Lee AF, Yong PJ. Nerve Bundles and Deep Dyspareunia in Endometriosis. Reprod Sci 2016;23:892-901. doi: 10.1177/1933719115623644. PubMed PMID: 26711313.

[10] Yong PJ. Deep Dyspareunia in Endometriosis: A Proposed Framework Based on Pain Mechanisms and Genito-Pelvic Pain Penetration Disorder. Sex Med Rev 2017. doi: 10.1016/j.sxmr.2017.06.005. PubMed PMID: 28778699.

[11] Yong PJ, Williams C, Yosef A, Wong F, Bedaiwy MA, Lisonkova S, Allaire C. Anatomic sites and associated clinical factors for deep dyspareunia. Sex Med 2017. doi: 10.1016/j.esxm.2017.07.001. PubMed PMID: 28778678.

[12] Brawn J, Morotti M, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. Hum Reprod Update 2014;20:737-47.

[13] Malykhina A. Neural mechanisms of pelvic organ cross-sensitization. Neurosci 2007;149:660-72.

[14] McAllister SL, Dmitrieva N, Berkley KJ. Sprouted innervation into uterine transplants contributes to the development of hyperalgesia in a rat model of endometriosis. PloS one 2012;7:e31758.

[15] Arendt-Nielsen L. Central sensitization in humans: assessment and pharmacology. Pain Control: Springer; 2015. p. 79-102.

[16] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10:895-926. Epub 2009/08/29. doi: 10.1016/j.jpain.2009.06.012. PubMed PMID: 19712899; PubMed Central PMCID: PMCPMC2750819.

[17] Harte SE, Harris RE, Clauw DJ. The neurobiology of central sensitization. Journal of Applied Biobehavioral Research 2018;23:e12137.

[18] Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686.

[19] Bajaj P, Bajaj P, Madsen H, Arendt-Nielsen L. Endometriosis is associated with central sensitization: a psychophysical controlled study. The Journal of Pain 2003;4:372-80.

[20] Neziri AY, Haesler S, Petersen-Felix S, Müller M, Arendt-Nielsen L, Manresa JB, Andersen OK, Curatolo M. Generalized expansion of nociceptive reflex receptive fields in chronic pain patients. PAIN® 2010;151:798-805.

[21] Stratton P, Khachikyan I, Sinaii N, Ortiz R, Shah J. Association of chronic pelvic pain and endometriosis with signs of sensitization and myofascial pain. Obstet Gynecol 2015;125:719-28. Epub 2015/03/03. doi: 10.1097/aog.0000000000000663. PubMed PMID: 25730237; PubMed Central PMCID: PMCPMC4347996.
[22] As-Sanie S, Harris RE, Napadow V, Kim J, Neshewat G, Kairys A, Williams D, Clauw DJ, Schmidt-Wilcke T. Changes in regional gray matter volume in women with chronic pelvic pain: a voxel-based morphometry study. Pain 2012;153:1006-14. Epub 2012/03/06. doi: 10.1016/j.pain.2012.01.032. PubMed PMID: 22387096; PubMed Central PMCID: PMCPMC3613137.
[23] Yosef A, Allaire C, Williams C, Ahmed AG, Al-Hussaini T, Abdellah MS, Wong F, Lisonkova S, Yong PJ. Multifactorial contributors to the severity of chronic pelvic pain in women. Am J Obstet Gynaecol 2016;215:760. e1-. e14.
[24] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine 2001;16:606-13.
[25] Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine 2006;166:1092-7.
[26] Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess 1995;7:524.
[27] Yong PJ, Sutton C, Suen M, Williams C. Endovaginal ultrasound-assisted pain mapping in endometriosis and chronic pelvic pain. J Obstet Gynaecol 2013;33:715-9. doi: 10.3109/01443615.2013.821971. PubMed PMID: 24127962.
[28] Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, Perez Y, Gatchel RJ. The development and psychometric validation of the central sensitization inventory. Pain Pract 2012;12:276-85.
[29] Cuesta-Vargas AI, Roldan-Jimenez C, Neblett R, Gatchel RJ. Cross-cultural adaptation and validity of the Spanish central sensitization inventory. Springerplus 2016;5:1837. Epub 2016/11/08. doi: 10.1186/s40064-016-3515-4. PubMed PMID: 27818875; PubMed Central PMCID: PMCPMC5074937.
[30] Kregel J, Vuijk PJ, Descheemaeker F, Keizer D, van der Noord R, Nijs J, Cagnie B, Meeus M, van Wilgen P. The Dutch Central Sensitization Inventory (CSI): Factor Analysis, Discriminative Power, and Test-Retest Reliability. Clin J Pain 2016;32:624-30. Epub 2015/09/30. doi: 10.1097/ajp.0000000000000306. PubMed PMID: 26418360.
[31] Bid Dibyendunarayan D, Soni Neela C, Rathod Priyanshu V, Thangamani Ramalingam A. Content validity and test-retest reliability of the Gujarati version of the Central Sensitization Inventory. Natl J Integr Res Med 2016;7:18-24.
[32] Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, Gatchel RJ. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain 2013;14:438-45.
[33] Vij M, Davies A, Dua A, Freeman R. The proportion of women with central sensitivity syndrome in gynecology outpatient clinics (GOPDs). Int Urogynecol J 2018:1-6.
[34] Neblett R, Hartzell MM, Cohen H, Mayer TG, Williams M, Choi Y, Gatchel RJ. Ability of the central sensitization inventory to identify central sensitivity syndromes in an outpatient chronic pain sample. Clin J Pain 2015;31:323-32.
[35] Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RJ. Establishing clinically relevant severity levels for the central sensitization inventory. Pain Pract 2017;17:166-75.
[36] Pitance L, Piraux E, Lannoy B, Meeus M, Berquin A, Eeckhout C, Dethier V, Robertson J, Roussel N. Cross cultural adaptation, reliability and validity of the French version of the central sensitization inventory. Man Ther 2016;25:e83-e4.

[37] Berna C, Leknes S, Holmes EA, Edwards RR, Goodwin GM, Tracey I. Induction of depressed mood disrupts emotion regulation neurocircuitry and enhances pain unpleasantness. Biological psychiatry 2010;67:1083-90.
[38] Klauenberg S, Maier C, Assion H-J, Hoffmann A, Krumova EK, Magerl W, Scherens A, Treede R-D, Juckel G. Depression and changed pain perception: hints for a central disinhibition mechanism. Pain 2008;140:332-43.
[39] Yong PJ, Williams C, Bodmer-Roy S, Ezeigwe C, Zhu S, Arion K, Ambacher K, Yosef A, Wong F, Noga H, Britnell S, Yager H, Bedaiwy MA, Brotto LA, Albert AY, Lisonkova S, Allaire C. Prospective Cohort of Deep Dyspareunia in an Interdisciplinary Setting. J Sex Med 2018;15:1765-75. Epub 2018/11/18. doi: 10.1016/j.jsxm.2018.10.005. PubMed PMID: 30446474.
[40] Aguila M-ER, Rebbeck T, Leaver AM, Lagopoulos J, Brennan PC, Hübscher M, Refshauge KM. The association between clinical characteristics of migraine and brain GABA levels: an exploratory study. J Pain 2016;17:1058-67.
[41] Choi Y. An Examination of the Validity of the Central Sensitization Inventory with Chronic Disabling Occupational Musculoskeletal Disorders. 2014.
[42] Robinson ME, Craggs JG, Price DD, Perlstein WM, Staud R. Gray matter volumes of pain-related brain areas are decreased in fibromyalgia syndrome. The journal of pain 2011;12:436-43.
[43] As-Sanie S, Kim J, Schmidt-Wilcke T, Sundgren PC, Clauw DJ, Napadow V, Harris RE. Functional connectivity is associated with altered brain chemistry in women with endometriosis-associated chronic pelvic pain. J Pain 2016;17:1-13.

488 **Table 1.** Eligibility criteria.

Inclusion Criteria	**Exclusion Criteria**
18-50 years old	Post-menopausal (spontaneous or surgical)
Newly or re-referred to the Centre between January 1, 2018 and June 30, 2018	Never sexually active
Endometriosis (previous surgical diagnosis, current endometrioma on ultrasound, or current deep infiltrating nodule on palpation or ultrasound)	Missing dyspareunia severity scores
Underwent pelvic exam to assess bladder/pelvic floor tenderness	Missing Central Sensitization Inventory scores
Consented to EPPIC	Missing pre-operative pelvic exam (e.g., due to severe vaginismus)

489

490

Table 2. Sample phenotyping.

Subgroup (n)	Deep dyspareunia (/10)	Bladder/pelvic floor tenderness	Potential Explanation for presence of deep dyspareunia	Hypothesis
1 (n = 55)	No/Low (0-4)	- (/+)*	No/low sexual pain	CSI low
2 (n = 47)	High (5-10)	-	Sexual pain due to other factors (e.g. related to endometriosis lesions)	CSI low
3 (n = 61)	High (5-10)	+	Sexual pain may have a central component	CSI high

*n = 43 had no BPFT; n = 12 had BPFT

The sample was phenotyped into three subgroups, and the CSI compared between the groups.

Table 3. Sample characteristics.

	Sample (n=163)
Characteristic	**Mean ± SD or Percentage (frequency)**
Age, years	36.4±6.8
Ethnicity	
Caucasian	72.4% (118)
Other	27.6% (45)
Education	
High school (grades 9-12)	12.3% (20)
Community college or vocational school	13.5% (22)
College	50.9% (83)
Graduate school	23.3% (38)
BMI	
Underweight (<18.5)	3.7% (6)
Healthy (18.5-24.9)	50.3% (82)
Overweight (25-29.9)	26.4% (43)
Obese (≥30)	19.6% (32)
Partnered (married or common-law)	
Yes	68.1% (111)
No	31.9% (52)
Smoke	
Yes	9.8% (16)
No	90.2% (147)
Alcohol Use	
Yes	63.8% (104)
No	36.2% (59)
Recreational drugs	
Never used	54.6% (89)
In the past but not now	25.2% (41)
Currently using	14.1% (23)
Prefer not to answer	6.1% (10)
Depression (PHQ-9)	
Moderate/severe (≥10)	41.7% (68)
No/mild (<10)	58.3% (95)
Anxiety (GAD-7)	
Moderate/severe (≥10)	19.6% (32)
No/mild (<10)	80.4% (131)
Pain Catastrophizing (PCS)	
High (≥30 or 75th percentile)	29.4% (48)
Low (<30 or 75th percentile)	70.6% (115)