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Central sensitization in women with endometriosis: a cross-sectional study

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Abstract

Background Pain is the primary symptom of endometriosis and may progress into a chronic, acyclic condition driven by neuroinflammatory mechanisms, leading to neuropathic and ultimately nociplastic pain. Central sensitization, a form of nociplastic pain, is associated with various chronic pain syndromes collectively known as Central Sensitivity Syndromes, such as fibromyalgia and irritable bowel syndrome. These central mechanisms may contribute to treatment failure and symptom recurrence in endometriosis, significantly impacting quality of life. The Central Sensitization Inventory (CSI), initially validated in patients with fibromyalgia, has demonstrated utility in identifying central sensitization in those with endometriosis. The primary outcome of this study was to assess the prevalence of central sensitization in patients with a diagnosis of endometriosis/adenomyosis. The secondary objective was to evaluate the association between the patient's demographic and clinical characteristics and the diagnosis of central sensitization syndrome.

Methods This was a single-center, observational, cross-sectional study. Between February 1, 2023, and August 31, 2023, we prospectively enrolled 142 patients with a diagnosis of endometriosis/adenomyosis, as determined by surgery/ultrasound, who attended the "Endometriosis and Pelvic Pain" unit within the Obstetrics and Gynecology Clinic in Udine. Demographic and clinical data were collected. The prevalence of central sensitization was assessed using a validated questionnaire, the Central Sensitization Inventory. A CSI score ≥ 40 was considered as an indicator of Central Sensitization Syndrome.

Results The prevalence of CS was 52.1%. Among the clinical characteristics, only dyspareunia and vulvodynia were significantly associated with CS in our patients ($p < 0.001$), while other symptoms and even the type of endometriosis were not. However, a significant association was found with the onset of symptoms being more than 5 years, compared to earlier-onset forms ($p < 0.001$). A strong association was also found between positive CSI and overlap syndromes.

Conclusions Given the high prevalence of central sensitization based on the CSI among this tertiary-referral cohort, identifying it precociously might be useful for counseling patients and choosing a multimodal treatment in addition to conventional strategies. Further studies are needed to confirm these findings in broader and non-selected

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populations and to validate the applicability of the CSI questionnaire as a screening tool for central sensitization in common practice.

Keywords Central sensitization, Endometriosis, Nociplastic pain, Chronic pain, Central sensitization inventory

Background

The primary symptom in patients with endometriosis is pain, ranging from menstrual pain to dyspareunia and dyschezia [1, 2]. Endometriosis is identified in 40–87% of women with chronic pelvic pain (CPP), making it the most frequently identified underlying cause of this condition [3, 4].

The progression and chronicization of pain symptomatology is explained by a neuroinflammatory process, which underlies the development of neuropathic pain and, ultimately, nociplastic pain [5]. Neuropathic pain may also arise from direct nerve infiltration or compression by endometriotic lesions, particularly in cases of deep infiltrating endometriosis [6].

The term "nociplastic pain" was proposed to describe a pain phenotype sustaining chronic pain conditions that are not characterized by evident ongoing nociceptive input or peripheral neuropathy, in which central nervous system dysregulation has become the primary mechanism of pain. It can be defined as pain arising from altered functioning of pain-related sensory pathways, both peripherally and centrally, leading to a state of hyperactivity [5–9]. Importantly, the development of nociplastic pain does not exclude the presence of initial nociceptive or neuropathic triggers; rather, it reflects a shift toward central mechanisms becoming the predominant source of pain.

Central sensitization (CS) is one of the key mechanisms contributing to this shift that can occur in response to persistent nociceptive or neuropathic input and that may ultimately lead to a nociplastic pain phenotype when central amplification becomes the dominant driver of symptoms.

It can be characterized by allodynia, hyperalgesia, mood disorders, and sleep disorders [5, 10, 11].

CS is thought to underlie numerous chronic pain conditions named as Central Sensitivity Syndromes (CSS), a group of conditions characterized by chronic nociplastic pain such as irritable bowel syndrome (IBS), chronic fatigue syndrome, restless leg syndrome, fibromyalgia, temporomandibular joint disorder, migraine or tension headaches, multiple chemical sensitivities, and neck injury [12]. Central changes may be the reason for medical/surgical treatment failure or pain recurrence in patients with endometriosis and may account for the overlapping CSS that can coexist in these patients [10]. This leads to the conclusion that patients with endometriosis, especially those in the presence of CS, experience a significant reduction in quality of life and may require additional treatments beyond conventional endometriosis medical and surgical therapies [10, 13].

The Central Sensitization Inventory (CSI) is a patient-reported survey designed to identify patients' symptoms related to CS. It was initially validated in fibromyalgia patients [14] and subsequently also in patients with endometriosis [10].

A few studies have used the test on patients with endometriosis, consistently highlighting a high prevalence of CS among them [10, 11, 15], ranging between 45% and 55%. A cutoff ≥ 40 is considered the threshold of clinical relevance, and higher scores are associated with a higher degree of CS [16]. In a recent review [17], it was found to have good psychometric properties, and its use is encouraged in research and clinical settings.

The primary objective of this study was to assess the presence of CS in patients with endometriosis/adenomyosis using the CSI and to investigate its relationship with specific condition-related demographic and clinical parameters.

Methods

This study was a single-center, cross-sectional analysis conducted at a tertiary-level referral center for endometriosis: the *"Endometriosis and Pelvic Pain"* specialized unit within the Obstetrics and Gynecology Clinic in Udine. Between February 1, 2023, and August 31, 2023, consecutive patients referred to our clinic, either for an initial consultation or follow-up, were invited to participate in this study if they had a diagnosis of endometriosis and/or adenomyosis. Data were collected prospectively at the time of clinical evaluation, following a predefined protocol.

Participants were of reproductive age and had a confirmed history of endometriosis/adenomyosis, either surgically verified or based on current imaging findings. The diagnosis, whether through ultrasound or surgery, could have been established before or during the consultation visit [18].

The following inclusion criteria were considered: patients aged > 18 and < 50 years, patients who spoke Italian or English, patients with endometriosis and or adenomyosis with a surgical, ultrasound [18–23] or Magnetic Resonance Imaging (MRI) diagnosis.

The diagnosis of endometriosis was accepted if previously established by surgery or confirmed at the time of evaluation through transvaginal ultrasound or MRI. Deep infiltrating endometriosis, superficial endometriosis and ovarian endometriomas were diagnosed using

validated ultrasound criteria and following the International Deep Endometriosis Analysis (IDEA) group recommendations [18–21]. For women previously undergoing surgery, the diagnosis of endometriosis was based on visual inspection by the operating surgeon, consistent with ESHRE guidelines [1], while histological confirmation was utilized when present but was not mandatory for classification.

Adenomyosis was diagnosed through ultrasound using validated criteria [22, 23], including asymmetric myometrial thickening, myometrial cysts, hyperechoic islands, fan-shaped shadowing, and junctional zone abnormalities; MRI was used as a second-line instrument.

The following exclusion criteria were also considered: patients in spontaneous or medically induced menopause and patients with neurological conditions that could impair central nervous system function.

For all enrolled participants, demographic and clinical data were obtained through medical history, while experienced specialists conducted gynecological examinations and ultrasound evaluations.

The primary exposure variables included the type of endometriosis (superficial, ovarian, or deep). Outcome measures encompassed pain symptoms commonly associated with endometriosis, such as dysmenorrhea, dyspareunia (superficial and deep), vulvodynia, chronic pelvic pain, dyschezia, and dysuria. These were assessed using a numerical rating scale (NRS), where zero indicated no pain and ten represented the maximum pain severity [10, 24], as well as a quality-of-life scale [25]. Moderate to severe pain was considered when the NRS rate was above five (> 5), in line with commonly accepted categorizations used for the NRS and other comparable visual and self-reported pain scales [24, 26]. Chronic pelvic pain was defined as non-cyclical pain localized to the pelvis, lasting ≥ 6 months, and severe enough to cause functional limitation or require medical evaluation, in accordance with international guidelines definitions (ACOG) [27]. Additional covariates prospectively recorded at the time of enrollment included demographic factors (e.g., age, BMI, smoking status), previous surgical history, information on current hormonal therapy for endometriosis management (e.g., combined oral contraceptives, progestins, GnRH analogues), and the duration of symptom onset (time of onset > or < 5 years), defined as the time elapsed between the self-reported onset of symptoms and the date of study assessment.

Eligible patients were then invited to complete the CSI. CSI (Figs. 1 and 2) was designed to quantify the degree of Chronic Overlapping Pain Conditions (COPCs) related symptoms, to establish the level of CS impairment among patients suffering from chronic pain [28]. It consists of 2 parts: part A, where patients were asked about the presence and intensity of 25 CS-related symptoms using a 0 – 4 scale as follows: 0 (never), 1 (rarely), 2 (sometimes), 3 (often), 4 (always). Part B investigates whether the patient has previously been diagnosed with one or more specific conditions, including seven COPCs (tension headache or migraine), IBS, fibromyalgia, restless leg syndrome, temporomandibular joint disorder, chronic fatigue syndrome, and multiple chemical sensitivity) and three CS-related disorders (depression, anxiety or panic attacks, and neck injury). A CSI score ≥ 40 was considered an indicator of Central Sensitization Syndrome [10, 14].

We chose not to apply surgical staging systems such as the revised American Society for Reproductive Medicine (rASRM) classification, because it was not feasible for all participants, as not all underwent laparoscopic surgery. Moreover, it is widely recognized that all existing endometriosis classification systems, including rASRM and ENZIAN, show only a weak correlation with pain severity, likely due to the contribution of mechanisms such as central sensitization [29]. Instead, lesion type (superficial peritoneal endometriosis, ovarian endometrioma, or deep infiltrating endometriosis) was preferred, as it represents a more clinically relevant and uniformly applicable variable aligned with the objectives of our study.

The primary outcome of the study was the prevalence of central sensitization (CS) in patients with endometriosis. The secondary outcomes included the associations between demographic and clinical factors and CS, as well as the time of symptom onset.

To minimize potential sources of bias, consecutive sampling was used to reduce selection bias by enrolling all eligible patients presenting to our center within the study period. Standardized procedures were applied during clinical assessments and ultrasound evaluations, all of which were performed by experienced gynecologists, to minimize measurement and observer bias.

Differences in demographic and clinical characteristics between patients with and without CS were evaluated using the chi-square test, Fisher's exact test, or t-test, where appropriate. Those variables that exhibited a significant association with CS were then included in a multivariable logistic regression model and further selected using a backward stepwise procedure, with significance levels for removal and addition set at 0.05. Concerning power analysis, we tested the null hypothesis that the possibility of correctly identifying CS could improve from 40%, as assessed by Raimondo et al., to the clinically relevant alternative of 55% [11].

The sample size was calculated according to the study design by Simon, using an α-error of 0.05 and a β-error of 0.90 [30]. Considering a patient dropout of approximately 20%, the study was planned to enroll a total of 142 patients. All categorical variables were summarized as counts and percentages, whereas numerical variables were summarized as means and standard deviations. The

Please circle the best response to the right of each statement.

1.	I feel tired and unrefreshed when I wake from sleeping.	Never	Rarely	Sometimes	Often	Always
2.	My muscles feel stiff and achy.	Never	Rarely	Sometimes	Often	Always
3.	I have anxiety attacks.	Never	Rarely	Sometimes	Often	Always
4.	I grind or clench my teeth.	Never	Rarely	Sometimes	Often	Always
5.	I have problems with diarrhea and/or constipation.	Never	Rarely	Sometimes	Often	Always
6.	I need help in performing my daily activities.	Never	Rarely	Sometimes	Often	Always
7.	I am sensitive to bright lights.	Never	Rarely	Sometimes	Often	Always
8.	I get tired very easily when I am physically active.	Never	Rarely	Sometimes	Often	Always
9.	I feel pain all over my body.	Never	Rarely	Sometimes	Often	Always
10.	I have headaches.	Never	Rarely	Sometimes	Often	Always
11.	I feel discomfort in my bladder and/or burning when I urinate.	Never	Rarely	Sometimes	Often	Always
12.	I do not sleep well.	Never	Rarely	Sometimes	Often	Always
13.	I have difficulty concentrating.	Never	Rarely	Sometimes	Often	Always
14.	I have skin problems such as dryness, itchiness, or rashes.	Never	Rarely	Sometimes	Often	Always
15.	Stress makes my physical symptoms get worse.	Never	Rarely	Sometimes	Often	Always
16.	I feel sad or depressed.	Never	Rarely	Sometimes	Often	Always
17.	I have low energy.	Never	Rarely	Sometimes	Often	Always
18.	I have muscle tension in my neck and shoulders.	Never	Rarely	Sometimes	Often	Always
19.	I have pain in my jaw.	Never	Rarely	Sometimes	Often	Always
20.	Certain smells, such as perfumes, make me feel dizzy and nauseated.	Never	Rarely	Sometimes	Often	Always
21.	I have to urinate frequently.	Never	Rarely	Sometimes	Often	Always
22.	My legs feel uncomfortable and restless when I am trying to go to sleep at night.	Never	Rarely	Sometimes	Often	Always
23.	I have difficulty remembering things.	Never	Rarely	Sometimes	Often	Always
24.	I suffered trauma as a child.	Never	Rarely	Sometimes	Often	Always
25.	I have pain in my pelvic area.	Never	Rarely	Sometimes	Often	Always
					TOTAL:	

Fig. 1 CSI part A

significance level was set at 0.05. The NCSS statistical software program, version 11.0 (Kaysville, UT), was used.

Results

During the study period, 149 consecutive women were asked to complete the CSI. Seven patients were excluded from the study because they did not meet the selection criteria: five patients did not have a diagnosis of endometriosis or adenomyosis, and two patients had a neurologic disease (multiple sclerosis). As a result, a total of 142 patients were enrolled in the study.

Demographic factors and clinical features of the study population are shown in Tables 1 and 2, respectively.

In the analyzed population, the mean age was 36.98 years (± 8.86 SD) and the mean BMI was 23.32 (± 4.23). 12.6% of the population had infertility, 63.3% had previously undergone abdominal surgery. Regarding clinical characteristics, a prevalence of 39.4% for adenomyosis

Have you been diagnosed by a doctor with any of the following disorders?

Please check the box to the right for each diagnosis and write the year of the diagnosis.

	NO	YES	Year Diagnosed
1. Restless Leg Syndrome			
2. Chronic Fatigue Syndrome			
3. Fibromyalgia			
4. Temporomandibular Joint Disorder (TMJ)			
5. Migraine or tension headaches			
6. Irritable Bowel Syndrome			
7. Multiple Chemical Sensitivities			
8. Neck Injury (including whiplash)			
9. Anxiety or Panic Attacks			
10. Depression			

Fig. 2 CSI part B

Table 1 Demographic factors of the study population

Characteristics	All (*N* = 142)	Central Sensitization YES (*N* = 74)	Central Sensitization NO (*N* = 68)	*p*-value
Age, yrs, mean ± SD	36.98 ± 8.86	37.37 ± 8.37	36.41 ± 9.14	0.568
Body mass index category, mean ± SD	23.32 ± 4.23	23.47 ± 3.92	23 ± 4.44	0.236
Infertility N (%)	18 (12.6%)	11 (14.8%)	7 (10.2%)	0.477
Smoking N (%)	34 (23.9%)	24 (32.4%)	10 (14.7%)	**0.018**
Previous abdominal surgery N (%)	90 (63.3%)	62 (83.7%)	28 (41.1%)	0.187

Bold text: Statistically significant ($p < 0.05$)

and 72.3% for endometriosis was observed (25.3% with only deep endometriosis, 30.9% with only endometrioma, and 16.1% with both). Twenty-two patients (15.4%) had a concomitant diagnosis of endometriosis and adenomyosis. 14.7% of the population was affected by vulvodynia. The most frequently reported pain symptoms were dysmenorrhea (31.6%), chronic pelvic pain (19.7%), and dyspareunia (15.4%), followed by less frequent symptoms such as dyschezia (2.1%) and dysuria (0.7%). The majority of the population was already undergoing hormonal therapy: 19.7% were taking combined estrogen-progestin pills, 41.5% were using progestin-only pills, and 0.7% were using GnRH analogs. The prevalence of central sensitization, with a CSI score ≥ 40, was found in 74 out of 142 patients with endometriosis or adenomyosis, representing 52.1% (95% CI, 43.9–60.3). 16 out of 21 patients with vulvodynia (76.1% of patients with vulvodynia) tested positive on the CSI.

No significant difference was found between patients with and without CS in terms of age and BMI ($p = 0.568$, 0.236). Infertility and previous abdominal surgery were more frequent in patients with CS, although these differences did not reach statistical significance. Smoking was the only demographic variable significantly associated with CS ($p = 0.018$) (Table 1). Concerning the site of endometriotic lesions, deep lesions were more frequent

Table 2 Clinical features of enrolled patients: distribution of endometriosis phenotype, pain characteristics, time since symptom onset, and current hormonal treatment between women with and without CS

Patient characteristic	All (*N* = 142)	Central Sensitization YES (*N* = 74)	Central Sensitization NO (*N* = 68)	*p*-value
Adenomyosis N (%)	56 (39.4%)	32 (43.2%)	24 (35.2%)	0.319
Adenomyosis AND Endometriosis N (%)	22 (15.4%)	16 (21.6%)	6 (8.8%)	**0.035**
Endometriosis site				
DIE[a] alone N (%)	36 (25.3%)	21 (28.3%)	15 (22%)	0.685
Endometrioma alone N (%)	44 (30.9%)	18 (24.3%)	26 (38.2%)	0.055
DIE[a] plus endometrioma N (%)	23 (16.1%)	13 (17.5%)	10 (14.7%)	0.288
Moderate to severe pain symptoms (NRS[b] ≥5)				
Dysmenorrhea N (%)	45 (31.6%)	26 (35.1%)	19 (27.9%)	0.282
Dyspareunia N (%)	22 (15.4%)	19 (25.6%)	3 (4.4%)	**0.001**
Dyschezia N (%)	3 (2.1%)	1 (1.3%)	2 (2.9%)	0.511
Dysuria N (%)	1 (0.7%)	1 (1.3%)	0 (0%)	0.941
Chronic pelvic pain N (%)	28 (19.7%)	19 (25.6%)	9 (13.2%)	0.107
Time since symptom onset (years)				
< 5 years	58 (40.8%)	20 (27%)	38 (55.9%)	
> 5 years	84 (59.2%)	54 (73%)	30 (44.1%)	
Hormonal therapy				
COC[c] N (%)	28 (19.7%)	13 (17.5%)	15 (22%)	0.535
Progestin-only pill N (%)	59 (41.5%)	31 (41.8%)	28 (41.1%)	0.409
GnRH analogs N (%)	1 (0.7%)	1 (1.3%)	0 (0%)	0.331

Bold text: Statistically significant ($p < 0.05$)

[a] Deep infiltrating endometriosis

[b] Numeric Rating Scale

[c] Combined oral contraceptive

in patients with CS; however, endometriomas were more characteristic of the group without CS. Adenomyosis was equally present in both subgroups. Moderate/severe dysmenorrhea was also similarly present in both subgroups ($p = 0.282$). Chronic pelvic pain had a prevalence of 66.2% (94 patients out of 142) in the studied population, 82.4% in the subgroup with CS (61 patients out of 74), and 48.5% in the subset without CS (33 patients out of 68). Moderate/severe dyspareunia and moderate/severe chronic pelvic pain were more prevalent in the subgroup with CS: 25.6% of patients with CS vs. 4.4% of patients without sensitization reported dyspareunia with an NRS ≥ 5, and 25.6% of patients with CS experienced chronic pelvic pain with an NRS ≥ 5 compared to 13.2% of patients without sensitization. These numerical differences between groups that did not reach statistical significance have to be interpreted with caution, and no definitive conclusions can be drawn from non-significant comparisons. A statistically significant correlation was found between moderate to severe dyspareunia and CS ($p = 0.001$, $p < 0.05$). Among patients with dyspareunia and CSI ≥ 40, the underlying diagnosis was adenomyosis in 4 cases, adenomyosis with DIE in 2 cases, DIE alone in 9 cases, endometrioma with DIE in 1 case, and endometrioma alone in 3 cases. Given the limited sample size of these subgroups, no statistical comparison was performed.

There was also a significant association between the onset of symptoms and the time of test positivity. In fact, a significant difference was found between the test and the onset time of symptoms > 5 years compared to an onset < 5 years (p 0.0001).

As regards the therapy prescribed to the patients, there were no differences between the two groups, and progestin-only pills prevailed according to the last guidelines [1].

All CSS were more frequent in patients with Central Sensitization (Table 3); in particular, Chronic Fatigue Syndrome, Fibromyalgia, Temporomandibular Joint Disorders, Anxiety/Panic Attacks, and Depression had a statistically significant difference.

Regarding Migraine/Tension-type headache and IBS, they were identified as the more frequent comorbidities in the population studied without differences between the two groups.

Discussion

Summary of main findings

Central changes may be the reason for conventional treatment failure and may account for the overlapping CSS that can coexist in endometriosis patients [10, 31–33]. Therefore, a tool with good reproducibility, feasibility, and validity is needed to identify this group of patients early in an outpatient setting and to treat them appropriately [17]. In this study, we aimed to estimate the prevalence of CS in women with a diagnosis of endometriosis/

Table 3 Results from CSI part B

Central sensitivity syndromes	All (*N* = 142)	Central Sensitization YES (*N* = 74)	Central Sensitization NO (*N* = 68)	*p*-value
Restless legs syndrome N (%)	10 (7%)	5 (6.7%)	5 (7.3%)	0.685
Chronic fatigue syndrome N (%)	11 (7.7%)	10 (13.5%)	1 (1.4%)	**0.001**
Fibromyalgia N (%)	14 (9.8%)	12 (16.2%)	2 (2.9%)	**0.001**
Temporomandibular joint disorders N (%)	9 (6.3%)	9 (12.1%)	0 (0%)	**0.001**
Migraine or tension-type headache N (%)	54 (38%)	30 (40.5%)	24 (35.2%)	0.545
Irritable bowel syndrome N (%)	28 (19.7%)	16 (21.6%)	12 (17.6%)	0.388
Multiple chemical sensitivity N (%)	1 (0.7%)	1 (1.3%)	0 (0%)	0.377
Neck injury (including whiplash) N (%)	26 (18.3%)	18 (24.3%)	8 (11.7%)	0.200
Anxiety or panic attacks N (%)	37 (26%)	27 (36.4%)	10 (14.7%)	**0.001**
Depression N (%)	18 (12.6%)	16 (21.6%)	2 (2.9%)	**0.001**

Bold text: Statistically significant ($p < 0.05$)

adenomyosis who were referred to our "Endometriosis and Pelvic Pain" specialized center. The prevalence, based on the positivity to the CSI test, was 52.1%, in line with previous literature. The link between symptom chronicity and severity suggests an important association with disease onset, underscoring the need for timely diagnosis and management.

Strenghts and limitations

A strength of this study is the fact that clinical data and CSI were collected in real time at the time of patient evaluation, according to a predefined protocol, rather than retrospectively from existing medical records. Standardized data acquisition that reduces recall bias and ensures high data consistencyAnother point of strength is the fact that the study provides further evidence about CS in patients with endometriosis. Compared with previous studies, our work provides novel insights by highlighting a significant association between symptom chronicity (> 5 years) and central sensitization. Furthermore, all clinical, ultrasound, and questionnaire assessments were performed by the same expert team, ensuring a high degree of methodological consistency and minimizing inter-observer variability. Finally, the finding that dyspareunia and vulvodynia are the pain domains most strongly correlated with central sensitization offers new perspectives for individualized pain management and early multimodal intervention.

Unfortunately, the sample size is small, and the single-center design limits the generalizability of the findings. However, we aim to expand it by continuing enrollment and data analysis, as well as investigating the response to multimodal treatment. Another promising direction we are currently pursuing involves evaluating outcomes in patients with a history of endometriosis surgery, comparing those with and without CS. This ongoing work may provide deeper insights into the mechanisms underlying persistent pain, even after complete surgical excision. Also investigating the relationship between central sensitization and treatment failure represents an important direction for future prospective longitudinal studies. Another limitation of this work is the absence of a control population and its cross-sectional design, which precludes the establishment of causal relationships between the duration or type of pain and the development of central sensitization. Longitudinal studies with follow-up will be needed to confirm the temporal associations suggested by our findings. Furthermore, the prevalence of COPCs may be underestimated in our study. CSI Part B relies on patients reporting previously known diagnoses, meaning that undiagnosed or subclinical conditions cannot be captured. This represents an inherent limitation of the CSI instrument rather than of our study design, and may lead to an underestimation of the true burden of overlapping pain syndromes in this population. Moreover, as a tertiary referral center for endometriosis, we may overestimate CS due to a selection bias resulting from enrolling only severe cases. This could have led to an overestimation of the prevalence of CS. Future cross-sectional design studies with random sampling will be needed to ensure that the results are generalizable.

Finally, although ongoing hormonal therapy was systematically recorded, the use of analgesic medications (e.g., NSAIDs, opioids, cannabinoids) was not collected in a standardized manner, as most patients used these drugs "as needed". Given the variability in type, dose, and timing of administration, reliable analysis was not feasible. This may limit the interpretation of pain scores and CSI results, and represents an additional limitation of the study. Also previous abdominal surgery was reported as a heterogeneous category, since the specific indication was not systematically collected; this may limit interpretation, although the type of prior surgery is not expected to influence central sensitization outcomes.

Results in the context of the existent literature

Orr et al. [9] first described in a study on 335 women with endometriosis a CS prevalence of 55% using the CSI questionnaire. The study aimed to evaluate CSI as a practical clinical tool for identifying patients with

endometriosis whose pain has a central component, compared with other patients with endometriosis who experience pain primarily related to disease-specific peripheral factors. This was one of the first large studies to apply the CSI to this population and to examine its diagnostic performance, finding that a CSI cutoff of 40 identified patients with endometriosis with 3 CSS with a sensitivity of 78% and a specificity of 80%.

Similarly, Raimondo et al. reported a prevalence of 42% in a recent study [11]. In another study, a CSI score > 40 was found in 75% of women with pelvic pain and was correlated with catastrophizing traits, bladder pain syndrome, and irritable bowel syndrome [34]. In 2023, Quintas Marques [35] found that the prevalence of CSI score > 40 was 59% in patients with deep endometriosis (DE). Patients with DE and a CSI value > 40 had a poorer health-related quality of life (HRQoL) and a higher risk of depression and anxiety.

Therefore, our data are consistent with the literature, which shows a high prevalence of positive CSI in these patients, particularly in specific subsets [15, 35].

It is also essential to understand the correlation between test positivity and disease variables, clinical aspects, and other potentially relevant aspects, such as certain epidemiological factors. In our study, the only demographic characteristic significantly associated with CS was smoking habits. Although infertility and previous abdominal surgery were clearly more prevalent in the CS group, this difference was not statistically significant. In Raimondo's study [11], the CS group showed a significantly higher rate of infertility. It can be hypothesized that the inflammatory environment of endometriosis, which already plays a role in infertility, also contributes to the stimulation of peripheral nerve fibers [36].

Deep lesions were more frequent in the CS group, but without statistical significance, in line with the literature [11]. DE has been largely associated with more frequent and severe pain symptoms compared with ovarian endometriosis; peripheral nerve compression or infiltration by DE can contribute as a major trigger to CS through multiple mechanisms of synaptic plasticity [11, 36–38].

Concerning pain, dyspareunia and chronic pelvic pain were found to be more frequent in patients with CS. Still, only the correlation between moderate to severe dyspareunia and CS was statistically significant ($p = 0.001$, $p < 0.05$). The correlation with more severe, persistent, and chronic symptoms is also observed in other studies [11, 15, 34].

Although CS may contribute to pain persistence and treatment refractoriness in a substantial proportion of women with endometriosis, particularly those reporting chronic pelvic pain [10, 31–33], our findings also underscore the heterogeneity of pain presentations. In this cohort, a proportion of patients, including some with a positive CSI score, did not meet criteria for chronic pelvic pain. This suggests that CS does not uniformly characterize all patients and that peripheral mechanisms may predominate in some cases, where conventional treatments may remain effective. Moreover, in addition to CS, other mechanisms such as progesterone resistance and lesion-specific factors may also contribute to treatment failure, highlighting the multifactorial nature of endometriosis-associated pain.

In the study by Orr et al., the subgroup with high deep dyspareunia and bladder and/or pelvic floor tenderness had a significantly higher score on the CSI than the other subgroups [15]. These findings could suggest a central component of sexual pain and chronic pelvic pain, which requires combined treatment.

Another critical correlation was with vulvodynia, considering that 76% of these patients were found to have CS. This highlights the significant central component of this condition [15, 39, 40]. Vulvodynia, in fact, is listed among the CSS conditions, although it is not included in Part B of the test [26].

The close connection between chronicity and more severe symptoms highlights the significant association with the onset of the disease. This is the first study to emphasize this aspect, with important implications for the timeliness of diagnosis and the importance of treating pain syndromes even in adolescence.

This is also one of the first studies to include adenomyosis in the evaluation of CS (and CSI). Indeed, while CS has been increasingly investigated in women with endometriosis, much less attention has been given to adenomyosis, despite its frequent coexistence with endometriosis, with which it shares physiopathological characteristics [41, 42], and its well-established association with chronic pelvic pain. Adenomyosis is characterized by persistent nociceptive input, neuroinflammatory processes, and altered pain perception [42, 43], features that overlap with mechanisms involved in nociplastic pain and CS. Including women with endometriosis and/or adenomyosis, therefore, allows a more comprehensive evaluation of CS and addresses a relevant gap in previous research focused on endometriosis alone.Moreover, CSI part B can discriminate between patients with COPCs or CSS and patients with chronic pain conditions without a central component of pain. CSS are a heterogeneous group of disorders in which persistent pain represents the most frequent symptom and CS appears to be at the basis of the pathogenesis, justifying the overlapping clinical features of these conditions [11, 15]. This reflects the shared neuroimmune mechanisms underlying pain chronification, inflammation and central sensitization. In accordance with previous studies, our analysis showed a higher frequency of CSS among patients with endometriosis compared to the general population [11, 15,

44–47]. Orr [15] emphasized that the CSI cutoff identified patients with endometriosis with 3 CSS with a sensitivity of 78% and a specificity of 80%, and Cetera et al. [17], in a recent review, highlighted that CSI is probably not a direct measure of CS, but rather a measure of vulnerability and presence of overlap conditions.

Finally, given the high prevalence of central sensitization in women with endometriosis, multimodal and mechanism-based treatment strategies should be considered. Non-pharmacological approaches such as pelvic floor physical therapy and cognitive-behavioral therapy are increasingly recommended. Pharmacological interventions targeting nociplastic pain, including SNRIs, gabapentinoids, and tricyclic antidepressants, may also be beneficial [1, 28]. Emerging treatments are under active investigation, including NMDA receptor antagonists: for example, esketamine infusion is currently being evaluated for chronic endometriosis-associated pain [48]. These approaches highlight the need for individualized and multidisciplinary management in patients with both endometriosis and central sensitization.

Conclusions

A gold standard test for CS is not yet available, but the CSI exhibits good psychometric properties in identifying patients with a central component of pain and overlap syndromes.

The results of this study have direct implications for the management of these patients, namely the need for, or even the necessity of, a multimodal and multidisciplinary treatment approach, in addition to conventional treatment, which is likely to fail in this patient group. Therapeutic failure, which is common in patients with endometriosis, must be correctly framed, as it may be related not only to the biological characteristics of the disease but also to the central components of pain and the presence of overlap syndromes. The aspect of chronic pain is of great importance in the timely management of patients, especially during the adolescent phase.

However, a positive CSI and central sensitization cannot yet be considered synonymous. The cut-off may indeed be validated in larger, multicenter studies that further evaluate the correlations with the disease, the onset time of symptoms, and additional patient clusters, such as those with vulvodynia and adenomyosis, as well as the test's ability to identify the response to appropriate and multidisciplinary therapy.

Abbreviations

CS	Central Sensitization
CSI	Central Sensitization Inventory
CSS	Central Sensitization Syndromes
NRS	Numeric Rating Scale
DIE	Deep Infiltrating Endometriosis

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Authors' contributions

All authors contributed to the conception and design of the study. AB: conceptualization, protocol development and original draft writing; FP: data collection and curation; IM: investigation; MD: writing - review and editing; SZ: formal analysis; VT: formal analysis; IP: formal analysis; RS: supervision; DR: supervision; MDM: supervision; MA: methodology; SR: methodology; LD: supervision; GV: project administration. All authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to ethical and privacy considerations, including the risk of patient re-identification. Anonymized data are available from the corresponding author upon reasonable request and subject to institutional and ethical approval.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study was approved by the Ethics Committee (Comitato Etico Unico Regionale - CEUR) of Friuli Venezia Giulia (protocol n. 65352, dated April 24th, 2024). Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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