Research on central sensitization of endometriosis-associated pain: a systematic review of the literature

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Abstract: Endometriosis-associated pain afflicts an enormous number of women who suffer from endometriosis. There is an urgent need to explore the pathogenesis of endometriosis-associated pain to identify targets for treatment of hyperalgesia. A search was conducted in PubMed, Web of Science, Embase, and the Cochrane Library using the search terms “endometriosis” AND (“pain” OR “hyperalgesia” OR “nociception” OR “allodynia”) AND “central sensitization”. The search was limited to articles published in English from 01/01/2008 to the present. Among the search results, 15 articles were eligible for systematic review, including 6 reviews, 6 human studies (one in the form of a conference abstract only), and 3 animal studies. The articles were classified into 4 lists to describe the mechanism of endometriosis-associated pain and synthesize different aspects of research on it. In conclusion, there is a need to explore the mechanism of endometriosis-associated pain in terms of innervation, vascularization, local inflammation, cross-correlated visceral sensitization, and central sensitization to identify the target molecules and signaling pathways of key genes and relevant biomarkers through new techniques, all with the goal of developing a more comprehensive treatment strategy for endometriosis than is currently available.

Keywords: endometriosis-associated pain, neurogenic inflammation, mechanism, central sensitization

Introduction

Endometriosis, a condition in which lesions made of endometrium form ectopically outside the uterus, is a common gynecological disease in reproductive-age women. One in ten women has been diagnosed with this type of lesion. Recently, several common effect of endometriosis, including pain (found in 80% of patients), infertility (60%) and/or pelvic mass (40%), have been classified as a syndrome. Studies have indicated that women with endometriosis-associated pain manifest several symptoms: chronic pelvic pain (CPP), dysmenorrhea, dyspareunia, and dyschezia. Additionally, substantial burdens can arise from associated nociceptive conditions such as viscerovisceral hyperalgesia syndrome, painful bladder syndrome (formerly called interstitial cystitis) and irritable bowel syndrome.

The diagnosis of endometriosis depends on laparoscopy, in which the cyst or nodule can be seen directly in the peritoneal cavity. Laparoscopy is also the most effective way to eliminate the ectopic lesion. However, most patients still suffer from persistent pain after surgery. Some women with this disease can relieve pain...
via oral acypterion, gonadotropin-releasing hormone agonist (GnRH-a), or nonsteroidal anti-inflammatory drugs. However, there remains a potential problem because clinically significant results require prolonged and repeated administration, which causes side effects in a large number of patients. Therefore, an imperative need exists for alternative, more mechanism-based treatments to ease the extreme hyperalgesic symptoms of endometriosis.

A growing body of evidence attests that patients with endometriosis endure pain associated with abnormal angiogenesis and the growth of novel nerve fibers in close proximity to ectopic lesions. Endometriotic lesions create an inflammatory environment and change the quality or quantity of inflammatory mediators or neurotransmitters, thereby stimulating peripheral nerve sensitization by remodeling the structure of peripheral synapses and accelerating conduction along nerve fibers. Berkely and McAllister discovered that ectopic cysts harvested from rat models with established endometriosis and from human patients develop their own C-fiber (sensory afferent) and sympathetic (autonomic efferent) nerve supply. The supply is rooted in nerve fibers innervating sites near the lesions; these fibers sprout branches into the growths. In 2003, Bajaj and his team proposed that central sensitization may be involved mechanistically in the development and maintenance of endometriosis-related pain. Those researchers hypothesized that persistent nociceptive input from endometriotic tissues might result in increased responsiveness among dorsal horn neurons processing input from the affected viscera and somatic tissues. Their subsequent study found a reduced pain threshold but improvement in the reaction to pricking and in mechanical hyperalgesia in 10 patients with laparoscopically confirmed endometriosis who suffered from pelvic pain. Spisak, by evoking blood-oxygen-level-dependent (BOLD) responses in a block-design functional magnetic resonance imaging (fMRI) experiment, identified that central sensitization to chronic pain can be observed as altered connectivity in key regions of the nociceptive network. An increasing number of studies focus on the relationship between differences in gene expression and the central sensitization mechanism of endometriosis-associated pain.

This review was organized with the aim of systematically synthesizing the literature published to date regarding the central sensitization mechanism of endometriosis-associated pain. The goal of this undertaking is to unearth the underlying pathogenesis and provide reliable evidence to aid the search for novel methods of nonhormone target therapy for endometriosis-associated pain.

**Methods**

**Literature search**

Articles and review papers retrieved from the databases PubMed, Web of Science, Embase, and the Cochrane Library. Gray literature was excluded. The following search terms were used: “endometriosis” AND (“pain” OR “hyperalgesia” OR “nociception” OR “allodynia”) AND “central sensitization”. The search was limited to articles published in English from 01/01/2008 to the present.

**Data selection**

All studies identified by the searches were screened for inclusion. If our inclusion criteria were not all addressed in the abstract, then the methods section of the paper was screened. The inclusion criteria were as follows: (1) women or animals as the study subjects; and (2) women with endometriosis accompanied by pain, or animals with induced endometriosis-like lesions and hyperalgesia. The types of study designs included for review were randomized controlled trials (RCTs), cohort studies, cross-sectional studies, observational studies and reviews. Articles in languages other than English were excluded. Some potentially useful papers were excluded from the present meta-analysis because their data were too heterogeneous. The abstracts were double-checked by at least two authors to determine whether the reports fit the inclusion criteria for this study (Figure 1).

**Data extraction**

The articles found in the search were classified into the categories of reviews, research articles and conference presentations; furthermore, the research articles were subdivided into human research and animal research. For data collection and analysis, two authors independently extracted key data from the selected studies into several data tables according to the above classification. The tables contained general information such as author name, year of publication, locations and other characteristics (study characteristics, eligibility criteria, interventions, outcome measurements, etc.). All included articles were stored in EndNote software to assist the reviewers in managing data and to enable a third author to eliminate
duplicate publications. All disagreements regarding study inclusion or data extraction were resolved by another author.

**Results**

Seventy-four publications were identified from PubMed, Web of Science, Embase and the Cochrane Library using the specified search terms. Twenty duplicates were removed from the list of search results, and the remaining studies were screened for inclusion and exclusion criteria by reading the abstracts and full texts. Ultimately, 15 articles were eligible for systematic review, including 6 reviews, 6 human studies (one of which was in the form of a conference abstract only), and 3 animal studies.

The 15 articles were classified into 4 categories in order to describe and synthesize information from similar study types. The human studies are summarized in Table 1; the animal studies are presented Table 2; the reviews are analyzed in Table 3, and the conference presentations are explained individually in Table 4.

**Discussion**

In recent years, studies on endometriosis-related pain have focused on CPP in women of reproductive age, but most patients with endometriosis have also shown some specific alodynia, such as abdominal myofascial pain syndrome, visceral cross-organ nociception and muscle fascial pain; therefore, in recent years, these ambiguous pain locations have become a research hotspot for endometriosis-related pain. Most of the researchers have reviewed some original research articles accumulated over years the years, involving case-control, prospective, retrospective, randomized controlled and nonrandomized controlled study designs. Generally, pain patients who were diagnosed laparoscopically with endometriosis were assigned to an experimental group, while pain patients without endometriosis were classified in a control group, and pain assessment was performed with a visual analogue scale (VAS) scoring system. The pain patients received an intervention, such as medication (oral or intravenous) or acupuncture, sometimes accompanied by adjuvant
<table>
<thead>
<tr>
<th>Author</th>
<th>Rocha et al⁷</th>
<th>Gurian et al¹⁰</th>
<th>Deitos et al¹¹</th>
<th>He et al¹²</th>
<th>Chen et al¹³</th>
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<tr>
<td>Year</td>
<td>2015</td>
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<td>2018</td>
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<td>Locations</td>
<td>Brasil</td>
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<td>China</td>
<td>USA</td>
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<tr>
<td>Participants</td>
<td>CPP=40 Group1: endometriosis, n=24 (age: 32.9±9.0); Group 2: abdominal myofascial pain syndrome, n=16 (age: 32.7±7.8)</td>
<td>CPP=58 (age: 43.3) G1: endometriosis=12, G2: myofascial syndrome=18, G3: others=28</td>
<td>Not given</td>
<td>pain-free controls n=37</td>
<td>Pain without endometriosis= 70 (age:33.4±7.1)</td>
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<td>N?</td>
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<tr>
<td>Control N?</td>
<td>Group3 a heathy, n=25 (age: 35.4 ±6.7)</td>
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<td>Typer of study</td>
<td>prospective</td>
<td>VAS=62; Basal pain threshold=d=14.2 electrical pain thresholds: G1=12.1; G2=16.1</td>
<td>VAS&gt;40mm (ie, moderate or severe pain), Pain associated with functional disability lasted &gt;3 months.</td>
<td>Prospective</td>
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<tr>
<td>Pain measurement</td>
<td>VAS=79.5±15.4, G2=85.9±11.0; threshold pain (kg/cm²): G1=1.0±0.1 G2=1.9±0.2 G3=2.6±0.2</td>
<td>VAS=39; electrical pain thresholds: G1=16.5; G2=19.3</td>
<td>VAS=39; electrical pain thresholds: G1=16.5; G2=19.3</td>
<td>VAS: G1=6.20 (1.74) G2=4.72 (1.71) MPQ: G1=1.14 (3.86) G2=9.19 (3.90) ST: G1=2.94 (0.83) G2=2.81 (0.85) PT: G1=11.25 (3.99) G2=13.60 (5.15)</td>
<td>VAS: G1=6.20 (1.74) G2=4.72 (1.71)</td>
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<td>Intervention</td>
<td>Injections of 2 mL 0.5% lidocaine in G1 and G2</td>
<td>Oral or physical therapy for 6 months</td>
<td>Not intervention.</td>
<td>Surgery</td>
<td>Surgery</td>
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<td>Parameter or Outcome</td>
<td>G1: VAS &amp; NO;r=0.67 (95% CI: 0.35 to 0.85), P&lt;0.0001; threshold &amp; NO: r=-0.53 (-0.78 to -0.14), P=0.0001 G2: VAS &amp; NO;r=-0.64 (-0.89 to 0.10), P=0.20; threshold &amp; NO;r=-0.12 (-0.65 to 0.49), P=0.88</td>
<td>Groups of patients with CSS presented higher expression: TNF-α=28.6±2.74pg/mL, BDNF=49.87 ±31.86ng/mL. Controls group: TNF-α=2.14±5.74pg/mL, BDNF=14.09 ±11.80ng/mL. BDNF screen CSS from controls: AUC=0.86, cutoff=13.31ng/mL, sensitivity=95.06%, specificity=56.76%; moderate-severe depressive symptoms: AUC=0.81 cutoff=42.83ng/mL, sensitivity=56.80%, specificity=100%. TNF-α: moderate-severe depressive symptoms: AUC=0.97 cutoff=22.11 pg/mL, sensitivity=90%, specificity=91.3%</td>
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therapy; subsequently, the effectiveness of the treatment was evaluated using a pain scale, such as the VAS, Iowa Pain Thermometer (IPT) or McGill Pain Questionnaire (MPQ), or a protein biomarker, such as BDNF, TNF-α, or the PEGylated form of a specific protein. Some studies have found that although the pain was relieved after the experimental treatment measures, it recurred after a few months; this phenomenon is related to the central sensitization mechanism of endometriosis.

Nagabukuro has confirmed that endometriotic pelvic lesions contain abnormal neurovascular proliferation. These phenomena may be caused by abnormalities in conduction after peripheral sensitization, leading to central neurological abnormalities in the phenomenon known as central sensitization. The five articles cited above are the most comprehensive studies on the central sensitization mechanism of pain in endometriosis. Their subject populations were mainly from Brazil, China and the United States. This geographical scope is relatively limited and not representative of the entire world. Consequently, the results of the analysis are applicable only to the region. In three studies of animal models of the central sensitization mechanism of endometriosis, the quality of evidence needs to be improved.

Table 1 (Continued).

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<th>Author</th>
<th>Conclusion</th>
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<tr>
<td>Rocha et al</td>
<td>The plasma NO level may be directly involved in the pathophysiologic pain</td>
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<td>of endometriosis</td>
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<td>Gurian et al</td>
<td>Increasing the electrical pain threshold may provide an additional evidence</td>
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<td>for reducing the pain intensity between central sensitization and CPP.</td>
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<td>Deitos et al</td>
<td>BDNF, TNF-α as neuroplasticity mediators could play a vital role as</td>
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<td>screening tools for central sensitivity pain patients.</td>
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<td>He et al</td>
<td>Central sensitization may be a possible mechanism underlying various forms</td>
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<td>of pain associated with endometriosis.</td>
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<tr>
<td>Chen et al</td>
<td>SFPN may support a more dynamic relationship between the peripheral and</td>
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<td>central sensitization in complex CPP.</td>
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Abbreviations: G1, Group1; G2, Group2; G3, Group3; CPP, chronic pelvic pain; VAS, visual analogue scale; NO, nitric oxide; CSS, Central sensitivity syndrome; BDNF, brain derived neurotrophic factor; MPS, myofascial pain syndrome; CTTH, chronic tension-type headache; FM, fibromyalgia; MPQ, McGill Pain Questionnaire; ST, Sensory threshold; PT, Pain threshold; SFPN, small fiber polyneuropathy; LUTS, Lower urinary tract symptoms.
Endometriosis-related pain is currently considered a form of neuropathic or neuroinflammatory pain. A large number of experimental studies, both human and animal, have demonstrated that abnormal microscopic neurogenesis and angiogenesis occur in ectopic lesions, supporting the development, density, infiltration and even metastasis of ectopic endometrium.\textsuperscript{4,17,20,33} The perception of pain is caused by this abnormal proliferation of nerve fibers and vessels. Inflammatory factors are released into the sensory afferent nerve at the distal end of the lesion by noxious stimuli, and the nociceptive signal is transferred to the nerve root of the dorsal horn of the spinal cord. After simple handling, the pain signal is transferred to the thalamus, the brain stem, and finally the cerebral cortex.\textsuperscript{34} If the lesion sites are stimulated persistently by those abnormal factors, the transmission of pain signals will change, magnifying future pain and forming more intense memories of pain in the cerebral cortex. During the process of signal transduction, the function of the corresponding immune cells and cytokines changes accordingly, promoting the enhancement and amplification of the pain signals to some extent.\textsuperscript{35} As-Sanie\textsuperscript{36} and his colleagues determined that women with endometriosis-associated CPP shown increased levels of combined glutamine and glutamate (Glx) within the anterior insula and increased anterior insula connectivity to the medial prefrontal cortex (mPFC), which may play a role in the pathophysiology of CPP independent of the presence of endometriosis. Of course, the degree of pain is positively correlated with the density of nerves at the lesion. The higher the density of nerve fibers, the more pronounced the pain. Reviews by Liu\textsuperscript{37} and

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<td><strong>Control, N=?</strong></td>
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<td><strong>Pain measurement</strong></td>
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**Abbreviations:** EMS, induced- endometriosis by surgery; Sham, Sham surgeries for controls; OVX, ovariectomised; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; DRG, dorsal root ganglia; GFAP, glial fibrillary acidic protein.
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<th>Author</th>
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<th>Location</th>
<th>Personality</th>
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| Asante et al<sup>17</sup> | 2011 | USA      | • Circulating Markers of Endometriosis: CA-125, ICAM-1.  
• Central sensitization was induced in dorsal horn neurons by an increasing in excitatory synaptic transmission, mediated via the NMDA and AMPA receptors, or by a loss of inhibitory synaptic transmission, mediated via GABA and glycine receptors.  
• Endometriosis-related pain is a type of neuropathic pain or a neurogenic inflammation pain.  
• Unique vascular and neural supplies via neuroangiogenesis were identified in location lesions.  
• Autonomic Nervous System Changes and defective immunosurveillance and inflammatory hyperresponsiveness.  
• Patients with DIE and bowel endometriosis show more several pain symptoms cause of a higher nerve fibres density compared to other sites. |
| Brawn et al<sup>18</sup> | 2014 | UK       | • Changes in brain structure: reduction in brain volume by neuroimaging.  
• Activity of the HPA axis.  
• Predisposition to other chronic conditions.  
• Nervous system response further increases peritoneal inflammation result from higher concentration of SP and CGRP in lesions, whilst NK1R gene polymorphism rs881 may be a pathogenic role in endometriosis.  
• TRPV1-positive nerve fibers is relevant to CPP.  
| Laux-Biehlmann et al<sup>19</sup> | 2015 | Germany  | • Noxious and innocuous stimuli in endometriotic lesions cause inflammatory pain.  
• Escherichia coli found in menstrual blood and peritoneal fluid validated that the DAMPs and PAMPs play a vital role in endometriosis-associated inflammation.  
| McKinnon et al<sup>20</sup> | 2015 | USA      | • Analyze the implication between endometriosis and the molecules in peritoneal fluid or neurogenic inflammation environment including: ENA-78, IL-1β, IL-6, IFN-γ, Leptin, MCP1, MK, NGF, OPG, PAEP, PAAPP-A, RANTES and TNFa.  
| Morotti et al<sup>21</sup> | 2017 | UK       | • Offer the precise terminology on assessment of pain.  
• TRPV1, CCL2, BDNF, VEGF, and NT4/5 in cysts are highly expressed.  
• Women with endometriosis-associated CPP were detected several volumetric modifications in specific brain areas, such as thalamus, insula, putamen, etc.  
• HPA axis, the endocrine pathway, present a dysfunction by central change, demonstrated a positive correlation between cortisol reductions and both infertility and dyspareunia.  
• A framework for evaluating such sensitization and myofascial trigger points in a clinical setting is presented.  
• Painful MTrPs may serve as an additional source of nociceptive input.  
• Botulinum Toxin Type A may obtain satisfactory therapy effect in alleviating the myofascial pelvic pain associated with endometriosis via blocking of signals that stimulate muscle fibers. |
| Aredo et al<sup>22</sup> | 2017 | USA      | Abbreviations: CA-125, cancer antigen-125 or carbohydrate antigen-125; ICAM-1, serum-soluble intercellular adhesion molecule-1; CPP, chronic pelvic pain; HPA, Hypothalamic–Pituitary–Adrenal; NMDA, glutamate N-methyl-D-aspartate; AMPA, α-amino3-hydroxy-5-methyl-4-isoxazole-propionate; GABA, γ-aminobutyric acid; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; TRPV1, transient receptor potential vanilloid 1; SP, neuropeptide substance P; CGRP, calcitonin gene-related peptide; NK1R, neurokinin 1 receptor, is one of the SP receptor; DIE, deep infiltrating endometriosis. |
Serrano\textsuperscript{38} hold that deep infiltrating endometriosis (DIE) and ectopic growths on the intestinal wall have greater neurologological density than ectopic lesions in other parts, meaning that this type of patient will have more severe pain.

The exploration of biomarkers has played an important part in research efforts to characterize the mechanism of endometriosis pain. CA125 has been widely used in the detection of endometriosis, but no study, to our knowledge, demonstrates clearly that the increase in CA125 is positively correlated with the degree of pain. Existing research merely indicates that the amount of CA125 in patients with endometriosis is elevated, which can serve as supplemental diagnostic sign.\textsuperscript{17,39} Some studies also suggest that ICAM-1 is associated with the degree of pain in endometriosis.\textsuperscript{17} A review by Brawn\textsuperscript{18} states that chronic, repeated local pain stimuli affect the normal activity of the hypothalamic–pituitary–adrenal (HPA) axis and may then exacerbate pain through a reduction in cortisol levels. Meanwhile, the structure of specific brain areas is changed, such as the periaqueductal gray (PAG), a vital region in the descending pain modulatory pathways;\textsuperscript{19} the volume of the PAG is increased in women with endometriosis pain compared to those without pain, as observed by seed-based resting functional connectivity magnetic resonance imaging (fcMRI). Laux-Biehlmann\textsuperscript{19} summarized the important role that damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) play in pain signaling from ectopic lesions. At the same time, it is also recognized that TRPV1, substance \textit{P} (SP) and calcitonin gene-related peptide (CGRP) show high expression in lesions and nearby sites that are subject to pelvic pain. On a related note, the NK1\textsubscript{R} gene polymorphism rs881 may play an important role in this process, providing a new possibility for pain treatment targets, but further verification is needed. From the review of McKinnon,\textsuperscript{20} it is not difficult to see that many other inflammatory factors such as Leptin, MCP1, MK, NGF, OPG, PAEP, PAAPP-A, RANTES and TNF-\textalpha are relevant to the pain associated with endometriosis, which merits further attention in the field of inflammatory pain. Morotti’s view is similar to that of Brawn and further proposes that volumetric changes in the thalamus, insula and putamen result from long-term endometriosis-related pain.\textsuperscript{21} Aredo\textsuperscript{22} took another perspective to explain endometriosis-related pain at sites such as myofascial trigger points (MTrPs); he noted that botulinum toxin type A can alleviate myofascial pain by blocking signal transmission.

A study presented by Guo et al\textsuperscript{23} also used questionnaires to evaluate the symptoms of CPP in patients. The investigators conducted a brief analysis of the underlying cause of intractable endometriosis-associated pain driven by central sensitization.

In summary, we can conclude that endometriosis-associated pain is closely related to central sensitization, as validated in both animal experiments and human case-control studies. Attention should be focused on the molecular pathways of pain signaling, with the intention of identifying the target-molecule signaling pathways of key genes and relevant biomarkers through new techniques, blocking the transmission of amplified signals by effective methods, and blocking or reversing the results of central sensitization from neurotoxic stimulation in order to relieve pain and improve quality of life in patients suffering from endometriosis-associated pain.

\textbf{Acknowledgment}

This study was supported by grant from the National Natural Science Foundation of China (81471440).
Disclosure
The authors report no conflicts of interest in this work.

References
30. Experimental pain tolerance is decreased and independent of clinical pain intensity in patients with endometriosis.


