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

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Objective: To investigate alterations in tactile, pain thresholds and pain tolerance thresholds in patients with endometriosis using a multimodality approach.
Design: Cross-sectional study.
Setting: Multidisciplinary referral center.
Patient(s): Women with proven endometriosis (N = 35) and healthy controls (N = 38).
Intervention(s): Pain processing was tested using quantitative sensory testing (QST) to investigate sensation, pain, and pain tolerance thresholds for thermal, electrical, and pressure stimuli.
Main Outcome Measure(s): Differences in QST measures in patients with endometriosis and in healthy controls on the endometriosis site and control sites, and the association between QST outcomes and patient characteristics.
Result(s): We observed a significantly decreased pain tolerance in patients with endometriosis, independent of clinical pain intensity or revised American Society for Reproductive Medicine stage, compared with healthy controls.
Conclusion(s): Increasing knowledge concerning mechanisms underlying the pain of women with endometriosis creates opportunities to develop new treatment options. More attention should be paid not only to treat endometriosis in a surgical or pharmacologic way, but also to desensitize by pain education or cognitive therapy. (Fertil Steril® 2018;110:1118–28. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Endometriosis, quantitative sensory testing, pain processing, intrasubject reliability, pain

Endometriosis is a complex disorder in which pain is the most prevalent symptom. It is a frequently occurring gynecological condition with an estimated prevalence of 6%–10% among women in their fertile phase. It is characterized by the presence of active endometrial tissue outside the uterine cavity with neuroendocrine and inflammatory aspects (1–5). Treating endometriosis-associated pain can be a major clinical challenge as pain symptoms may become chronic and success rates of treatment are frequently disappointing (1, 6–8). Pain relief is only perceived in 40%–70% of women with endometriosis and symptoms frequently relapse after cessation of treatment (7–10). We therefore see a pressing need for the development of new therapeutic strategies for endometriosis. Fundamental to the improvement of therapeutic options is the question of how pain is processed by patients with endometriosis. Some researchers have proposed that endometriosis-associated pain is caused

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in part by the development of new blood vessels and nerve fibers (neuroangiogenesis) in the endometriosis lesions and in the peritoneum near the lesions (11–15). Other investigators have hypothesized that the intensity of pain symptoms can be attributed to the degree of tissue damage resulting from endometriosis lesions, as well as to the amount of pain-producing agents in the peritoneal fluid (PF), such as cytokines, growth factors, and chemokines, disturbing the intra-abdominal environment (3, 4, 16, 17). However, pain symptoms in endometriosis correlate poorly with the number and size of the endometriosis lesions and often return after surgical excision, even without visual confirmation of recurrence of lesions as observed during surgery (3, 4, 17, 18). This suggests that pain perception is influenced by other factors than the presence of lesions alone (11, 12, 19–21).

When the focus is taken from the lesions and shifted to the pain, it should be noted that although pain is perceived in a specific peripheral anatomic area, the central nervous system is responsible for the conscious experience of pain (4, 11, 22, 23). It is generally accepted that the central nervous system contributes to the modulation of pain in patients with chronic pain, potentially including the modulation of pelvic pain and pain in women with endometriosis (4, 11, 16, 22). The presence of chronic pain may modify the structure and function of the central nervous system, potentially resulting in alterations in pain processing, including the occurance of allodynia, hyperalgesia, or central sensitization (4, 11, 12, 15, 23–25). Allodynia is a pain sensation resulting from a stimulus normally not provoking pain and can be measured as a reduced pain threshold. Similarly, hyperalgesia is a sign of altered pain processing, which is defined as an increased pain sensitivity (i.e., an exaggerated and prolonged response to a noxious stimulus). Central sensitization is an abnormal state of responsiveness or increased gain of the nociceptive system to nociceptive and non-nociceptive stimuli with a spread of tenderness beyond the receptive field (25–27). These alterations in the processing of sensory input may eventually become independent of the peripheral noxious input after the central nervous system has been modified in such a way that pain memories generate painful sensations without true nociceptive input (25, 26, 28, 29).

In the present study, we examined pain processing by measuring the response to experimentally induced pain using quantitative sensory testing (QST). This method is shown to be reliable in quantifying the sensory function at the peripheral and central level of the nervous system in a number of chronic pain conditions (30–33). We compared QST measurements between women with endometriosis and healthy controls to gain insight into pain processing by these women. Data were collected in patients with endometriosis in various revised American Society for Reproductive Medicine (ASRM) disease stages and clinical pain intensity. These women were treated with hormonal therapy conforming to international guidelines and were using analgesics when required (6).

The goal of the present study was to provide more insight into pain processing in women with various revised ASRM stages of disease and different clinical pain intensities. This may ultimately be used to develop improved treatment options for women with endometriosis.

MATERIALS AND METHODS

Study Population

Patients with endometriosis were recruited from the Rijnstate multidisciplinary referral center for women with endometriosis (Arnhem, the Netherlands). Patients registered in the endometriosis database were approached when they were currently under treatment and their travel distance to the research center was within a reasonable measure (according to the participants' perception). They received written information from their gynecologist, after which they were contacted by telephone and asked for consent. Patients between 18 and 49 years who had laparoscopically or magnetic resonance imaging (MRI) confirmed peritoneal, ovarian, and/or deep endometriosis were included. Indication for laparoscopy was case-dependent and could either be pain or infertility. During laparoscopy, corrective surgery was performed where indicated. In women who had undergone laparoscopy, endometriosis was staged using the revised ASRM classification and treated according to international guidelines (6, 34). According to this classification, disease stages were classified as minimal (stage I), mild (stage II), moderate (stage III), or severe (stage IV). In addition, the type of endometriosis was established as either an ovarian, peritoneal, or deep endometriosis according to the type of lesions that were the most prominent. Disease severity and type varied between patients. A healthy control group was recruited by advertisement on social media, the hospital's website, and posters in the hospital, and consisted of women of fertile age, without a clinical diagnosis of endometriosis, between 18 and 49 years of age.

All participating women were on hormonal medication before study entry and none had a menstrual cycle, to rule out hormonal cycle influences. Patients were instructed to continue their current pain medication throughout the experiment. Occasional pain was not an exclusion criterion, but participants who used analgesics in a chronic manner for pain, other than endometriosis, were excluded from the study. Other exclusion criteria were pregnancy, pharmacologic treatment of psychological or psychiatric disorders, as well as chronic pain other than from endometriosis.

Pain Intensity Scores

To indicate the severity of pain in patients with endometriosis, the Verbal Numerical Rating Scale was used. The Verbal Numerical Rating Scale is an 11-point numerical rating scale that ranges from 0 (no pain) to 10 (unbearable pain). This is the most commonly used pain rating measurement method in clinical settings (35). Patients were asked to score their average endometriosis-related pain symptoms during the month prior to inclusion in one composite Verbal Numerical Rating Scale score. Average pain scores have been shown to provide a better impression of the influence of pain on a patient's daily life, compared with a one scoring moment of "worst pain" and are therefore considered a reliable measure

of pain severity in patients with chronic pain (36, 37). An average pain score of <4 was considered as a mild pain intensity and ≥4 as a moderate-to-severe pain intensity (37–39).

Quantitative Sensory Testing

Quantitative sensory testing is a noninvasive technique used to assess and quantify sensory functions by determining sensation and pain thresholds with the use of different stimulants (e.g., pressure or electric stimuli). We used a modified version of the German Neuropathic Pain Network QST paradigm based on a previously validated protocol in which we made small adjustments (30, 40, 41). A multimodality, standard testing approach was applied to detect sensation, pain, and tolerance thresholds of thermal, pressure, and electrical stimuli.

First, thresholds of pressure pain were measured in kilogram-force measurement units using a pressure algometer with a 1.0-cm^2 probe (WAGNER FDX). With this algometer, the minimum level of pressure stimulation at which the first sensation of pain was perceived (pressure pain detection threshold [pPDT]) and measured. Pressure was consistently increased at a rate of 2.5 kg/s until the pPDT was reached. Pressure thresholds were obtained for muscles overlying the bone on the dominant body side. The dominant body side is referred to the side of the body in accordance with left/right-handedness. We used the dominant and nondominant sides instead of left or right body site according to the German Neuropathic Pain Network QST paradigm as pain sensitivity is shown to be influenced by this feature (42–44).

Second, thresholds of electrical constant current skin stimulation were measured. Three thresholds were measured. Initially, the minimum level of stimulation intensity at which the first sensation was perceived (electrical skin sensation threshold [eSST]) was measured. Then, after intensifying the stimulation, the minimum level at which the electrical stimulus was perceived as painful was measured (electrical pain detection threshold [ePDT]). Finally, the maximum level of intensity of the electrical stimulus that the participant is willing to tolerate (electrical pain tolerance threshold [ePTT]) was measured (27). Measurements were recorded in milliamperes using a VARIO nerve stimulator (PAJUNK MultiStim), type BF with a pulse frequency at 100 Hz and a pulse width of 0.3 ms using adjacent self-adhesive electrodes. Electrical thresholds were measured on the nondominant body side to avoid overstimulation of one body side and stimulation was consistently increased at a rate of 0.4 mA/s with a maximum stimulation of 50 mA.

Pain thresholds were measured on dermatomes. We selected a dermatome representing the genital tract as the endometriosis site and dermatomes representing other tracts as control sites. The lower back (L1) dermatome was selected as the endometriosis site. Painful stimuli delivered to this dermatome are processed by the same dorsal neural horn neurons as nociceptive stimuli native to the internal genital tract. Dermatomes more distant from the genital area were selected to examine generalized sensitization (e.g., thumb [C6 dermatome], shoulder [C8 dermatome], sternum [T2 dermatome, only pressure stimulus thresholds were measured, no electrical stimulus thresholds], and knee [L4 dermatome]). These areas are unlikely to be affected by nociceptive input native to the genital area, as the nociceptive pathways are separated at both peripheral and spinal levels and therefore are classified as control sites.

The testing took place, according to previously validated protocols, using a standard test sequence by a trained team of investigators who were blind to participant status (30, 31, 41). Testing was not standardized with regard to the menstrual cycle as all participating women used hormonal treatment to suppress the menstrual cycle.

A first subgroup of patients (N = 19) and controls (N = 14) underwent two QST sessions with a mean interval of 15 days (±SD 4 days). Both QST sessions were identical, as the standard test sequence was followed. In this subgroup, test–retest reliability was analyzed. The second subgroup, consisting of 16 patients and 24 controls, underwent one QST session. The ePTT threshold was measured only on the L1 dermatome in the first subgroup and in addition was measured at all mentioned dermatomes in the second subgroup.

Conditioned Pain Modulation

The conditioned pain modulation (CPM) paradigm was performed to test the participants' ability to generate descending inhibitory pain modulation. Descending pain modulation can be induced by administering a conditioning stimulus (in the present study, the cold pressor test was used) and can be quantified by applying a test stimulation (in the present study, pressure stimulation was used) before and directly after the induction of the conditioning stimulus (45). The test stimulus is applied at a distinct site of the lower limb, contralateral from where the conditioning stimulus is applied on the upper limb, according to earlier recommendations of Yarnitsky et al. (45). During the cold pressor test, the participant was asked to immerse her nondominant hand in cold water (melting ice, 0–2°C) and to remove the hand when the pain was considered to be unbearable. Maximum immersion time was set at 180 seconds. The pPDT and pPTT were determined directly before and after the cold pressor test (45). The pPDT and pPTT were carried out by pressure stimulation on the quadriceps muscle ± 10 cm above the patella (L4 dermatome) of the dominant body side. The pressure stimulation was performed in the same way as the QST test sequence.

Statistical Methods

Statistical analysis was performed using SPSS version 22.0. *P* values of <.05 were considered significant unless specified otherwise.

Three participants (1 patient, 2 controls) appeared to be outliers on dermatome T12, and two participants (1 patient, 1 control) on dermatome L1 on the eSST measurement, according to Chauvenet's criteria, and were therefore removed from the analysis of the eSST (46). With respect to the CPM effect, one control participant was an outlier and therefore removed from analysis.

Test–retest intrasubject reliability was analyzed with the intraclass correlation coefficient (ICC) using a two-way random method (47, 48). This parameter quantifies the degree of agreement between two measurements within the same subject (47, 48). The ICC values range from 0–1, in which a value closer to 1 indicates a higher reproducibility. The ICC values were divided into four classes according to the guidelines of Cicchetti (49): a value <0.4 was considered a poor agreement, values between 0.4 and 0.59 were considered a fair agreement, values between 0.6 and 0.75 were scored as a good agreement, and >0.75 as an excellent agreement. To obtain normal Gaussian distributed data, we performed a Blom transformation on the test–retest data (50).

We used the Mann-Whitney *U* tests for potential group differences in our QST parameters. The Wilcoxon signed rank test was used for potential differences within the patient group in our QST parameters. Associations between patient characteristics and the QST findings were made with a Kruskal-Wallis test. In the first subgroup, participants underwent two QST measurements. To analyze the QST results, we used the data collected during the first QST measurement, as the second subgroup of participants also had only one QST measurement.

The CPM effect was determined by calculating the relative change (%) in pressure pain detection and tolerance threshold levels before and after the cold pressor test. Differences between the patient and control groups regarding the CPM effect or cold pressor test times were measured using independent sample *t*-tests.

Ethical Approval

This study was approved by the Ethics Committee of the Radboud University Faculty of Social Sciences (file number: ECSW2014-2411-275). Participants provided written informed consent. Data collection and analysis were performed anonymously.

RESULTS

Demographics

A total of 82 participants were included in the study (40 patients and 42 controls). Table 1 shows the clinical characteristics and sociodemographics of the participants. A small group of patients were diagnosed by MRI. As the revised ASRM staging system is a surgical scoring system, these patients could not be staged and were therefore reported as "missing" in the overview of disease stage. All patients were on hormonal treatment and used analgesics for pain symptoms when necessary. However, still 40% of patients suffered from moderate-to-severe pain despite the treatment.

One MRI-diagnosed patient was excluded from the study as she showed no signs of endometriosis during laparoscopy. Eight participants withdrew their consent or were not able to perform the QST measurement due to illness, social, or work-related reasons, leaving a total of 35 patients and 38 controls who underwent the QST measurement.

QST: Pressure Stimulation and Electrical Stimulation

No differences were found in pain threshold levels for either site between patients and controls using pressure stimulation (pPDT on endometriosis site U = 647.5; Z = −0.193; *P*=.847; pPDT on control sites U = 551.00; Z = −1.087; *P*=.277) (Fig. 1A). Using electrical stimulation, two thresholds were measured on all body sites: eSST and ePDT. No differences were found between patients and controls in either sites for eSST (endometriosis site U = 575; Z = −0.623; *P*=.533; control sites U = 579.00; Z = −0.756; *P*=.450) (Fig. 1B) or in ePDT (endometriosis site U = 598.0; Z = −0.565; *P*=.572; control sites U = 572.50; Z = −0.845; *P*=.398) (Fig. 1C).

A significant difference in pain tolerance was observed between patients and controls with regard to the electrical stimulus at the endometriosis site. Patients' pain tolerance was significantly lower than controls' pain tolerance (ePTT on endometriosis site U = 478.5; Z = −2.353; *P*=.019; ePTT on control sites U = 113.00; Z = −1.393; *P*=.164) (Fig. 1D). In addition, when comparing the pain tolerance for electrical stimulation on both sites in patients, it was observed that patients had a significant lower pain toleration on the endometriosis site than on the control sites (mean ePTT on endometriosis site 19.23 mA versus mean ePTT on control sites 39.57 mA; Z= −2.803; *P*=.005). In patients, the disease stage according to the reviseed ASRM classification and the QST findings on the endometriosis site were not significantly associated (ePDT *P*=.954; ePTT *P*=.989) (Fig. 2A). Neither was there a significant association between the QST findings and the clinical pain intensity in patients with endometriosis (ePDT 0.167; ePTT *P*=.179) (Fig. 2B).

Conditioned Pain Modulation

Baseline pressure pain detection for dermatome L4 did not significantly differ between patients and controls (6.8 [±SD 2.9] vs. 6.8 [±SD 2.9]; t (70) = −0.023; *P*=.982). No differences were observed between patients and controls in tolerance time regarding the cold pressor test (66.1 seconds [±SD 56.14] vs. 89.0 seconds [±SD 67.41]; t (70) = 1.563; *P*=.123).

The calculated CPM effect was not different between the patient and control group (9.7% [±SD 16.51] vs. 4.7% [±SD 20.61]; t(70) = −1.114; *P*=.269). Consequently, no difference was found in conditioned pain modulation between patients and controls.

Test–Retest Reliability of Pressure Stimulus Testing

The test–retest reliability of pressure stimulus testing is shown in Supplemental Tables 1 and 2 (available online). The pPDT for the endometriosis site was poor in both groups (patients, ICC 0.22; controls, ICC 0.12). The reliability of the pPDT in the control sites were variable among the two study groups (patients, ICC -0.12–0.85; controls, ICC 0.05–0.77).

TABLE 1

Characteristics of participating women (N = 82).

Characteristics	Patients (N = 40)	Controls (N = 42)	*P* value
Mean age (y)	34.0 (SD 7.1)	34.1 (SD 6.7)	.951[a]
Mean BMI (kg/m$^{2)}$	25.1 (SD 4.0)	25.2 (SD 5.1)	.628[b]
Education level (Verhage)			
5	19 (47.5%)	15 (35.7%)	
6	15 (37.5%)	10 (23.8%)	
7	6 (15.0%)	17 (40.5%)	.052[b]
Current marital status			
Single	8 (20%)	9 (21.4%)	
Living with partner	32 (80%)	33 (78.6%)	.874[b]
Occupation			
Student	3 (7.5%)	0 (0.0)	
Employee	31 (77.5%)	41 (97.6%)	
Housewife	2 (5.0%)	1 (2.4 %)	
Unable to work	4 (10.0%)	0 (0.0)	.448[b]
Hormonal use			
Oral contraceptives or progestagens	22 (55.0%)	41 (97.6%)	
GNRH agonist	8 (20.0%)	0 (0.0)	
Ovariectomy	6 (15.0%)	0 (0.0)	
Lactation amenorrhoea	0 (0.0)	1 (2.4%)	
Ullipristal acetate	1 (2.5%)	0 (0.0)	
Combination of treatments	3 (7.5%)	0 (0.0)	
Endometriosis confirmed			
MRI	7 (17.5%)		
Surgery	33 (82.5%)		
Mean number of years since diagnosis of endometriosis	5.5 (SD 6.0)		
ASRM classification			
1	2 (5%)		
2	3 (7.5%)		
3	7 (17.5%)		
4	21 (52.5%)		
Missing (no surgery performed)	7 (17.5%)		
Type of endometriosis			
Ovarian	5 (12.5%)		
Peritoneal	5 (12.5%)		
Deep	30 (75%)		
Average NRS score last month			
<4	18 (45%)		
≥4	16 (40%)		
Missing	6 (15%)		
Pain medication used (when necessary)			
None	7 (17.5%)		
Paracetamol	9 (22.5%)		
NSAID	17 (42.5%)		
Opioid	6 (15%)		
Neuropathic analgesics[c]	4 (10%)		
Missing	1 (2.5%)		
Type of endometriosis-pain			
Dysmenorrhoea	19 (47.5%)		
Dyspareunia	20 (50%)		
Dysuria	18 (45.0%)		
Dyschezia	19 (47.5%)		
Lower abdominal pain	29 (72.5%)		
Lower back pain	22 (55.0%)		

Note: Sociodemographic data of all participating women. No significant differences were observed between the two groups. In addition, medical data regarding the disease severity of the patients with endometriosis are displayed. ASRM = American Society for Reproductive Medicine; BMI = body mass index; GNRH = Gonadotropin-releasing hormone; MRI = magnetic resonance imaging; NRS = Verbal Numerical Rating Scale; NSAID = nonsteroidal anti-inflammatory.

[a] Independent *t*-test.

[b] Mann-Whitney *U* test.

[c] for example, amitriptyline, gabapentin.

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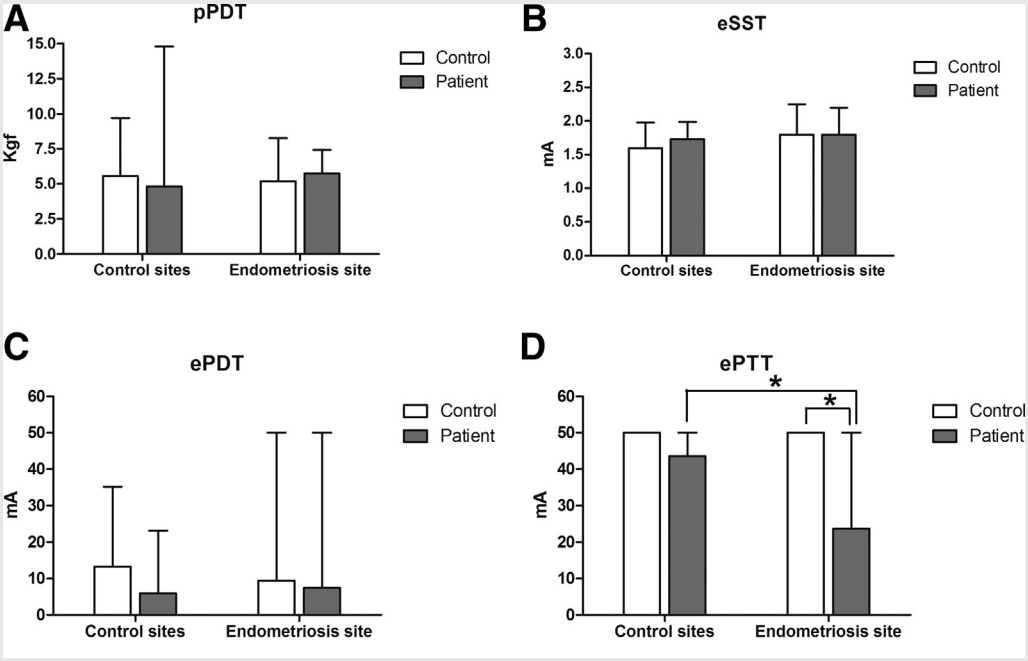
Test–Retest Reliability of Electrical Stimulus Testing

The test–retest reliability of electrical stimulus testing is shown in Supplemental Tables 1 and 2. The eSST at the endometriosis site showed a poor reliability in patients (ICC 0.06) compared with a fair reliability in controls (ICC 0.47). Overall, a poor–fair reliability in the control sites was seen for both groups.

FIGURE 1



Quantitative sensory testing results. Four different measurement thresholds for controls (*black*) and patients with endometriosis (*white*) (median with interquartile range) are shown according to the measurement site. Depicted on the X-axis are the two measurement sites on the body: control sites or the endometriosis site. **(A)** Pressure pain detection thresholds (pPDT), measured in kilogram-force (Kgf). **(B)** Electrical skin sensation thresholds (eSST), measured in milliamperes (mA). **(C)** Electrical pain detection threshold (ePDT), measured in milliamperes (mA). **(D)** Electrical pain tolerance threshold (ePTT), measured in milliamperes (mA). *$P<.05$.

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The ePDT, however, showed a good reliability at the endometriosis site for the patient group (ICC 0.72) (Fig. 3A). In controls, this test–retest showed a poor agreement (ICC 0.37) (Fig. 3A). For the control sites, overall reliability of ePDT was good–excellent in both groups (Fig. 3B). The ePTT test–retest reliability for the endometriosis site was good in patients (ICC 0.71) compared with a fair reliability among the control group (ICC 0.58) (Fig. 3C).

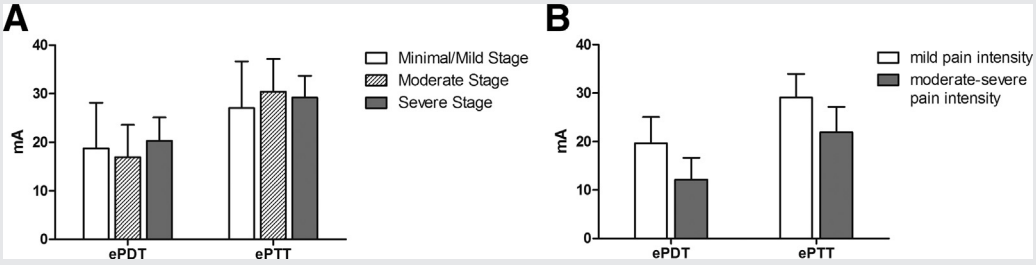
Test–Retest Reliability of CPM Effect

The CPM effect test–retest reliability was considered poor in the endometriosis group (ICC 0.34). In the control group, a poor test-retest reliability was also observed (ICC −0.13).

DISCUSSION

In the present study we investigated pain processing using QST in women with and without endometriosis. We observed

FIGURE 2



Pain sensitivity and patient characteristics. Electrical pain sensitivity for the patients with endometriosis in relation with the revised American Society for Reproductive Medicine (ASRM) classification and the clinical pain intensity. **(A)** Electrical pain detection threshold (ePDT) and the electrical pain tolerance threshold (ePTT) (mean with SEM) in relation with the revisedASRM severity stage. **(B)** ePDT and ePTT (mean with SEM) in relation with the clinical pain intensity, which is divided into a patient group suffering from mild pain and a group suffering from moderate-to-severe pain intensity.

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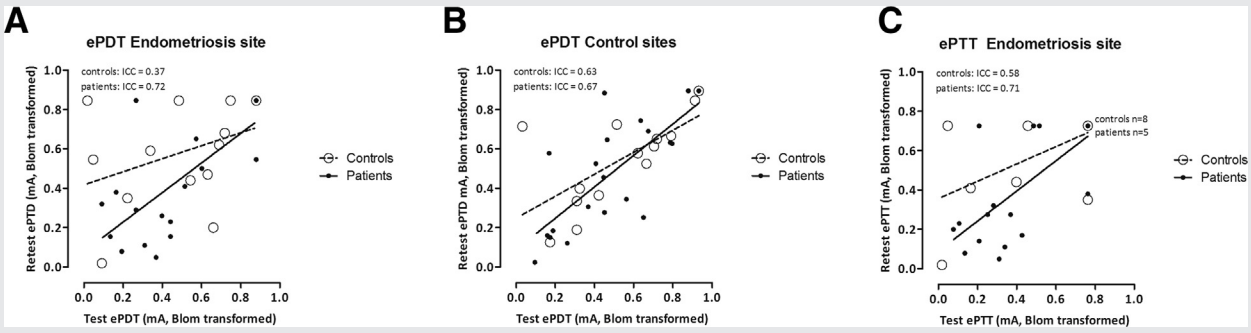
FIGURE 3



Test–retest reliability for electrical stimulation. The test–retest reliability for electrical stimulation in the endometriosis site and control sites are represented for patients (*black line*) and controls (*dotted line*). **(A)** Intraclass correlation for electrical pain thresholds in the endometriosis site, measured in milliamperes (mA). **(B)** Average intraclass correlation for electrical pain threshold in the control sites, measured in milliamperes (mA). **(C)** Intraclass correlation for electrical pain tolerance threshold in the endometriosis site, measured in milliamperes. *This data point depicts eight controls and five patients. ePDT = electrical pain detection threshold; ePTT = electrical pain tolerance threshold.

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a significantly decreased pain tolerance in the pelvic area of women with endometriosis, as these women showed a lower pain tolerance for the electrical stimulation on the endometriosis site when compared with the control sites and with healthy controls. In addition, we found a high test–retest reliability for electrical QST measurement on the endometriosis site with regard to pain detection and pain tolerance threshold, indicating that these findings are robust.

Our hypothesis was that patients with endometriosis process pain in a different way than women without chronic pelvic pain. In the present study, we used the noninvasive QST method. This is an extensive, standardized testing sequence to objectively quantify pain. Using this QST method, we found a decrease in pain tolerance in patients with different stages of endometriosis and different levels of pain intensity. This finding suggests alterations in pain processing mechanisms in women with endometriosis. These alterations start at a peripheral level and specifically in the endometriosis lesions, as lesions are capable of developing their own peripheral nerve fibers (4, 11–13, 51). These newly developed nerve fibers in the pelvic area are surrounded by PF. The PF from women with endometriosis contains high amounts of cytokines, chemokines, and growth factors. These are inflammatory agents that may cause the nerve endings to become activated and sensitized, thereby lowering the thresholds of action potentials of peripheral nerve fibers to fire nociceptive impulses (11, 12, 52). The pain hypersensitivity that consequently emerges can be measured as a sensitivity to pain for test stimuli and is referred to as regional hyperalgesia (11, 23, 53–56).

To our knowledge this study is the first to investigate test–retest reliability of pressure pain stimulation, and electrical pain stimulation in women with visceral pain due to endometriosis. We demonstrated that the reliability of ePDT and ePTT at the endometriosis site and the control sites was high in patients as well as in controls, indicating that QST using electrical stimulation is a reliable test for studying pain processing in endometriosis.

In contrast with the alterations in pain tolerance between patients and controls, as observed with QST, we did not see differences between patients and controls regarding the CPM. As is known from other chronic pain conditions, we expected to find dysfunction in the pain inhibition pathways in patients with endometriosis (23). However, our absence of CPM differences between patients and controls has been reported earlier (57, 58) and has been ascribed to a high interindividual variability. In addition, in the absence of a standard in CPM testing, there is no "normal range" to qualify the CPM effect, making it a difficult test to interpret (57). Another reason for caution is the presumed publication bias and the poor test–retest reliability of the CPM. Our poor test–retest CPM results are consistent with the findings of Olesen and co-workers (30) in patients with chronic pancreatitis. They explained their finding of poor CPM test–retest reliability as being a consequence of increased variability in a single CPM measure, as this measure is calculated based on two measures (before and after conditioned stimulus pain thresholds), each with their own variability. We have followed their suggestion to increase reliability by changing the test stimulus of pPTT to assess the CPM into the pPDT. Unfortunately, this change in protocol failed to increase our test–retest reliability in CPM.

We included patients from a multidisciplinary referral hospital with a variety in disease severity and pain intensity. All participants were treated with hormonal therapy and used analgesics if necessary. This design may have reduced pain symptoms and therefore have resulted in the absence of generalized hyperalgesia at a group level, because patients with mild pain symptoms are less likely to manifest generalized sensitization compared with patients with severe pain symptoms (59). This phenomenon is also shown by As-Sanie et al. (60), who observed that patients with endometriosis and severe chronic pelvic pain had lower pain thresholds compared with patients with endometriosis but without severe chronic pelvic pain. Other studies (61–63) on sensitization in endometriosis only included a specific

group of untreated women with severe pelvic pain. However, consistent with international guidelines, many patients with endometriosis are treated with hormonal therapy and/or pain killers (6, 34). We assumed that women with endometriosis using hormonal treatment and pain relief were the representative patient population. There is no difference in pain reduction depending on the type of hormonal treatment and therefore we accepted different hormonal regimens as long as they all suppressed the menstruation (6, 64, 65). In our opinion it is unjustifiable to refrain from giving women their hormonal or pain medication during participation in a study. In our patient population, we found no association between experimental pain sensitivity and clinical pain intensity or disease according to the revised ASRM stage. These results are consistent with previous studies (66, 67) in which pressure pain sensitivity was not related to the ASRM classification of endometriosis or the intensity of pain symptoms. In addition, in these studies (66, 68) it was observed that among all participants with pelvic pain, the presence of endometriosis or comorbid pain syndromes (e.g., interstitial cystitis) was not associated with pain sensitivity. These findings are in line with other chronic pain conditions, as experimental pain sensitivity in chronic pancreatitis, fibromyalgia, low back pain, and rheumatoid arthritis is not correlated with the clinical pain symptoms (67, 69). Altogether, these results imply that the chronic aspect of pain can trigger changes in neural processing and may help to clarify the absence of a relationship between disease severity and reported pain symptoms (17, 70). Consequently, we emphasize that treatment options targeting pain sensitivity (e.g., centrally acting drugs) could be beneficial for all patients with endometriosis. Because this affects all patients, we regard pain processing and sensitivity as an urgent research area.

With increased knowledge of the mechanisms underlying the pain of patients with endometriosis, opportunities are created to develop new treatments options to alleviate their pain. More emphasis might be given to administration of drugs targeting different components of pain processing such as the activation of the pain inhibiting pathways by the increase of serotonin (selective serotonin reuptake inhibitors). In addition, these drugs have a positive influence on the psychological aspects of pain perception, improving the patients' ability to deal with the pain (23, 53). Furthermore, centrally acting drugs, such as gabapentin or pregabaline, are already proven to be successful in the treatment of chronic pain (23, 53, 71, 72). These drugs increase the available amount of gamma aminobutyric acid, an inhibitory neurotransmitter that is known to contribute to the etiology of central sensitization when decreased (23, 53). The value of these and other centrally acting drugs in the (personalized) treatment of endometriosis could be promising and has been suggested by other investigators (11, 16). In addition, conservative treatment approaches, including transcutaneous electrical nerve stimulation, exercise therapy, pain education, and cognitive behavioral therapy, can be used to target (cognitive-emotional) sensitization (53, 73, 74). These latter two methods changes pain cognition (e.g., pain catastrophizing, anxiety, and hypervigilance) and consequently improves the quality of life in patients with sensitization pain (53). Previous research has already shown that patients with endometriosis suffer from a negative pain cognition that harmfully influences the quality of life independent of pain intensity (75). Besides, in other groups of patients with sensitization pain, this negative pain cognition also contributes to the sensitization by suppressing the descending pain inhibition pathways (53, 73, 76, 77). Changing these negative beliefs, together with exercise therapy, can enhance endogenous analgesia and therefore help to desensitize (53, 73). Still, international guidelines, such as the European Society of Human Reproduction and Embryology (ESHRE) and the ASRM, on management of endometriosis are mainly aimed at pharmacological and surgical treatment of endometriosis lesions (6, 78). Considering the growing body of evidence on sensitization in patients with endometriosis, we suggest that more attention should be paid on the pharmacological or conservative treatment, such as cognitive behavioral therapy, in the updates of these guidelines.

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La tolerancia al dolor experimental es disminuída e independiente de la intensidad del dolor clínico en pacientes con endometriosis

Objetivo: Investigar alteraciones en tacto, umbrales de dolor y umbrales de tolerancia al dolor en pacientes con endometriosis utilizando un enfoque multimodal.

Diseño: Estudio transversal.

Ámbito: Centro de referencia multidisciplinario.

Paciente(s): Mujeres con endometriosis probada (N=35) y controles sanos (N=38).

Intervención(es): El proceso de dolor fue testeado utilizando test sensorial cuantitativo (TSC) para investigar sensación, dolor y umbral de tolerancia al dolor para estímulo térmico, eléctrico y de presión.

Principal(es) variable(s) de resultado(s): Diferencias en las medidas de TSC en pacientes con endometriosis y controles sanos en el sitio de endometriosis y el sitio control, y la asociación entre los resultados de TSC y las características del paciente.

Resultado(s): Nosotros observamos una disminución significativa de la tolerancia al dolor en pacientes con endometriosis, independiente de la intensidad del dolor clínico o del estadío de la Sociedad Americana de Medicina Reproductiva revisado, comparado con controles sanos.

Conclusión(es): El aumento del conocimiento acerca de los mecanismos subyacentes del dolor de mujeres con endometriosis crea oportunidades para desarrollar nuevas opciones terapéuticas. Se debe prestar más atención no sólo a tratar la endometriosis en forma quirúrgica o farmacológica, sino también a desensibilizar por educación del dolor o terapia cognitiva.