CENTRAL SENSITIZATION IN VULVODYNIA AND ENDOMETRIOSIS: WHAT HAVE WE BEEN OVERLOOKING SO FAR?

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ABSTRACT

Importance: Women experience more frequent and greater pain than men, although they receive less adequate treatment and are perceived as more anxious than males. Recent clinical research has lead to hypothesize a common etiology for overlapping chronic pain conditions and mood disorders, namely central sensitization, which originates from an alteration of pain processing pathways in the central nervous system.

Objective: The aim of this review was to collect all available evidence regarding the potential role of central sensitization in vulvodynia and endometriosis.

Evidence Acquisition: A systematic literature search was performed between July and August 2022 using the electronic database PubMed. The extracted data was summarized using a narrative approach.

Results: Ten articles were chosen for the review. Participants' mean age was 39.2 years (SD = 5.1). Among serum markers of central sensitization, nitric oxide levels were greater in women with endometriosis than in controls, while brain-derived neurotrophic factor and S100B levels differed among pain conditions with structural anomalies and those without. Functional MRI showed different resting state networks between patients with endometriosis and controls. In neurophysiology studies, cases had reduced pain thresholds, compared to healthy controls. Lastly, self-reported questionnaires suggested a central component of pain in women with endometriosis-related dyspareunia and associated bladder/pelvic floor tenderness.

Conclusions and Relevance: The management of vulvodynia and endometriosis may benefit from a new perspective, which considers their possible central etiology. It is

compelling that treatment of pain starts to be considered a therapeutic goal in its own right.

Target Audience: Obstetricians and gynecologists, family physicians

Learning objectives:

After completing this activity, the learner should be better able to:

1. Describe central sensitization as a common etiology for vulvodynia and endometriosis. Have a better knowledge of central sensitization.
2. Explain how to investigate the presence of central sensitization with various techniques.
3. Identify the possible origin of vulvodynia and endometriosis pain.
4. Discuss the importance of considering treatment of pain as a therapeutic goal.

INTRODUCTION

Although chronic pain is the most prevalent health condition worldwide and it accounts for the highest number of years lived with disability, both patients and clinicians still find it hard to recognize it as a health condition in its own right (1, 2).

Often, health care providers find it challenging to consider patients as credible reporters of pain and resort to psychogenesis even in the presence of organic etiologic factors (3, 4). Patients may be led to questioning the existence of their pain, surrendering to the idea that it is merely attributable to psychological distress (2). These considerations are especially true for women. In fact, despite experiencing and reporting more frequent and greater pain than men, female patients receive less adequate treatment for their painful symptoms compared to their male counterparts (3, 5). This may be due to the fact that women are often perceived as anxious rather than in pain, although it is also true that in many cultures men are brought up to report hurt and distress less than women (3).

Despite this background, in recent years the scientific community has made a great effort to identify new, effective therapeutic options for gynecological pain conditions, although there have been no major breakthroughs. However, clinical research has lead to a re-thinking of neurophysiopathology and has included mood and pain disorders in a larger perspective. A third new category of pain transmission, which overcomes the dichotomy between nociceptive and neuropathic pain, namely nociplastic pain, has been introduced and a common etiology for overlapping chronic pain conditions has been hypothesized (6). The presence of chronic pain in one location has been found to more than double the risk of developing chronic pain in another location, suggesting an alteration in the functioning of pain processing pathways in the central nervous system (7). A new point of view which embraces other chronic pain conditions and focuses on the painful symptoms *per se* more than on the anatomical region in which the pain is perceived, namely central sensitization, may be the key we have been looking for.

Central sensitization is a physiopathological process by which neurons in the central nervous system develop an increased responsiveness to normal or sub-threshold afferent inputs. In particular, the secondary or projection neuron, that is the neuron whose nucleus is in the dorsal horn of the spinal cord and whose dendrites make synaptic contact with the primary somatosensory neuron, responds at a higher frequency to both nociceptive and non-nociceptive primary inputs, a phenomenon known as windup (5). This causes hyperalgesic and allodynic responses as well as an increase in the receptive field size. Moreover, a poor functioning of endogenous analgesic mechanisms has been reported in these patients (1, 5). It is still not clear whether this process starts from an abnormal conduction in the peripheral or in the central nervous system (8).

Vulvodynia and endometriosis are the two gynecological diseases included in the National Institutes of Heath Pain Consortium list of Chronic Overlapping Pain Conditions (COPCs) (7). These are a set of conditions, which often co-occur and appear to share common underlying mechanisms, above all central sensitization (7). The percentage of women with endometriosis also suffering from vulvodynia is as high as 15%, according to Hauser *et al* (9).

Various factors have been taken into consideration to support the hypothesis of a central, neurologic etiology for COPCs. Among these, neuroimaging studies have shown differences in resting-state connectivity and gray matter volume in sensory regions of the brain between patients with COPCs and healthy controls. Furthermore, these patients have presented altered serum concentrations of various bio-humoral markers and have reported an increased sensitivity to experimental stimuli in areas of the body not related to the COPC. Lastly, constitutional symptoms such as sleep disturbances, cognitive dysfunction and asthenia are common co-morbidities in patients with COPCs (7).

The aim of this review was to collect all available evidence regarding the potential role of central sensitization in vulvodynia and endometriosis.

METHODS

We carried out this narrative review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (10). The complete PRISMA checklist is provided in **Supplemental Table 1**. Not all items of the checklist were applicable to our review, as we summarized data using a qualitative approach.

A systematic literature search was performed between July and August 2022 using the electronic database PubMed. The last search was conducted on August 12th

2022). The search strategy included terms combined with the Boolean operators “OR” and “NOT”; the final string research was the following: vulvodynia OR vestibulodynia OR endometriosis AND (pain OR hyperalgesia OR nociplastic OR allodynia) AND "central sensitization" NOT (dysmenorrhea).

Non-original articles, abstracts, studies performed on animal models and papers not written in English were excluded. No time restrictions were applied.

Three authors (GEC, CEMM and CC) assessed the papers and independently selected the articles considered eligible for the review. Studies were included if they met the following criteria: reporting of original data, adoption of a clear definition of vulvodynia in accordance with the intersocieties document agreement (11) and/or adoption of a clinically and/or surgically and/or histologically confirmed diagnosis of endometriosis studies on human study populations. Reference lists were analyzed to identify additional studies meeting inclusion criteria. Discrepancies were resolved by discussion between the three abovementioned authors.

GEC and CEMM independently extracted data regarding authors, date and country of publication, study design and methods, number and mean age of enrolled patients, outcome measures, treatment and study results for each paper. Extracted information was organized in an Excel spreadsheet.

Due to the exiguous number of retrieved studies and the heterogeneity in outcome measures, the extracted data was summarized using a narrative approach, rather than a quantitative methodology. The analytic process consisted in reading and coding of all articles and in the subdivision of articles into four major categories on the basis of their prominent themes, i.e. “studies analyzing bio-humoral markers”, “neuroimaging studies”, “neurophysiology studies” and “studies based on validated questionnaires”

(12). The quality of the articles included in the review was evaluated using the modified version of the Newcastle-Ottawa quality assessment scale (13).

RESULTS

A total of 77 articles with publication dates included between 2003 and 2022 were initially identified. Among these, 26 were considered eligible for in-depth reading as 51 were excluded after screening of titles and abstracts. Reasons for exclusion were not being relevant (6 articles); not being original articles (21 articles), not being written in English (2 articles), not analyzing human subjects (22 articles).

Among the 26 articles eligible for in-depth reading, 16 were further excluded as they did not evaluate proper outcomes. Ten articles were chosen for the review (14-23). The flowchart of the selection process is represented in **Figure 1**.

Overall, 68 subjects with vulvodynia/provoked localized vulvodynia (PLVD), 348 with endometriosis, 283 with other chronic pain conditions (abdominal myofascial pain syndrome, osteoarthritis, fibromyalgia, tensional headache and irritable bowel disease) and 221 controls were included in the review. Participants' mean age was 39.2 years (SD = 5.1). Two studies were case series including patients with endometriosis or vulvodynia (13, 14), five studies included cases of endometriosis or vulvodynia and controls (16-20), while three case-control studies included other chronic pain conditions as well vulvodynia and endometriosis (21-23). Details regarding the included studies are reported in **Table 1**.

Studies analyzing bio-humoral markers

Two Brazilian research groups analyzed bio-humoral markers in subjects with chronic gynecological pain conditions (21, 23). Rocha and co-workers conducted a prospective study on a total of 60 women (25 healthy pain-free controls, 24 women with histologically-confirmed endometriosis and 16 with a clinical diagnosis of abdominal myofascial pain) (21). Four years later, Cadore Stefani and co-workers carried out a cross-sectional study on a broader population, which included 315 patients with chronic pain conditions (36 with endometriosis, 88 with osteoarthritis, 117 with fibromyalgia, 33 with tensional headache and 41 healthy controls) (23).

Study design and objectives

Rocha and co-workers studied the association of plasma nitric oxide (NO) levels with pain intensity and pain threshold in women with endometriosis and in women with abdominal myofascial pain syndrome and compared values with those of healthy controls. Blood samples were taken before and after treatment, which in patients with endometriosis consisted either in laparoscopic ablation and/or excision of superficial lesions or in cystectomy of endometriomas. Conversely, patients with abdominal myofascial pain syndrome received injections of 2mL 0.5% lidocaine directly to the trigger points during five weekly sessions (21).

In their study, Cadore Stefani *et al* analyzed serum concentrations of brain-derived neurotrophic factor (BDNF) and S100B, a calcium-binding protein, in women with chronic pain conditions, distinguishing between those with recognizable somatic or visceral structural anomalies (endometriosis, osteoarthritis) and those without (fibromyalgia, tensional headache) (23).

Serum bio-humoral markers

NO is a mediator and a regulator of the inflammatory response which plays a role in the modulation of nociception both at a peripheral and at a central level (22). Increased NO levels have been detected in the plasma of patients with chronic pain disorders. In these patients, the production of NO and/or prostaglandins has been associated to the activation of N-methyl-D-aspartate (NMDA) receptors in the spinal cord (22).

BDNF is a marker of neuronal activity and NMDA receptor-dependent neuronal plasticity. It is also a facilitator of long-term potentiation in regions involved in learning and memory, which may be related to the generation of pain memory. In humans, higher levels of BDNF have been found in patients with fibromyalgia, headache and myofascial pain and have been correlated with a decreased functioning of the central inhibitory system (23).

S100B is a calcium-binding protein, which has been associated with an up-regulation of Interleukin 1-beta, Tumor Necrosis Factor and nuclear factor kappa-light-chain-enhancer of activated B cells in microglia and astrocytes. In humans with fibromyalgia it has been associated with reduced pain thresholds (23).

Study results

Pretreatment NO levels were lower in controls (47 ±12.7) than in subjects with myofascial pain (64.2±5.0, $p=0.01$) or endometriosis (99.5±12.9, $p<0.0001$). Moreover, pain thresholds measured in body areas far from the genital area were significantly higher in controls (2.6±0.2) than in women with endometriosis (1.0±0.1, $p<0.0001$) or in those with myofascial syndrome (1.9±0.2, $p=0.007$). A reduction of plasma NO levels following treatment was observed in the endometriosis group (99.5±12.9 vs 61.6±5.9, $p=0.002$) but not in the myofascial group (64.2±5.0 vs

61.1±8.2, p=0.70). NO reduction in women with endometriosis was directly associated with an increase in pain threshold (21).

BDNF concentrations were increased in patients with fibromyalgia and chronic tension headache compared to endometriosis, osteoarthritis and healthy groups ($p<0.01$). Results were controlled for factors such as depression, pain levels, and use of analgesics (23).

Concentration of S100B were higher in patients with osteoarthritis and endometriosis ($p<0.01$), compared to patients without structural anomalies (23).

Neuroimaging studies

Only one study analyzed brain connectivity in patients with gynecological pain conditions using whole brain functional MRI (fMRI) (22).

Gupta and co-workers studied differences in sensorimotor, salience and default mode resting state networks in 87 premenopausal, naturally cycling women. Among these, 29 had a diagnosis of LPVD, 29 of irritable bowel syndrome (IBS) and 29 were healthy controls.

<u>Brain networks</u>

Gupta and coworkers analyzed three brain networks. The sensorimotor network, which receives sensory input from the periphery and is involved both in body sensation awareness and in the generation of appropriate motor responses; the salience network, which monitors the homeostatic state of the body and adjusts to real or expected disturbances through behavioral and autonomic responses, and lastly the default mode network, which plays a role in self-referential thinking and is engaged at rest (22).

Study results

As regards sensorimotor network connectivity, compared to IBS, LPVD patients showed greater connectivity of the bilateral supplementary motor area and of the primary motor cortex. Supplementary motor area connectivity was moderately correlated with the total muscle tenderness scores and to the intensity of pain not related to intercourse.

Within the salience network, a greater connectivity for the basal ganglia and the anterior mid-cingulate cortex was found in women with LPVD, compared to both women with IBS and healthy controls, and was associated with greater reports of vulvar pain ratings. These findings suggest greater impairments in LPVD patients' ability to appraise, process and respond to sensory information from the pelvis. Also, sub-regions of bilateral dorsal medial pre-frontal cortex (PFC) showed less connectivity with the salience network in the LPVD group, compared to the two other groups. This finding was moderately correlated with pain not related to intercourse in LPVD. The medial PFC plays a prominent role in cortico-limbic inhibition providing inhibitory input in the amygdala and anterior insula and may also play a role in the cortical input to descending pain modulation.

Regarding default mode network connectivity, greater connectivity of known attentional regions was observed in women with LPVD compared to those with IBS and healthy controls. Also, reduced connectivity for the dorsal/ventral posterior cingulate cortex was observed. This was correlated with increased pain duration in LPVD and with increased vaginal muscle tenderness scores. The functional correlates of these findings remain unknown (22).

Neurophysiology studies

The majority of neurophysiology studies included in this review were based on quantitative sensory testing (QST) (14, 17-20). This is a procedure used for testing myelinated and unmyelinated sensory nerves which involves stimulating the patient with quantified sensory stimuli and determining thresholds for sensory perception, based on the patient's response (25).

Both Bajaj and He's groups compared women with endometriosis with controls. Study populations were organized as follows: 10 cases and 10 controls in Bajaj *et al's* manuscript (16), 100 cases and 70 controls in He *et al's* (18). Conversely, Foster, Zhang and Basha's groups compared women with vulvodynia with controls. Study populations comprised of ten cases and ten controls (17), 12 cases and 20 controls (19) and 17 cases and 16 controls (20), respectively. Napadow and co-workers only included 15 women with endometriosis in their study (14).

<u>Somatosensory evaluation</u>

Bajaj and co-workers evaluated pain intensity, somatic hyperalgesia, and the entity of referred pain areas in response to induced muscle pain both within (low back) and outside (dorsal interosseous muscle of the hand, FDI) areas of menstrual pain referral. Pain was induced with an intradermal injection of hypertonic saline and was recorded independently for each site on an electronic visual analogue scale. Pressure pain threshold (PPT) and tactile threshold (TT) were also determined on abdomen, back, thigh, arm and FDI before and after saline injection (16).

Similarly, Foster *et al* performed intradermal injections of either 10μg capsaicin or 0.9% saline placebo in peripheral skin areas, far from the vulva (17). Capsaicin is an inflammatory substance which binds to the vanilloid receptor VR-1,

initiating nociceptive C-fiber activity, thus causing enhanced cutaneous sensitivity (punctate hyperalgesia and dynamic allodynia). Spontaneous pain was measured with a visual analogue thermometer (VAT), while punctate hyperalgesia was evaluated using von Frey hairs and dynamic allodynia with a calibrated spring apparatus.

Both He and Napadow's groups evaluated women's somatosensory profile on peripheral areas, far from the genital area, before and after treatment (14, 18). While He *et al* studied sensory and pain thresholds as well as ischemic pain intensity before and after surgical excision of endometriotic lesions (18), Napadow *et al* analyzed responses to both evoked tonic deep tissue mechanical stimuli and repeated mechanical stimuli that produce windup before and after respiratory-gated auricular vagal afferent nerve stimulation (RAVANS) or non-vagal auricular stimulation (NVAS), an active control procedure (14). RAVANS is a non-invasive form of transcutaneous stimulation of the auricular branch of the vagal nerve, which is synchronized to the respiratory cycle. Respiration, in fact, cyclically modulates the activity of both input and output vagal brainstem regions. Previous studies on vagus nerve stimulation (VNS) have demonstrated its anti-nociceptive effects, as well as its effect on raising pain thresholds and on mitigating the wind-up phenomenon following mechanical stimuli. Additionally, fMRI studies have demonstrated that VNS modulates limbic brain regions, inducing positive effects on mood (14).

Zhang and co-workers used vibrotactile stimulation on the right hand to evaluate vibrotactile detection threshold, amplitude discrimination capacity (i.e. the ability to detect differences in the intensity of two stimuli delivered simultaneously to two different fingers) and adaptation (i.e., the impact of a conditioning stimulus on amplitude discriminating capacity) (19).

Lastly, Basha *et al* used evoked mechanical and thermal stimuli to evaluate pain thresholds, both in the vulva and in the forearm (20).

Study results

In Bajaj and co-workers' study, women with endometriosis experienced significantly more intense pain ($p<0.01$) and larger pain areas ($p<0.05$) than controls after injection of hypertonic saline in non-referral areas. Conversely, no differences were found when the solution was injected in referral areas (lower back). Patients with endometriosis showed a decreased PTT compared to controls both in menstrual pain referral areas and in non-referral areas, not only before ($p=0.02$) but also after saline injection ($p=0.01$). However, TT was not significantly different between cases and controls, neither in referral nor in non-referral areas (16).

In their randomized, double-blinded, cross-over trial, Foster and co-workers found a greater post-capsaicin pain response among women with vulvodynia for measures of spontaneous pain ($p<0.005$), punctate hyperalgesia post-injection ($p<0.005$) and dynamic allodynia post-injection ($p<0.005$). No differences were found for placebo. No correlation between pain measures and anxiety was found (17).

When comparing pain intensity and sensory and pain thresholds, He *et al* found that the excision of endometriotic lesions significantly improved dysmenorrhea intensity ($p<2.5 \times 10^{-11}$), ischemic pain intensity in body areas far from the pelvic area ($p<1.6 \times 10^{-14}$) and pain threshold ($p=4.6 \times 10^{-8}$). No difference in the sensory threshold was observed between cases and controls ($p=0.17$). It must be pointed out that mean VAS scores for dysmenorrhea in cases was 4.24 at baseline (SD ±3.07), just above what is considered as mild pain (18).

In Zhang *et al's* study, women with vulvodynia had a tendency to report lower tactile thresholds compared to controls, although the difference was not statistically significant. When dividing women in two subgroups according to the duration of their pain, those who had experienced pain the longest showed a significantly reduced impact of adaptation due to conditioning stimuli on the sensory percept (3% versus 30%, $p<0.01$) (19).

As regards Napadow and co-workers' results on the use of RAVANS, pain intensity in response to tonic deep tissue mechanical stimulation was reduced from baseline to each following time point in both the RAVANS and the NVAS group ($p<0.05$), although the reduction was greater following RAVANS (the difference was not statistically significant). Significant changes in wind-up from baseline values were observed only during RAVANS ($p=0.05$). Endometriosis-related pain ratings did not differ between RAVANS and NVAS sessions, as was expected, given that chronic pain was assessed after a single 30-minute treatment. Anxiety was reduced during and following RAVANS stimulation compared to baseline ($p<0.01$), while no change in anxiety was detected during or following NVAS sessions ($p>0.3$). Also, treatment-associated changes in anxiety and in pain responses were largely independent (14).

In conclusion, Basha *et al* found that thermal detection thresholds were similar between patients and controls, while left forearm cold and heat pain thresholds were significantly lower in the PLVD group ($p<0.01$), as compared to controls. Regarding the vestibule, pain thresholds for cold and for heat were significantly lower on the right emi-vulva ($p<0.05$) in the PLVD group. Pressure pain thresholds were approximately 2-fold lower on both sides of the vestibule, compared to controls (20).

Studies based on validated questionnaires

In their cross-sectional analysis, Orr *et al* enrolled 163 women with a clinical or surgical diagnosis of endometriosis, and phenotyped them into three subgroups: those with high deep dyspareunia (HDD) and bladder/pelvic floor tenderness (BPFT), in whom a central component of pain was hypothesized; those with HDD and no BPFT and those with low or absent dyspareunia (15).

All patients were asked to complete the Central Sensitization Inventory (CSI), which is a self-reported validated questionnaire that assesses the severity of symptoms associated with central sensitization. CSI scores were compared among the three abovementioned groups.

Study results

Women with HDD and BPFT had significantly higher CSI scores than those with HDPP and no BPFT ($p<0.001$) and than those with no or low dyspareunia ($p<0.001$). Women with HDD and no BPFT had significantly higher CSI scores than women with no or low dyspareunia ($p=0.028$). No differences in CSI scores were observed when comparing women with BPFT but no or low deep dyspareunia with women without BPFT. When stratifying patients according to depressive symptoms, participants with HDD and moderate to severe depression had higher CSI scores.

DISCUSSION

Pain is a complex perception, which results from the processing of sensory-discriminative stimuli, affective and emotional components, cognitive factors and previous experience (5).

Although the role of the central nervous system in the elaboration of pain has long been demonstrated, clinicians often misinterpret this aspect as a psychological origin of pain (3).

According to the 2020 ACOG practice bulletin on chronic pelvic pain, criteria for major depression are met in approximately 12-33% of women living with chronic pelvic pain (26). Numerous other studies have shown that chronic pelvic pain is more prevalent in women with a history of childhood physical abuse (OR 4.3; 95% CI, 1.8-10.4), sexual abuse (OR 4; 95% CI 1.8-8.8) and verbal or emotional abuse (OR 3.2; 95% CI 1.5-6.8), compared with pain-free controls (27). However, when interpreting this data on the basis of the results of several large prospective studies which show how pain predisposes to the development of mood disorders to a much greater degree than the reverse, pain appears to be much more complex process than a mere manifestation of psychological distress (7).

Based on this evidence, an increasing number of research groups have started analyzing the potential role of central sensitization in vulvodynia and endometriosis. Speculations as to why not all women with endometriosis suffer from chronic pain and as to why women with vulvodynia report pain in the absence of objective etiological factors have included numerous hypotheses. Among these, the existence of a central “memory” of pain, which is sustained by an overactive transmission of sensory stimuli and by a deficient central inhibitory system, has been suggested.

In half of the neurophysiology studies included in this review, cases were found to have similar sensory thresholds but reduced pain thresholds, when compared to healthy controls (16, 18, 20), both in disease-specific pain-referral areas and in non-referral areas (16, 20). This piece of evidence suggests two important considerations. Firstly, the nerve transmission of sensory stimuli appears to be intact among these

patients, thus implying an abnormal functioning of pain fibers only. Secondly, the presence of an increased sensitivity to pain stimuli in sites distant from the genital or pelvic regions leads to hypothesize the existence of central anomalies as well as peripheral ones.

As regards hyperalgesia, allodynia and increased receptive field size, which are considered neurophysiological markers of central sensitization, both Bajaj *et al* and Foster *et al* found greater pain responses in cases when compared to healthy controls and to placebo (16, 17). However, it must be noted that while the former study group used normal saline injections as painful stimuli, the latter group used normal saline as a placebo. A further important result is that obtained by Foster's group, which found no correlation between pain measures and anxiety, thus reducing the potential study bias linked to hypervigilance, which is the tendency to anticipate painful stimuli, thereby causing a lower pain threshold (16, 17).

Among the three studies analyzing the effects of therapeutic interventions on markers of central sensitization, Napadow *et al* observed significant changes in wind-up following vagal nerve stimulation, while He and co-workers found a reduction in provoked ischemic pain and pain threshold after surgical treatment of endometriosis (14). Conversely, in Rocha *et al's* study post-treatment NO levels were reduced in the endometriosis group but not in the myofascial pain group (21). Moreover, NO reduction in women with endometriosis was directly associated with an increase in pain threshold. Rocha's results may be explained by the fact that while endometriosis was treated with surgical removal of the lesions (sources of pro-inflammatory and nociceptive molecules), myofascial pain was treated conservatively.

Cadore Stefani also evaluated the concentration of bio-humoral markers in patients with chronic pain conditions, although a major limitation of the study is

represented by the fact that the analyzed markers are not specific for central senstitization syndromes, as they have been also found in psychiatric disorders and conditions of inflammation and trauma (23).

The only study in which patients affected by the same condition, i.e. endometriosis, were stratified according to the presence or absence of painful symptoms was Orr *et al's* (15). Distinguishing between symptomatic and asymptomatic patients with endometriosis in clinical trials may indeed be fundamental to widen our knowledge about pain mechanisms in COPCs and the interrelatedness of mind and body in these conditions. In fact, although a significant body of medical literature has started to support the existence of a psycho-biological process whereby an increased sensitivity to external stimuli is combined with hyper-reactivity of the nervous system and a reduced efficacy of the central inhibitory system, the *primum movens* of this vicious circle is yet to be identified. What is known to date is that this vicious cycle is often preceded by trauma, inflammation or excessive stress, which can dysregulate the limbic system, causing catastrophic misinterpretation, selective attention, fear-based conditioning and sensitization (8, 28). This data, together with the evidence that patients with COPCs often report a history of early life stressors and/or past or present mood disorders, should lead clinicians to address these patients' psychological comorbidities as an integral part of their treatment. In conclusion, the introduction in clinical practice of self-reported screening tools such as the Central Sensitization Inventory, may aid health care professionals in the recognition of the presence of CS and, consequently, in the categorization, the severity identification and the treatment planning of these patients (29).

CONCLUSIONS

The management of vulvodynia and endometriosis may benefit from a new perspective, which includes these conditions among the COPCs. It is compelling that treatment of pain starts to be considered a therapeutic goal in its own right and that women with central sensitization receive multidisciplinary care, including psychotherapy for the treatment of comorbid mood disorders, when present, independently from the fact that these are a cause or a consequence of their pain condition. However, it should be pointed out that considering the role played by psychological factors in people's subjective pain experience does not mean disqualifying pain symptoms as exaggerated, or unreal ("it is all in your head"). Given the connection between mind and body, assessing psychological issues – such as for instance mood disorders, psychological traumas, and pain catastrophizing – should be routinely included in multidisciplinary clinical practice with individuals suffering from COPCs.

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Figure 1: flowchart of the selection process

Table (in MS Word, each table saved and uploaded as a separate file)

Table 1: table of inclusion of the selected studies

Author, year	**Country**	**Study design**	**Number patients**	**Diagnosis (vvd, lpvd,endometriosis)**	**Study outcome**	**Outcome measure (questionnaires)**	**Mean age**	**Treatment**	**Results**	**Quality of study**
Bajaj, 2003	Denmark	Prospective study	20	Endometriosis and healthy controls	Primary outcome: evaluation of somatic hyperalgesia and the extension of pain areas in response to saline-induced muscle pain within and outside areas of menstrual pain (hand and low back) in patients with endometriosis compared to healthy controls. Secondary outcomes: evaluation of pressure pain and touch threshold in patients with endometriosis compared to healthy controls	Pain intensity was recorded on an electronic visual analogue scale (VAS). Quality of pain was evaluated with the McGill Pain Questionnaire (MPQ). Pain areas were evaluated using anatomic maps. Pressure pain threshold (PPT) was measured using a hand-held electronic alogmeter. Touch threshold (TT) was evaluated using von Frey hairs.	33.9	NA	The endometriosis group experienced significantly more intense pain than controls after injection of hypertonic saline in the hand ($p<0.01$). No differences were found when the solution was injected in the back. Pain areas after injection of hypertonic saline into the hand were larger for the endometriosis group compared to controls for both dorsal pain and palmar pain ($p<0.05$). Patients with endometriosis showed a decreased PPT compared to controls both in menstrual pain referral areas (abdomen and low back) and in nonreferral areas (upper arm, mid-thigh, hand), not only before ($p=0.02$) but also after saline injection ($p=0.01$). Patient with endometriosis did not show significant differences compared to controls for the TT at referral and nonreferral areas.	7
Foster, 2005	USA	Randomized, double-blind, two-session cross over trial	20	Vulvodynia and healthy controls	Evaluation of spontaneous pain, punctate hyperalgesia and dynamic allodynia before and after intradermal injection of 10µg capsaicin or of 0.9% saline placebo in women with vulvodynia and controls.	Spontaneous pain was measured with a visual analogue thermometer (VAT); punctate hyperalgesia with von Frey hairs; dynamic allodynia using a calibrated spring wire apparatus; cutaneous blood flow was measured by a laser diode probe; the sensory	31.8	NA	Post-capsaicin pain response was greater in VVD cases for measures of spontaneous pain ($p<0.005$), punctate hyperalgesia of the forearm and foot 10 minutes post-injection ($p<0.005$) and dynamic allodynia of the forearm 10 minutes post-injection ($p<0.005$). Placebo failed to statistically differ for measures of spontaneous pain, punctate hyperalgesia and dynamic allodynia in cases and controls.	6

Author, year	Country	Study design	Number patients	Diagnosis (vvd, lpvd,endometriosis)	Study outcome	Outcome measure (questionnaires)	Mean age	Treatment	Results	Quality of study
						and affective components of pain were evaluated by the means of the Brief Symptom Inventory of Derogatis and Melisaratos (BSI).				
He, 2010	China	Prospective study	170	Endometriosis and healthy controls	Evaluation of sensory threshold, pain threshold and ischemic pain intensity in patients with endometriosis before and after surgical excision of lesions (3 and 6 months after surgery), compared to healthy controls.	Sensory threshold and pain threshold were evaluated using PainMatcher. Ischemic pain intensity was rated using the Visual Analog Scale (VAS) and the short-form McGill Pain Questionnaire (MPQ). Dysmenorrhea severity was quantified using a Visual Analog Scale (VAS) and a 4-point Verbal Descriptor Scale (VDS).	33.9	Laparoscopic or laparotomic excision of all visible endometriotic lesions. 60% of patients also received hormonal treatment with gonadotropin-releasing hormone (GnRH) agonists, progestins or combined hormonal contraceptives for 3 months following surgery.	No difference was found for the sensory threshold ($p=0.17$). A significant difference in ischemic pain intensity and pain threshold was found between cases and controls ($p<0.002$). Surgery significantly improved dysmenorrhea intensity ($p<2.5$ x10^-11), ischemic pain intensity ($p<1.6 \times 10^{-14}$) and pain threshold ($p=4.6 \times 10^{-8}$).	6
Zhang, 2011	USA	Prospective study	32	Vulvodynia and healthy controls	Comparison of vibrotactile detection threshold on the fingertip, amplitude discrimination capacity and determination of the impact of conditioning stimuli on the amplitude discrimination capacity between women with	Pain intensity was determined by a portable 4-site vibrotactile stimulator. Stimulation of varying frequencies were measured in Hertz (Hz) and amplitudes in micrometers. There were two sessions: the experimental one and	not reported	NA	Patients with vulvodynia demonstrated a tendency to have lower tactile thresholds than controls although the difference was not statistically significant. The difference in amplitude discriminative capacity was not statistically significant. When patients with vulvodynia were divided in two subgroups according to the duration of their pain, those who had experienced pain the longest had a significantly	7

Author, year	Country	Study design	Number patients	Diagnosis (vvd, lpvd,endometriosis)	Study outcome	Outcome measure (questionnaires)	Mean age	Treatment	Results	Quality of study
					vulvodynia and healthy controls.	the sensory testing session that assessed: (1) vibrotactile detection threshold on the fingertip measured using a 20-trial 2 Alternative Forced Choice (2AFC) tracking protocol; (2) amplitude discrimination capacity assessed using a 2AFC tracking protocol; and (3) the impact of conditioning stimuli on amplitude discrimination capacity.			reduced impact of adaptation due to conditioning stimuli on the sensory percept (3% vs 30%, $p<0.01$).	
Napadow, 2012	USA	Pilot, crossover study	15	Endometriosis	Primary outcomes: modification of pain responses such as tonic deep tissue mechanical stimuli, repeated mechanical stimuli that produce windup and diffuse noxious inhibitory controls (DNIC) before and after respiratory-gated auricular vagal afferent nerve stimulation (RAVANS) or non-vagal auricular stimulation (NVAS). Secondary outcomes: clinical pain raitings and verbal ratings of anxiety before and	Pain intensity was measured with a 0-100 verbal pain intensity scale. Clinical pain ratings were measured on a 0-10 scale. Anxiety was measured on a 0-100 verbal anxiety scale.	36.3	Respiratory-gated afferent auricular vagal afferent nerve stimulation (RAVANS)	Pain intensity in response to tonic deep tissue mechanical pain was reduced from baseline to each following time point for both RAVANS and NVAS ($p<0.05$); the reduction was greater following RAVANS although the difference was not statistically significant. Significant changes in wind-up from baseline values were observed only during the RAVANS stimulation ($p=0.05$). A DNIC effect was not observed in these patients. Clinical pain ratings did not differ between RAVANS and NVAS sessions. Anxiety was reduced during or following RAVANS stimulation compared to baseline anxiety rates ($p<0.01$), while there was no change in anxiety rates during or	6

Author, year	Country	Study design	Number patients	Diagnosis (vvd, lpvd,endometriosis)	Study outcome	Outcome measure (questionnaires)	Mean age	Treatment	Results	Quality of study
					after RAVANS/NVAS.				following NVAS sessions compared to baseline (p>0.3).	
Rocha, 2015	Brazil	Prospective study	65	Endometriosis, abdominal myofascial pain syndrome and healthy controls	Measurement of plasma NO levels before and after treatment, evaluation of the association of plasma NO levels with pain intensity and pain threshold	Pain intensity was evaluated with a VAS score Pain threshold was assessed with an Instrutherm DD-500 pressure algometer on the thenar region of the nondominant hand.	33.7	Endometriosis group: electrosurgical ablation and/or excision of superficial lesions and/or cystectomy of endometriomas. Abdominal myofascial pain syndrome group: 2mL injections of 0.5% lidocaine directly on the trigger point (5 weekly sessions).	Pretreatment NO levels were lower in controls (47 ±12.7) than in the myofascial (64.2±5.0, p=0.01) or endometriosis groups (99.5±12.9, p<0.0001). Pain thresholds of controls were significantly higher (2.6±0.2) than those of women with endometriosis (1.0±0.1, p<0.0001) or myofascial syndrome (1.9±0.2, p=0.007). There was a reduction of plasma NO levels after treatment in the endometriosis group (99.5±12.9 vs 61.6±5.9, p=0.002) but not in the myofascial group (64.2±5.0 vs 61.1±8.2, p=0.70).	7
Gupta, 2015	USA	Prospective study	87	Localized provoked vestibulodynia, irritable bowel syndrome, healthy controls	To determine whether the intrinsic connectivity of regions comprising the sensimotor, salience and default mode networks are different in women with LPVD, compared to those with IBS and healthy controls. The secondary outcome was to evaluate whether the differences in the intrinsic connectivity at rest are associated with key symptoms of LPVD.	Pain intensity, duration and level of unpleasantness were evaluated using the Gracely Differential Descriptor Pain Scale (GDDPS). Provoked vulvar pain was evaluated on a 0-50 point scale, which was created by adding the pain scores from 0 to 10 of five different vestibule sites. Vaginal muscle tenderness was evaluated with a 0-50 score, created by adding pain scores	30.3	NA	Compared to IBS, LPVD patients showed greater connectivity of the bilateral supplementary motor area and primary motor cortex with the sensorimotor network, even after controlling for affect. Supplementary motor area connectivity was moderately correlated with the total muscle tenderness scores and pain not related to intercourse. Compared to both HCs and IBS subjects, greater connectivity within the salience network for basal ganglia and anterior mid-cingulate cortex was found in LPVD subjects. The connectivity was associated with greater reports of total vulvar pain and highest daily pain ratings. Also, subregions of bilateral dorsal medial pre-frontal cortex (PFC) showed less	6

Author, year	Country	Study design	Number patients	Diagnosis (vvd, lpvd,endometriosis)	Study outcome	Outcome measure (questionnaires)	Mean age	Treatment	Results	Quality of study
						(0-10) for 5 different muscle sites. Levels of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). Childhood traumatic life events were evaluated by the means of the Early Traumatic Inventory. Pain catastrophizing was rated with the Pain Catastrophizing scale. Whole brain functional resonance imaging (fMRI) data was acquired using a 3.0 T MRI scanner, resting state scans were acquired.			connectivity with the salience network when LPVD was compared to the two other groups. This was moderately correlated with pain not related to intercourse in LPVD. Greater connectivity of medial and lateral parietal regions with the default mode network was observed for LPVD compared to HCs and IBS, as well as a reduced connectivity for the dorsal/ventral posterior cingulate cortex. This was correlated with increased pain duration in LPVD and with increased total vaginal muscle tenderness scores.	
Basha et al, 2019	U.S.A.	Cross-sectional study	33	Localized Provoked vulvodynia and healthy controls	Comparison of the somatosensory profile of women with PLVD and controls, analyzing pain thresholds to thermal and mechanical stimuli both in the vestibule and in the forearm.	PHQ-9 (semistandardized questionnaire on patient health which analyzes demographics, clinical characteristics and visual analogue scales for genital pain with sexual intercourse and with daily activity).	32.7	NA	Forearm pressure pain threshold tended to be lower in the LPVD group although the difference wasn't significant, instead left forearm cold and heat pain thresholds were significantly lower in the LPVD group ($p<0.01$) compared to controls. Regarding the vestibule, pain thresholds for cold were significantly lower on right ($p<0.01$) and left ($p<0.05$) in the LPVD group, the same was	6

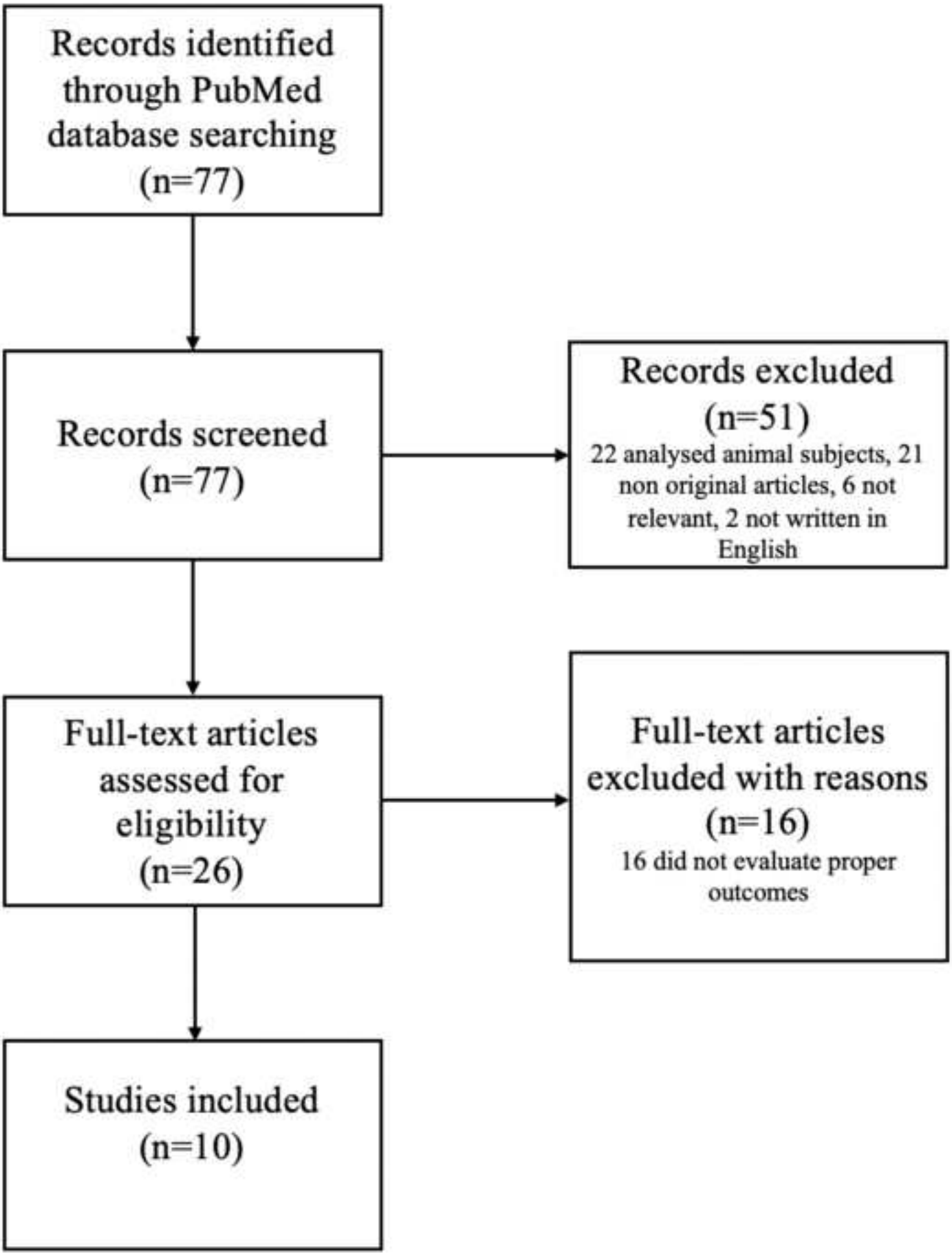
Author, year	Country	Study design	Number patients	Diagnosis (vvd, lpvd,endometriosis)	Study outcome	Outcome measure (questionnaires)	Mean age	Treatment	Results	Quality of study
									observed for heat pain threshold on the right side ($p<0.05$). Pressure pain thresholds were approximately 2-fold lower on both sides of the vestibule compared to controls.	
Cadore Stefani et al, 2019	Brazil	Cross-sectional study	315	Endometriosis, osteoarthritis, fibromyalgia, tensional headache and controls	BDNF and S100B serum concentrations in patients with chronic pain syndromes	Hamilton Depressing Rating Scale(HDRS) and Beck Depression Inventory (BDI)for depressive symptoms	media ponderata 48,80	NA	BDNF concentrations were increased in patients with fibromyalgia and chronic tension headache compared to endometriosis, osteoarthritis and healthy groups ($p<0.01$). Concentration of S100B were higher in patients with osteoarthritis and endometriosis ($p<0.01$) compared to patients without structural anomalies.	7
Orr et al, 2020	Canada	Cross-sectional study	163	Surgical or clinical diagnosis of endometriosis	Difference in CSI scores among three different groups of patients: 1) women with high deep dyspareunia and BPFT 2) women with high deep dyspareunia without BPFT 3) women with no or low deep dyspareunia	-CSI for central sensitization evaluation - PHQ-9 for the evaluation of patient health status	36.4	NA	Women with HDD and BPFT had significantly higher CSI scores than those with HDPP and no BPFT ($p<0.001$) and those with no or low dyspareunia ($p<0.001$). It was also higher in those with BPFT than in those without BPFT ($p<0.001$). Women with HDD and no BPFT also had significantly higher CSI scores than women with no or low dyspareunia ($p=0.028$). No difference in CSI scores was observed when comparing those with no or low deep dyspareunia and BPFT and those without. When stratifying patients according to the depression symptom questionnaire (PHQ-9), participants with HDD and moderate to severe depression had higher CSI scores.	6

Author, year	Country	Study design	Number patients	Diagnosis (vvd, lpvd,endometriosis)	Study outcome	Outcome measure (questionnaires)	Mean age	Treatment	Results	Quality of study

LIST OF ABBREVIATIONS:

BDI: Beck Depression Inventory; BPFT: Bladder or Pelvic Floor Tenderness; BSI: Brief Symptom Inventory of Derogatis and Melisaratos; CSI: Central Sensitization Inventory; DNIC: Diffuse Noxious Inhibitory Controls; fMRI: Functional Magnetic Resonance Imaging; GDDPS: Gracely Differential Descriptor Pain Scale; HADS:Hospital Anxiety and Depression Scale; HC: Healthy Control; HDD: High Deep Dyspareunia; HDRS: Hamilton Depressing Rating Scale; IBS: Irritable Bowel Syndrome; LPVD: Localized Provoked Vulvodynia; MPQ: McGill Pain Questionnaire; N/LDD: No or Low Deep Dyspareunia; NA: Not Applicable; NVAS: Non-Vagal Auricular Stimulation; PFC: Pre-Frontal Cortex; PHQ-9:Patient Health Questionnaire; PPT: Pressure Pain Threshold; RAVANS: Respiratory-gated Afferent Auricular Vagal Afferent Nerve Stimulation; TT: Touch Threshold; VAS: Visual Analogic Scale; VAT: Visual Analogue Thermometer; VDS:Verbal Descriptor Scale; VVD: Vulvodynia; 2AFC:2 Alternative Forced Choice.

Figure 1


Records identified through PubMed database searching (n=77)
Records screened (n=77)
Records excluded (n=51)
22 analysed animal subjects, 21 non original articles, 6 not relevant, 2 not written in English
Full-text articles assessed for eligibility (n=26)
Full-text articles excluded with reasons (n=16)
16 did not evaluate proper outcomes
Studies included (n=10)