Chapter

Nociplastic Pain in Gynecology: Understanding This Painful Experience in Women

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Abstract

The term "nociplastic pain" was introduced in 2017 by the International Association for the Study of Pain (IASP) to describe pain that results from impaired nociception despite no clear evidence of actual or potential tissue damage causing activation of peripheral nociceptors or evidence of disease or lesion of the somatosensory system causing the pain. It is a definition born from the need to recognize early the presence of central sensitization of the nervous system in patients with chronic pain; we can find ourselves in the co-presence of nociceptive or neuropathic pain and nociplastic pain. In gynecological pathology, nociplastic pain plays an important role characterizing some important pathologies that can be associated with chronic pelvic pain in women. It is essential to understand the mechanisms of pathogenesis and maintenance of nociplastic pain in order to undertake a multidisciplinary path for the treatment of these patients.

Keywords: pain, gynecology, vulvar pain, pelvic chronic pain, nociplastic pain

1. Introduction

The term "nociplastic pain" was introduced in 2017 by the International Association for the Study of Pain (IASP) to describe pain that results from impaired nociception despite no clear evidence of actual or potential tissue damage causing activation of peripheral nociceptors or evidence of disease or lesion of the somatosensory system causing the pain. The term was first proposed in 2016, as a mechanistic descriptor for chronic pain states not characterized by obvious activation of nociceptors or neuropathy, but in whom clinical and psychophysical findings suggest altered nociceptive function [1]. Nociplastic pain refers to a physiologically based category that is particularly applicable to chronic primary pain conditions outlined in the new International Classification of Diseases, 11th edition, published by WHO.

The IASP has subdivided chronic primary pain conditions into the following five categories [2]:

1. chronic widespread pain;

2. complex regional pain syndrome;

3. chronic primary headache and orofacial pain;

4. chronic primary visceral pain;

5. chronic primary musculoskeletal pain.

Nociplastic pain can be mechanistically defined as pain arising from the altered function of pain-related sensory pathways in the periphery and central nervous system, causing increased sensitivity. It can occur in isolation or as a comorbidity in individuals with chronic pain conditions that are primarily nociceptive or neuropathic. Nociplastic pain is often associated with other symptoms, such as fatigue, sleep, memory, and mood problems, leading experts to propose expansive terminology to include the term "syndrome," namely nociplastic pain syndrome. Caring for patients with nociplastic pain is challenging; the pain complaint is often difficult to describe. There are associated subjective symptoms and pathognomonic clinical findings, or biomarkers are absent. Nociplastic pain conditions are frustrating for both healthcare professionals and patients, with physicians uncertain regarding diagnosis and patients resentful that their symptoms are doubted [3].

2. Physiopathologic mechanisms of nociplastic pain

Nociplastic pain is a phenotypic expression of multifactorial processes. It represents a dynamic interplay of various mechanisms causing or amplifying pain, arising de novo or triggered by pain generators. It originates from different inputs, which could be either a bottom-up response to a peripheral nociceptive or a neuropathic trigger, or a top-down central nervous system-driven response [4].

The mechanistic common denominator of nociplastic pain is the amplified processing of and/or decreased inhibition of pain stimuli at multiple levels in the nervous system. The amplified processing of a noxious stimulus is called "wind-up" and it occurs, for example, when there is an enhanced spinal neuron response after C-fiber or, less commonly, A-δ stimulation [5]. Diminished descending modulation, instead, might manifest as hyperalgesia—increased pain in response to painful stimuli—and allodynia—pain in response to normally nonpainful stimuli [6].

There are probably numerous initiating routes that lead to a final common pathway of the amplification of nociceptive perception, transduction, and transmission, and a lot of these mechanisms have yet to be discovered [7].

When a traumatic noxious stimulus occurs, pain hypersensitivity can arise, mediated by both peripheral and central nervous system changes. This phenomenon is called "central sensitization," and it is strictly associated with chronic pain such as fibromyalgia, irritable bowel syndrome (IBS), and interstitial cystitis [8]. The involvement of central nervous system and the widespread of pain signals is the reason why these diseases are often characterized by an emotive component and symptoms such as fatigue, sleep, mood alterations, and memory difficulties, and sensitivity to non-nociceptive sensory stimuli such as light and sound.

Central sensitization is the phenomenon by which a neural signaling undergoes an amplification in the central nervous system that spurs pain hypersensitivity outside the primary area of tissue injury or damage. It represents the major underlying

mechanism of nociplastic pain syndrome [9]. Chronic pain can often be found in the absence of a peripheral pathology or because of a discrepancy between the tissue damage and the magnitude of the resulting pain and disability [10].

Behind this process, there are mechanisms of central sensitization, which consist of altered sensory processing in the brain, malfunctioning of descending pain inhibitory mechanisms, increased activity of pain facilitatory pathways, and temporal summation of second pain or wind-up [11]. When a noxious stimulus occurs, there is an activation of peripheral C-fibers axons with the transmission of the signal to the spinal cord and the central nervous system. This mechanism causing a "first pain," that is the immediate painful sensation, and a "second pain," that is a painful sensation that starts a few seconds after and lasts longer, even when the stimulus ceases. Low-frequency repetitive stimulation of unmyelinated C-fibers is called "wind-up." The "wind-up" occurs when dorsal spinal horn neurons receive stimulations with a frequency higher or equal to 0.33 Hz [12]. This process results in a progressive increase of pain intensity when noxious stimulation remains constant or disappears: a phenomenon called temporal summation of "second pain" [13]. Neziri et al. showed how spinal cord hypersensitivity and temporal summation second pain are greater in patients with chronic pelvic pain than controls. They used spinal withdrawal reflex to assess the extension of receptive fields in patients with endometriosis and chronic pelvic pain and patients without a pain syndrome, showing larger fields and lower threshold to induce pain in patients with chronic pelvic pain [14].

Involvement of the central nervous system has also been demonstrated in voxel-based morphology studies, showing changes in gray matter density and volume in patients having chronic pelvic pain. Studies reported greater decreases in gray matter volume in regions of the pain system including thalamus, cingulate cortex, putamen, insular cortex, and areas involved in pain modulation, such as the prefrontal cortex. Regional increase in gray matter volume was found in right inferior and middle frontal gyrus, left amygdala, and mesencephalon, which are all pain modulatory-related areas [15].

Both top-down and bottom-up mechanisms play an important role in the pathophysiology of nociplastic pain, and accumulating evidence suggests that it is also driven by neuroinflammation in the peripheral and central nervous system. For example, peripheral injury or other stressors trigger the release of proinflammatory cytokines, with the consequent activation of spinal cord glia with cyclooxygenase-2 and prostaglandin E2 expression in the central nervous system [16]. Neuroinflammation is a form of inflammation that occurs in both the peripheral and central nervous systems, characterized by four features: vasculature changes that result in increased vascular permeability, infiltration of leukocytes and macrophages, activation of glial cells, and production of inflammatory mediators [17].

Pain was one of the four cardinal signs of inflammation, as recorded by Celso in the first century AD. As previously mentioned, peripheral axons of nociceptors carry the painful stimulus into the dorsal root ganglia and then into the spinal cord. They are pseudounipolar neurons with their distal axonal branches innervating a peripheral organ and their proximal axonal branches innervating the dorsal horn of the spinal cord. The repetitive stimulation of these fibers not only provokes a sensory hypersensitivity, but also the release of neuropeptides which increase inflammatory processes, such as calcitonin gene-related peptide (CGRP) and substance P (SP). These peptides are released from both the distal and proximal axons. The last one innervates the dorsal horn of the spinal cord, where afferent neurons of other peripheral organs arrive. The cross-activation of afferent neurons coming from other tissues that are not primarily damaged causes a release of neuropeptides

Spinal mechanisms	Supraspinal mechanisms	Peripheral features
• Regional clustering and convergence of signals from different pain loci • Spinal cord reorganization • Amplified spinal reflex transmission • Diminished spinal inhibition • Wind-up and temporal summation • Glial cell activation	• Hyper-responsiveness to pain stimuli • Hyperactivity and connectivity in and between brain regions involved in pain • Decreased activity of brain regions involved in pain inhibition (e.g., descending inhibitory pathways) • Elevated cerebrospinal fluid substance P and glutamate concentrations, decreased GABAergic transmission • Changes in the size and shape of gray and white matter regions involved in pain processing • Glial cell activation	• Minor local muscle pathology • Peripheral sensitization (e.g., expansion of receptivefields, elevated cytokine, and chemokine concentrations) • Hyperalgesia, dysesthesia, and allodynia • Localized or diffuse tenderness, or both

Ref. [3].

Table 1.
Mechanisms of nociplastic pain.

into the uninjured peripheral organs, provoking neurogenic inflammation and diffuse pain [18]. That is the reason why in chronic pain syndromes there are often viscero-visceral and viscero-somatic sensitization, for example, colon-to-bladder cross-sensitization in patients affected by irritable bowel syndrome [19]. A recent review summarizes a list of chemicals that are released from the soma of neurons within dorsal root ganglia in inflammatory and visceral sensitization processes (ATP, CGRP, SP, glutamate, GABA, galanine, NO, and BDNF) [20]. Soma of nociceptors in ganglia do not contract synapses with each other, but they are connected by satellite glial cells (SGCs). The nearness between neurons and SGCs implements a paracrine mechanism, according to which SGCs are stimulated by neuropeptides (e.g., BDNF that binds TrkB on the surface of the glia) and in response, they produce "gliotransmitters" (e.g., interleukines, NO, and TNF-alpha) that are sent back to the neurons. Pseudounipolar neurons also produce colony stimulating factor-1 (CSF-1) that attracts and spurs proliferation of macrophages in the nearby axons [21]. Macrophages produce proinflammatory factors. The persistent upregulation of production of proinflammatory factors is a crucial mediator in the development of chronic pain syndromes (**Table 1**).

3. Nociplastic pain in gynecology

In gynecological pathology, nociplastic pain plays an important role characterizing some important pathologies that can be associated with chronic pelvic pain in women. It is essential to better understand the basis of these kinds of conditions and to undertake a multidisciplinary path for the treatment of these patients.

Chronic pelvic pain is estimated to affect 26% of the world's female population [22].

Chronic pelvic pain is a pain that originates from the pelvis, noncyclic or cyclic or related to menstruation (dysmenorrhea) and intercourse (dyspareunia), typically lasting more than 6 months. It is often associated with negative cognitive, behavioral, sexual, and emotional consequences and symptoms suggestive of lower urinary tract, sexual, bowel, myofascial, or gynecologic dysfunction. The 6-month cut-off is not a

requirement if central sensitization pain and nociplastic mechanisms (with cognitive, behavioral, and emotional impairment) are documented [23].

There is an interconnection between visceral and somatic structures in the female pelvis, known as viscero-visceral cross-sensitization, in which activity in one organ (e.g., uterus) can hypersensitize another organ (e.g., bowel or bladder). Cross-sensitization among pelvic structures may contribute to chronic pelvic pain of unknown etiology and involves convergent neural pathways of noxious stimulus transmission from two or more organs. Besides the viscera, somatic areas may also be involved. Given enough time, trigger points can develop in peripheral somatic tissue in response to increased nociceptive visceral input: This is called viscero-somatic sensitization [24]. Persistent input from malfunctioning pelvic muscles, injury, or surgery can lead to visceral dysfunction characterized by bowel symptoms such as constipation and bladder symptoms such as urgency, frequency, and incomplete emptying. The viscero-visceral cross-sensitization can enhance nociplastic pain mechanisms by amplifying central nervous system responsiveness and decreasing pain inhibition descending pathways, resulting in overall pain hypersensitivity and central sensitization presenting as widespread pain (outside the pelvic area), sleep disturbance, and deterioration in mood and coping [25, 26].

3.1 Fibromyalgia

An example of a chronic pain condition, which represents a struggle for gynecologists because it often occurs in a female population, is fibromyalgia. According to the latest guidelines elaborated by Fibromyalgia Working Group members, fibromyalgia is defined as a chronic pain disorder: In other words, all patients would be required to have chronic pain to be diagnosed with fibromyalgia. Fibromyalgia was defined as a "widespread" pain syndrome, and it is still counted in this category according to the IASP. The American College of Rheumatology (ACR) redefined the diagnostic criteria in 2010 by renaming it as a "multisite" pain syndrome [27]. In fact, when a patient has pain in a self-reported number of sites distributed throughout the body, including joint sites, this is sufficient for defining fibromyalgia. The number of pain sites needed to define "multisite" pain in fibromyalgia is found to be ≥8. Furthermore, fibromyalgia is associated with sleep disturbance, fatigue, and other cognitive and somatic features that are now considered core symptoms of this condition [28].

3.2 Vulvodynia

Although no epidemiological study of prevalence has been carried out worldwide, it is estimated that vulvodynia affects 8–10% of women of all ages [29]. Vulvodynia is defined as vulvar pain lasting at least 3 months, without a clear identifiable cause, which may have potential associated factors that contribute to the development and perpetuation of this clinical condition [30]. These associated factors include (i) psychosocial factors, such as anxiety, depression, posttraumatic stress, and sexual problems; (ii) chronic pain conditions in the pelvic area, such as urological or coloproctological pain syndromes or irritable bowel syndrome; and (iii) chronic pain conditions in other areas of the body, such as fibromyalgia [31]. It suggests that there could be the same neurophysiological substrate underlying these chronic pain syndromes. Vulvodynia has been always defined as a neuropathic pain due to its burning nature and because of the hypersensitivity of the vulvar mucosa. This can be justified by a greater nerve fiber proliferation in the vulvar vestibule; indeed, some studies

have found an increase in the density of C nociceptor endings [32]. However, it is reductive because of all the associated factors known.

Changes derived from central sensitization such as hyperalgesia and allodynia have been demonstrated in vulvodynia not only in the perineal area but also in distant regions of the body [33]. Central sensitization involves abnormal long-term potentiation that can begin after physical precipitating events such as recurrent vulvovaginal candidiasis, lower urinary tract infections, or dermatologic pathology.

Then, we can conclude that vulvodynia is thus considered to be one of the nociplastic pain syndromes, characterized by nociceptive/inflammatory pain, neuropathic pain, and dysfunctional pain, in the absence of clinically evident pathology [34].

Regarding the therapeutic approach of vulvodynia, a stepwise method of pelvic floor dysfunction treatment, adequate psychological support, and sexual healthcare is recommended along with medical therapies [35]. Intermittent use of topical lidocaine cream may be useful for women with intense vestibular touch pain, prior to sexual intercourse [36].

Other pharmaceutical strategies are oral or topical NSAIDs, amitriptyline and other tricyclic antidepressants, hydrocortisone, vulvar interferon, anticonvulsants – such as gabapentin, botulinum neurotoxin injection, antifungal, or combined approach [37].

3.3 Painful bladder syndrome (PBS) and interstitial cystitis (IC)

In women, symptoms of interstitial cystitis are difficult to distinguish from those of painful bladder syndrome and they appear to overlap with those of urinary tract infection, chronic urethral syndrome, overactive bladder, vulvodynia, and endometriosis [38].

In terms of symptoms, the two conditions can be superimposable; the differential diagnosis with other pathologies such as endometriosis, vulvodynia, overactive bladder can be very complex, although identifying interstitial cystitis and painful bladder syndrome in women with more than one of these diseases may be difficult.

Interstitial cystitis is nowadays associated with painful bladder syndrome and not distinguished. It can be categorized into two major subtypes, mainly based on the bladder histological findings. The first type or "classical" interstitial cystitis presents itself with Hunner's lesions: mucosal lesions accompanied by abnormal capillary structures. The second type presents itself without Hunner's lesions, has no obvious bladder etiology, and is most frequently accompanied by common systemic comorbidities or chronic pelvic pain with symptoms that involve other pelvic structures [39].

The etiology and pathophysiology remain uncertain with many different hypotheses proposed over the years, including injury of the bladder epithelium and increased barrier permeability, neurogenic inflammation with mast cell infiltration without a bacterial infection, autoimmune involvement [40].

Painful bladder syndrome is a disease that affects the bladder and manifests itself with persistent pain and difficulty urinating. This syndrome can be counted among the causes of nociplastic pain in women.

Painful bladder syndrome was defined by the European Society for the Study of Bladder Pain Syndrome/Interstitial Cystitis (ESSIC) as a chronic (>6 months) pelvic pain, feeling of pressure or discomfort perceived to be related to the urinary bladder, with at least one other urinary symptom such as persistent voiding urgency or frequency [41].

The precise cause of painful bladder syndrome is still unknown, but it is believed to be the result of a combination of factors, such as inflammation of the bladder, increased nerve sensitivity, and immune system dysfunction.

Painful bladder syndrome urinary symptoms can vary from person to person, but the most common include the following:

- Pain in the pelvic area and bladder, which may be constant or intermittent;
- Urgency to urinate frequently, even when the bladder is not full;
- Pain when urinating;
- Feeling of burning or pressure in the bladder;
- Difficulty urinating or holding urine.

Diagnosing painful bladder syndrome can be difficult as symptoms can be similar to those of other urinary disorders.

Treatment of painful bladder syndrome can include a combination of therapies, such as pain medications, physical therapies, dietary modifications, and behavioral therapies.

The European Association of Urology (EAU) proposed a stepwise approach for treatment of interstitial cystitis/bladder painful syndrome which consists of [42]:

- First-line therapy: education, physiotherapy, behavioral modification (e.g., bladder training), psychological therapies for stress modulation;
- Second-line therapy: pharmacotherapy: pentosan polysulfate sodium, low-dose tricyclic antidepressants, antispasmodics;
- Third-line therapy: intravesical injections with local anesthetic, dimethyl sulfoxide or heparin, or intradetrusor botulinum toxin A injection;
- Fourth-line therapy: neuromodulation (e.g., percutaneous tibial nerve stimulation).

In some cases, surgery may be required only when all conservative treatments have failed [43].

3.4 Irritable bowel disease (IBD)

Irritable bowel disease is defined by Rome IV Criteria as pain on at least 1 day per week in the last 3 months associated with two or more of the following symptoms: abdominal pain; change in stool frequency; change in stool appearance; variations of defecation with predominant constipation (IBS-C) or with predominant diarrhea (IBS-D) or with mixed bowel habits (IBS-M if the patient refers >25% constipation and > 25% diarrhea; IBS-U if the patient refers <25% constipation and < 25% diarrhea). The onset of symptoms has to be at least 6 months before diagnosis. Diagnosis is clinical and based on these criteria [44].

In irritable bowel syndrome, motility disturbance is associated with sensory hypersensitivity, altered mucosa and gut microbiota, local and systemic immune system dysfunction, and impaired central nervous system processing (with central and viscero-visceral sensitization). Moreover, irritable bowel syndrome has been

associated with high prevalence of psychological disorders and significantly higher anxiety and depression levels than the general population [45].

Initiation of treatment of IBS should start with identifying the severity and predominant symptoms of the disorder. According to NICE guidelines first-line treatment consists of dietary and lifestyle modification, even exercise can be beneficial. If lifestyle advice is not effective, pharmacological therapy can be practiced and based on severity. Psychological interventions are useful, moreover, if not responsive to pharmacological treatments after 12 months. NICE discourages use of acupuncture and reflexology [46].

4. Conclusions

The traditional conceptualization of chronic pain syndromes has been historically dualistic either as a result of organic-physical mechanisms or as psychological mechanisms. Despite the advances in the understanding of idiopathic pain and the recognition of neuroplastic changes as the cause of chronic and complex pain conditions, multiple pathophysiological mechanisms are still unclear. Nociplastic pain is an important substrate of many gynecological and nongynecological chronic pain syndromes. That is why a multidisciplinary approach is needed. Moreover, these conditions are due to somatic or visceral noxious agents interacting with psychosocial, epigenetic, and emotional factors. In order to manage these patients, our aims for the future is to better understand pathognomonic clinical findings or biomarkers of nociplastic pain syndromes, and to implement the multidisciplinary team work, not only with specialists from the various branches of medicine but also with a psychological support for our patients.

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