

Does biological sex influence the mechanisms, assessment and treatment of pain? Disproportions in modern pain medicine



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There are clear biological differences in the anatomy and functioning of nociception systems in humans depending on their biological sex. At the same time, despite the growing understanding of sex-related differences in pain perception and modulation in humans and mammals, much preclinical research still fails to address biological sex as an important variable, and even less has addressed sex differences in pain in humans.

Women constitute over 60% of adults suffering from chronic pain [1]. It is estimated that in Poland there are over 5.1 million women who suffer from chronic pain of various intensity and etiology, with approximately 1/5 of them stating that they would not be able to tolerate stronger pain [1]. The female sex is mentioned among the risk factors for chronic pain, along with a patient's older age and living in a rural area [2]. The biological mechanisms underlying significant sex differences in pain perception between men and women depend primarily on the influence of sex hormones during adolescence, when the neuroplasticity of the nervous system is high. Sex hormones can influence pain perception in humans in a variety of ways [3] as follows:

- altering pain sensitivity by affecting pain control pathways, mainly by affecting descending antinociceptive pathways,
- influence on biological processes related to pain (e.g. inflammation),
- influence on hormone-dependent pathologies (e.g. endometriosis),
- effects on mood, which may affect the perception of pain.

Evidence supporting the influence of the menstrual cycle on sensitivity to noxious stimuli in healthy women is equivocal, with most well-designed studies suggesting at most a modest effect [4]. Estrogens are key pain-

reducing hormones in higher concentrations because they activate inhibitory pathways in the spinal cord, but have the opposite effect on pain in lower concentration.

It has been observed that a higher level of estrogens in women reduces the risk of musculoskeletal pain or chronic post-traumatic pain [5, 6]. Experimental studies have revealed differences in the analgesic effects of estrogens, also depending on the pain model – pain intensity in the inflammatory and visceral model, neuroprotective effect in models of neuropathic pain [7]. Stability of estrogens levels plays a greater role in nociception in women, which translates into better pain control, and fluctuations in estrogens levels have a pro-pain effect, as exemplified by headache episodes associated with the menstrual cycle [8]. Progesterone appears to be a pain-intensifying hormone, although pregnancy is associated with decreased pain sensitivity (“pregnancy-induced analgesia”) This effect is particularly pronounced in studies on animal models and less pronounced in observations in women [9]. Testosterone reduces the severity of pain in both men and women. This may be due to its activating effect on descending antinociceptive pathways, increasing the expression of opioid and cannabinoid receptors [3]. Testosterone modulates the functions of numerous receptors involved in nociception (e.g. TRPV1) and reduces the severity of neurogenic inflammation by reducing the production of pro-inflammatory cytokines such as tumor necrosis factor [10]. Although hormones are commonly used to treat gynecological pain (period pain, pain associated with endometriosis/adenomyosis), it is well known that they can also cause headaches, migraines, vulvar and joint pain. The natural reduction in hormone levels observed during perimenopause and postmenopause is also associated with a change in the nature of pain. These relationships are complex; some pains subside during this time, while

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Received: 20.06.2020 **Accepted:** 21.06.2024

Table I. Mechanisms underlying nociception influencing the clinical picture of pain in women

Mechanisms underlying nociception in women
1. Greater sensitivity to various pain stimuli was observed in women in experimental models in healthy volunteers, although the literature data are ambiguous and the differences between women and men were only moderate
2. Higher intensity of temporal summation in women after repetitive pain stimuli, which is interpreted as facilitating the afferent noxious input, but at the same time, a higher degree of adaptation and habituation in relation to a given stimulus was observed in women
3. Lower activity of pain-inhibiting systems
4. Less intense placebo effect in women
5. Higher intensity of the nocebo effect in women
6. Women describe their pain as stronger, more extensive and longer lasting compared to the description of the same stimulus given to men
7. Women more often use emotional descriptions of pain, which in practice means that men describe pain mainly quantitatively, while women describe it qualitatively

others worsen, and some begin in women who have not previously suffered from pain [11].

The female sex predisposes to pain syndromes characteristic of women: pain associated with pregnancy, childbirth, postpartum, dysmenorrhea, endometriosis, and headaches associated with the menstrual cycle. Up to 90% of girls may experience discomfort and/or pain related to menstruation, and this may be an important risk factor for chronic pain later in their life [11]. Scientific evidence from experimental studies supports the existence of sex-specific differences in the molecular mechanisms underlying the development and control of pain, including:

- dimorphism relating to the role of immunocompetent cells and inflammatory pathways in the development of pain at the peripheral, spinal, and supraspinal levels [12],
- activation of microglia at the spinal level, purinergic receptors and the brain-derived nerve factor pathway are more important in the development of inflammatory and neuropathic pain in males [13],
- the influx of T cells is more important in the mechanisms of chronic pain in females, and the key hormone that regulates this is testosterone [13],
- hypersensitivity to topically administered calcitonin gene-related peptide (CGRP) occurs only in female mice and does not occur in male mice, and drugs acting on CGRP in the treatment of migraine work much better in women than in men [14].

The biological mechanisms underlying nociception influencing the clinical picture of pain experiences in women are listed in Table I [11, 15].

However, the still existing disproportions regarding sex and pain perception biases constitute a significant problem in modern pain medicine, which may lead to discriminatory actions [11]. A sex bias may influence communication regarding pain assessment and treatment decisions in clinical practice. The study by Zhang et al. [16] showed that the intensity of pain in women

was underestimated by observers compared to men, although the subjects reported the same subjective pain intensity. Observers also believed that women would benefit more from psychotherapy than from pharmacological treatments for pain relief. A review of research from 2000 to 2015 found that, compared to men, women are more likely to have to fight to have their pain seen as legitimate in clinical settings [17]. Their pain is perceived as more psychogenic, and rated as unreliable depending on their appearance (e.g. they look too good or don't look good enough) [17]. In the case of acute pain, women in emergency departments were statistically significantly less likely to receive analgesic treatment, waited longer for an analgesic to be administered, and were less likely to receive opioids compared to men reporting the same pain complaints [18]. Similar observations were made with regard to postoperative pain, with women reporting higher postoperative pain intensity than men but receiving lower doses of analgesics than men in more than half of the studies reviewed [19]. Women treated for chronic pain receive more referrals for psychological treatment, less opioid analgesics and more antidepressants compared to men in the same clinical setting [17].

Conclusions

Experimental and clinical studies indicate that there are significant differences in the perception of pain depending on biological sex, which is important in the diagnosis and treatment of pain. However, existing and relatively well-known biological differences cannot translate into prejudices, stereotypes and symptoms of discrimination against women in relation to the assessment and underestimation of pain intensity, neglect of the treatment of pain syndromes characteristic of women, for example dysmenorrhea or childbirth pain, and inadequate treatment of acute and chronic pain syndromes. The first step to counteracting sex bias is

to raise awareness of sex differences in clinical practice and at the level of society.

Disclosures

Conflict of interest: The author declares no conflict of interest.

Funding: No external funding.

Ethics approval: Not applicable.

Data availability: Not applicable.

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