Opinion

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Menstruation pulls the trigger for inflammation and pain in endometriosis

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Endometriosis is a chronic, hormone-dependent, inflammatory disease, characterized by the presence and growth of endometrial tissue outside the uterine cavity. It affects 5–10% of the female population of reproductive age and is frequently associated with moderate to severe pain, subfertility, and a marked reduction in health-related quality of life. Here, we propose a new pathophysiological concept of endometriosis, summarizing recent findings in one unifying picture. We propose menstruating tissue as the trigger for inflammatory pain in endometriosis through the activation of innate immune cells and peripheral nerve endings. We speculate how innovative treatment modalities beyond hormonal treatment will improve patients' lives.

The burden of endometriosis

Endometriosis is defined as the presence of uterine stroma and glands outside the uterine cavity. It is one of the most frequent disorders of the female reproductive tract, affecting approximately 5–10% of women of reproductive age and represents a significant disease burden [1–3]. Key symptoms are: (i) abdominal pain in different forms, such as chronic pelvic pain (CPP), dysmenorrhea (see Glossary), dyspareunia, or dyschezia (Box 1); and (ii) subfertility. More than 50% of patients have these symptoms, which impact their relationships, their work, and their health-related quality of life [1–3]. Bleeding disorders, such as short cycle length, heavier menstruation, and longer flow duration, are also frequently observed and known as risk factors [4,5]. Endometriosis symptoms are also difficult for patients to handle because there is an average delay of 6.7 years between disease onset and final diagnosis [5,6]. The burden of endometriosis has also significant economic consequences with healthcare expenses and costs due to productivity loss similar to those of other chronic diseases, such as diabetes, Crohn's disease, or rheumatoid arthritis [3].

The pathophysiology of the disease is incompletely understood. The risk of developing endometriosis is greater in women with increased quantity of menstruation due to abnormal uterine bleeding [7–10]. Furthermore, the biology of eutopic endometrium is different in women with endometriosis compared with controls [11,12], which probably is a consequence of the development of endometriosis according to preliminary evidence in baboons [13]. Among the different hypotheses, Sampson's theory of retrograde menstruation is the most widely accepted [14]. During menstruation, menstrual debris travels not only anterogradely to the vagina, but also in a retrograde manner through the fallopian tube into the peritoneal cavity [14]. Additional sources of tissue debris are endometriotic lesions, which have been observed to bleed during menstruation [15,16]. Here, we introduce the term 'extra-uterine menstruation' to combine bleeding endometriotic lesions and retrograde transfer of tissue from uterine menstruation (retrograde menstruation). However, retrograde menstruation occurs in most women, while only a minority develops the disease. This implies additional causative factors, such as genetic susceptibility, autoimmunity, or anomalies in the inflammatory response [8,17–19]. As an example, genetic susceptibility factors have been identified in genome-wide association studies, although these currently cannot fully explain the disease in affected women [20].

Endometriosis has features of a hormone-dependent disease, because its symptoms are usually restricted to the reproductive period and are responsive to hormonal treatment (Figure 1A). Sex hormones might influence the disease through their proliferative, pro-nociceptive, and proinflammatory effects [1,21,22]. However, beyond hormonal aspects, extra-uterine menstruation, inflammation, and peripheral nerve endings have a major role in the pathophysiology of the disease (Figure 1B,C). Recent reviews focused on the interaction of immune cells and sensory nerves in the generation of endometriotic pain

Glossary

Abnormal uterine bleeding: bleeding from the uterine corpus that is abnormal in duration, volume, regularity, and/or frequency.
Deep infiltrating endometriosis: infiltration of endometriotic lesion into any given structure to a depth of at least 5 mm (e.g., uterosacral ligaments, rectum, rectovaginal septum, vagina, or urinary tract).
Dyschezia: painful defecation.
Dysmenorrhea: pain associated with menstruation.
Dyspareunia: painful sexual intercourse due to a medical condition.
Nociception: neural process of encoding noxious stimuli.
Nociceptive neurons: central or peripheral neurons of the somatosensory nervous system that are capable of encoding noxious stimuli.
Progestin: natural or synthetic substance having progesterone-like activity.

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Box 1. Pain in endometriosis

Endometriosis-associated pain, the main symptom of the disease, is heterogeneous and complex. The most common symptoms are dysmenorrhea, dyspareunia, and CPP. Two types of pain perception system can be involved, depending on the localization of the lesions in the pelvic cavity. Somatic pain comes from the stimulation of the sensory nerves present in the skin or deep tissues, such as the parietal peritoneum [91]. In opposition, pain arising from internal organs, such as the uterus, bladder, or rectum, is called visceral pain [92]. The mechanisms underlying the generation of pain are divided in two main categories, nociceptive and neuropathic pain [93]. It is under debate which of these is predominant in endometriosis [23]. Importantly, the involved pathophysiological mechanisms differ and, consequently, the therapeutic strategies are not the same [93,94]. Neuropathic pain is a pathologic condition caused by a lesion or a disease of the somatosensory nervous system that leads to an altered neural processing [95,96]. Nociceptive pain arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptive neurons. When nociceptive pain is associated with inflammation, it is called inflammatory pain [95,97]. Peripheral sensitization of nociceptive neurons can occur in both, leading to an increased responsiveness to noxious (hyperalgesia) and innocuous (allodynia) stimuli.

Both neuropathic and inflammatory pain are often cited in the context of endometriosis-associated pain [98]. In contrast to what is often claimed in the endometriosis field, we believe that neuropathic pain aspects are not in general representative of the pathophysiology underlying pain in the disease. Central sensitization is described in women with endometriosis-associated pain, and this is often used as an argument for neuropathic pain. In these patients, an increased excitability of the CNS to normal and/or innocuous stimuli leads to increased pain hypersensitivity and larger referred pain areas [98,99]. However, central sensitization can arise in the context of both neuropathic and inflammatory pain, and occurs in several inflammatory-driven painful diseases, such as migraine and irritable bowel syndrome [100]. The neurotrophic properties of endometriotic lesions are also often used as argument for neuropathic pain in endometriosis, but they are also strongly related to inflammatory pain mechanisms, especially through NGF [101,102]. Finally, the positive effect of the surgical removal of endometriotic lesions on pain symptoms undermines that neuropathic pain mechanisms are key in endometriosis [103]. Nevertheless, surgically induced neuropathic pain occurs in 10–40% of patients following general surgery [104]. It may also be one of the causes of recurring pain following laparoscopic surgery in the absence of detectable lesions [105,106].

To summarize, endometriosis is a sterile inflammatory disease within the peritoneal cavity and, as described here, there is abundant evidence suggesting that endometriotic pain originates, to a large extent, from inflammation.

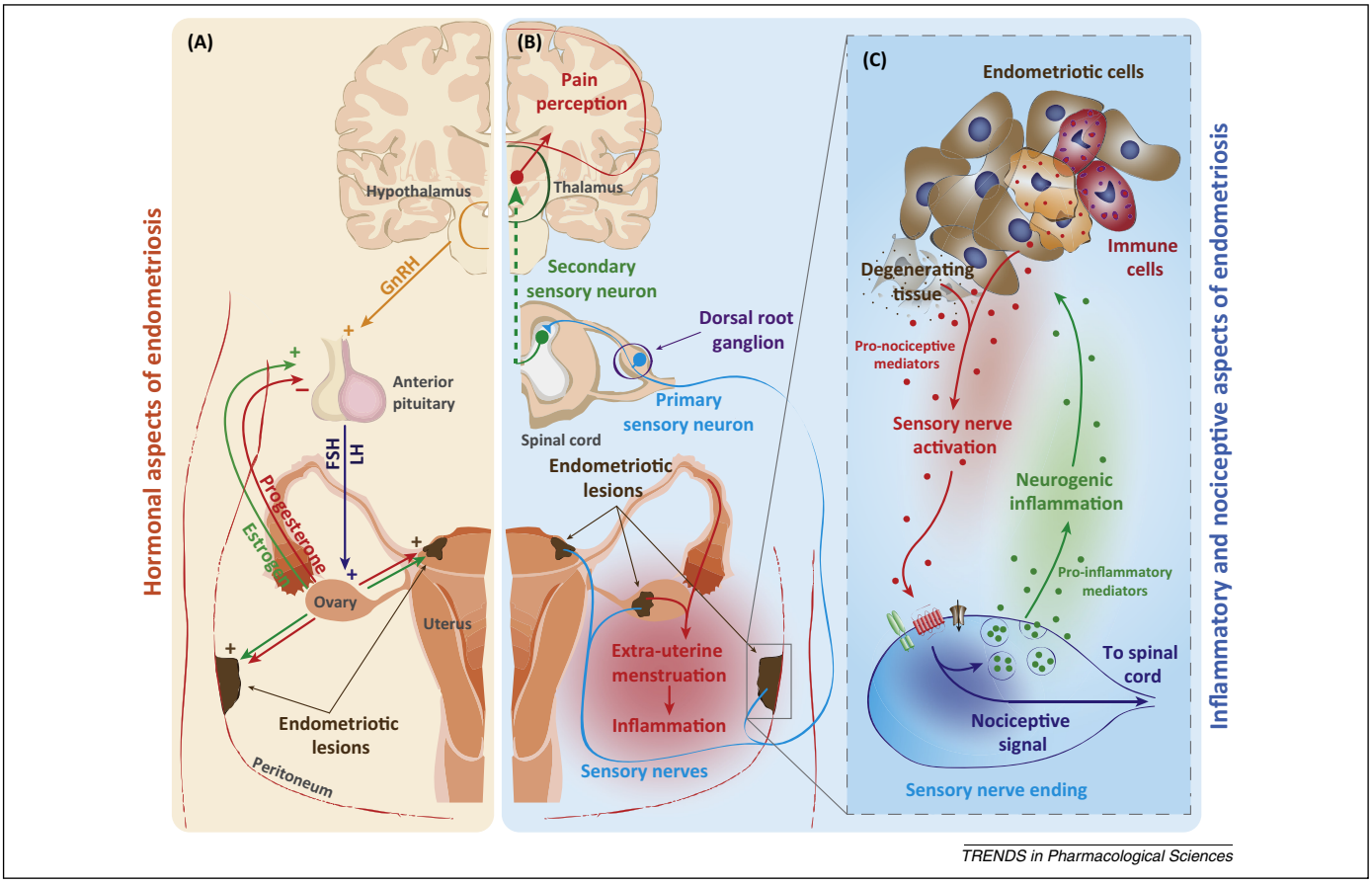

Figure 1. Schematic representation of the complex pathophysiology of endometriosis. Endometriosis is a complex, multifactorial disease. In this figure, hormonal aspects **(A)** are opposed to inflammatory and nociceptive components **(B,C)**. Endometriosis is a hormone-dependent disease characterized by the presence and growth of endometrial tissue in various locations of the pelvic cavity, such as the peritoneal wall and ovaries. Its symptoms are modulated by sex hormones (e.g., estrogen and progesterone). Sex hormones are under the control of the hypothalamic–pituitary–gonadal axis and gonadotropin-releasing hormone (GnRH) agonists have positive effects on endometriosis-associated symptoms (A). Beyond hormonal aspects, bleeding endometriotic lesions and retrograde menstruation into the pelvic cavity (extra-uterine menstruation) induce inflammation (B). Together, endometriotic cells, degenerating tissue, and immune cells release pro-nociceptive mediators, which activate sensory nerve endings in endometriotic lesions. In response, sensory nerve endings contribute to neurogenic inflammation through the release of proinflammatory mediators (C). Activation of primary sensory neuron endings leads to the generation of the nociceptive signal, which is conveyed to the central nervous system (CNS). The nociceptive signal is then integrated in the spinal cord and carried by secondary sensory neurons to higher centers in the brain (B,C). Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.