Endometriosis in Reproductive Years: The Origin of Pain in Endometriosis and Adenomyosis

15

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Contents

15.1 Pathogenesis of Endometriotic Lesions

Endometriosis (EM) is a condition that is defined by endometrial-like lesions that occur outside the uterine cavity. Primarily, the disease was described as ectopic lesions on the peritoneum of the internal genital organs (endometriosis genitalis externa); lately it also comprises an emigration of endometriotic lesions into the myometrium (endometriosis genitalis interna = adenomyosis uteri (AM)). The high coincidence of these two endometriosis subtypes may arise in one common pathogenesis [1].

The "tissue injury and repair theory", by G. Leyendecker, describes the uterus as the origin of the disease. Uterine hyperperistalsis cause micro traumatization in the junctional zone (JZ), released mediators induce additional aromatase expression,

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and the locally released oestrogen promotes proliferation and angiogenesis. This leads to changes within the JZ that can be seen sonographically as an echo-poor hem (halo phenomenon) that represents the attachment of the endometrium; in 3D ultrasound a variability of forms becomes visible [2, 3]. A new term, *archimetriosis*, describes these early changes [4]. Locally released oxytocin in turn strengthens local peristalsis and thus initiates a cycle that leads to an increasing destruction of the JZ. Presumably, within the processes of mechanical alteration and wound healing, stem cells are activated, which then leave their niche and either enter the abdominal cavity through retrograde menstruation and there cause EM or infiltrate into the myometrium and lead to AM [5, 6]. In this context of endometrial-myometrial interface disruption (EMID), an upregulation of HIF-1a (hypoxia-inducible factor 1-alpha) is likely, thereby triggering hypoxia-related molecular biological mechanisms that could also be involved in the establishment of the lesions [7]. With these ectopic lesions, extensive immunological changes occur. Extensive inflammatory reactions and multiple immunological changes are detectable in both the peritoneum and the peritoneal fluid [8]. These immunological findings are strongly associated with the occurrence of corresponding lesions, and chronic inflammation plays an increasing role within the pathophysiological theories. In line is the fact that the ectopic EML, no matter where they are located (peritoneal lesion, endometrium at the ovaries or DIE or in extragenital manifestation in the navel, the abdominal wall or the groin), consist not only of epithelial and stromal cells but also of smooth muscle cells. They all express oxytocin and vasopressin receptors as well as oestrogen and progesterone receptors [9, 10]. Therefore, these lesions not only are endometrial-like settlements but *miniature uteri*. Endometriotic lesions are always associated with surrounding fibrotic changes. It remains unclear if the surrounding tissue or the lesions themselves trigger these changes.

So a composition of uterine-like tissue (epithelial, stromal as well as smooth muscle cells) in a different variety of growth patterns (superficial or deep infiltrating), localized on different anatomical positions (intra- and extragenital) often accompanied by inflammation and fibrosis, is the root for a couple of problems.

15.2 Pathophysiologic Origin of Pain

In addition to the development of the various lesions, the effects of these are also important to understand the origin of pain. EM is a chronic disease. It recurs after surgical removal and leads to persistent treatment needs in 50% of affected cases [11]. Pain and infertility are the central problems of our patients.

15.2.1 Endometriosis-Associated Pain

The typical complaints caused by EM, such as severe dysmenorrhea, cyclic and acyclic lower abdominal pain (UBS), cyclic dysuria, dyschezia, dyspareunia as well as infertility, are well known, and yet the disease is diagnosed on average only

Table 15.1 Endometriosis related symptoms (modified from Greene et al. [12])

Typical symptoms	Unspecific symptoms
Pain	Unspecific bladder disorder
Dysmenorrhea	Unspecific bowel dysfuntion
Cyclic pelvic pain	Bloating (endobelly)
Acyclic chronic pelvic pain	Spotting, high menstrual bleeding
Dyspareunia	Vegetative concomitants: vomiting, emesis, cyclical
Cyclic dyschezia	diarrhoea, gastric disorders
Cyclic dysuria	Headache, dizziness
Other cyclical symptoms like shoulder	Painful ovulation (Mittelschmerz)
or umbilical pain	Irregular pelvic pain
	Lower back pain
	Pain emission in the legs
	Chronic fatique
	All symptoms together
Infertility	

10 years after the onset of the symptoms. In addition to EM-specific symptoms, non-specific complaints (Table 15.1) may lead to consultations of various medical disciplines [12]. Why are the complaints so difficult to assess and to integrate into a diagnosis of EM, and why should an early diagnosis not be feasible? After all, more than 60% of those diagnosed with EM report that the complaints started before the age of 20 [13]. There is a clear correlation between the duration and the intensity of the complaints and to the extent of the EM [13]. In this context, evolutionary aspects of endometriosis are important [4]. It is discussed that in the past young women with good uterine contractility fell pregnant easily and had a better birth outcome and thus a survival advantage. Because pregnancies and breastfeeding followed each other repeatedly in the past, there was no formation of EM/AM or at least to a lesser extent. Today, however, the primigravidas are in their 30s. Thus, women with primary dysmenorrhea and with uterine hyperperistalsis are at risk of developing archimetriosis followed by EM/AM. Therefore, the uterus has one to two decades to turn an inherently good functionality into a self-destructive force before reproduction is aspired [4].

Caused by the slow development of the disease associated with the late diagnosis, the patients develop complex complaints. Knowledge of nature and distribution of possible formations allows a better understanding of the possible effects. In general, all lesions can cause various symptoms (Fig. 15.1). Complaints usually appear in combinations; isolated symptoms are rather rare. Typical is the combination of cyclic lower abdominal pain/dysmenorrhea and dyspareunia. Depending on where the lesions are located, somatic (peritoneum, pelvic wall) or visceral (uterus, bladder or intestine) pain occurs. These two pain characteristics differ: visceral pain is dull and spasm-like, radiate, visceral organs interact with each other, so that bladder pain can be hardly distinguished to uterine-induced pain. In addition, the autonomous, visceral innervation interacts with the visceral sensory neurons that pass through the autonomous ganglia. So in severe pain also, vegetative reactions such as nausea, vomiting, collapse tendency and above all cyclic menstrual-associated

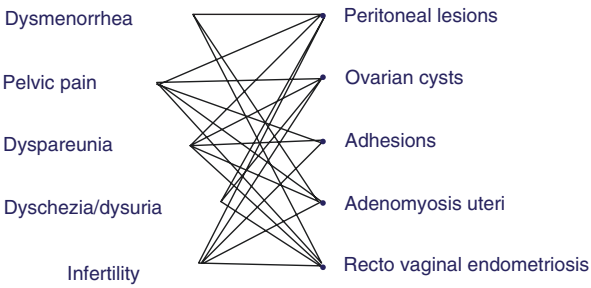

Fig. 15.1 Endometriosis-associated symptoms in correlation to the localisation of the lesions

diarrhoea are common [14]. Somatic pain, on the other hand, is rather pointed/sharp and point-shaped. Due to the high density of sensitive nerve fibres in the parietal peritoneum, they can be located more specifically.

15.3 Principles of Pain Development

A biochemical signal is needed (1), which is converted into a neural signal (2) (sensitization of pain nerve fibres via activation of the nociceptors). At the spinal level, this signal is modulated (3) and it is referred (attenuated/amplified) to the brain, where the pain perception occurs (4). Steps 1 and 2 are called peripheral and steps 3 and 4 central sensitization. Disorders of pain perception can occur at all levels.

15.3.1 Pathogenesis of Specific Forms of Pain

Dysmenorrhea and cyclic lower abdominal pain caused by peritoneal lesions can initially be understood as nociceptive inflammatory pain. There is a cyclic release of pain and inflammatory mediators. These activate visceral and peritoneal nerve fibres and lead to pain sensitivity. Inflammation and cell damage cause the pain and it disappears as the reaction subsides. This form of pain is well manageable via non-steroidal anti-inflammatory drugs (NSAIDs). Moreover, with the initiation of hormonal therapy and therapeutic amenorrhea, since then the cycle-related release of the mediators does not take place, the pain may completely disappear. Typical in AM-related dysmenorrhea is that even withdrawal bleeding under hormonal therapy with combined oral contraceptives (COC) in cyclical mode can still be painful. The mechanisms are not well understood, but it is likely that the primary disorders of the uterine layers with hyperperistalsis still result in the release of pain mediators and thus in the activation of pain fibres. Note: Persistent strong painful withdrawal bleeding under OC is to be seen as a warning! If the disease progresses, with the development of DIE (vaginal, intestinal or bladder infiltration), cyclical symptoms may also occur. In the case of rectovaginal EM, dyschezia typically occurs due to the proximity to the intestine or due to bowel infiltration. Caused by the cyclical swelling of the foci, there may also be cramp-like pain before bowel movement, stool irregularities and even cyclical subileus. Constipation followed by diarrhoea,

paradoxical, or even pencil stools may occur. To look for these specific findings may help to identify a potential stenosis. A stenosis can affect the rectum, sigmoid or even the caecal pole region. If the EML infiltrates completely through the entire intestinal wall, cyclical hematochezia may occur. In addition, due to the localization of the lesion, acyclical dyspareunia is common; hence the nodes are hyperinnervated and painful when pressure is applied [15]. Bladder endometriosis typically leads to cyclical dysuria but may also cause unspecific symptoms such as pollakiuria and/or pain after voiding the bladder. Only if the bladder wall is completely infiltrated and the urothel is affected cyclical haematuria occurs.

15.3.2 Neurogenic Inflammation

Some patients develop acyclic lower abdominal pain under hormonal therapy (with and without therapeutic amenorrhea). This is an important indication that EML develops mechanisms that can be active independently of hormones. Extensive analyses have been performed regarding the innervation of these lesions [16]. Peritoneal lesions show hyperinnervation of sensitive but loss of sympathetic nerve fibres. In analogy to rheumatism research, an imbalance in the release of pro-inflammatory and anti-inflammatory sympathetic neurotransmitters seems to occur. The consequence of this imbalance may result in a neurogenic inflammation and may lead to acyclic pains. In DIE lesions, this phenomenon is known too. Therefore, especially the hormone therapy-resistant pain is important in order to adjust therapy decisions accordingly. A further complicating factor may be adhesion-related pain, which can be both somatic and visceral. The transition from initially cyclic to acyclic lower abdominal pain is characteristic.

Due to the chronic pain, patients often develop reactive depression and somatoform pain disorders, which make the clinical picture appear even more complex. Besides EM, the most important differential diagnoses of chronic lower abdominal pains are postoperative adhesions (non-EM-related), interstitial cystitis and non-specific intestinal dysfunction, the irritable colon. It is known that there is not necessarily a correlation between the extent of EM and pain intensity [14]. Therefore – and this is certainly the most difficult phenomenon for physicians to understand in the case of EM – even “inconspicuous” examination findings can cause severe pain, and conversely, patients with complex EM can be largely free of pain.

15.3.3 Development of Central Sensitization with Spinal Hyperalgesia

Physiologically, pain is a warning signal. If pain is ignored, it may increase. Moreover, pain is an individual event; the perception of pain is subjective. If severe dysmenorrhea (menstrual pain that leads to bedriddenness and incapacity to go to school or to work without the use of analgesics) remains untreated, i.e. it recurs monthly, this pain is initially perceived as nociceptive pain as described above,

which also subsides as the release of the inflammatory and pain mediators decreases. If this pain occurs repeatedly, however, the body's own warning signals take effect, the pain is classified as threatening, and the modulation on the spinal level does not regulate it down, but rather increases it. At the spinal level, the release of neurotransmitters is altered and a number of modulating mechanisms are set in motion; the nociceptive field is expanded; and dysuria and/or dyschezia may occur [17]. This leads to spinal hyperalgesia with a lowered pain threshold and the perception of pain even with slight stimuli such as touch. Increasing pain frightens patients and makes pain processing more difficult. Severe cramps with pain, also accompanied by a vegetative reaction, also lead to the patient adopting a relieving posture, which is used to seek pain relief. Reactively, this leads to a reflex contraction of the pelvic floor muscles and thus to pelvic floor dysfunction, which increases the pain and can lead to dyspareunia [18]. If these tensions persist, dyspareunia develops and intensifies. Fear of pain during intercourse can strongly influence the ability to relax, and a disorder manifests itself, which takes on ever-greater proportions and no longer causes problems only cyclically, but increasingly manifests itself permanently. This phenomenon explains the often-severe pain that accompanies patients, even in the absence of pathological findings. It is essential to offer the patient pain-relief therapy. There is a correlation between the duration of pain and the occurrence of reactive depression, because patients are increasingly desperate and look for advice and help, but are often not understood [19] Fig. 15.2 illustrates the process of spinal hyperalgesia. Changes at central level develop. Functional MRI assessment demonstrates the first morphological adjustments of the brain after a pain latency of 2 years

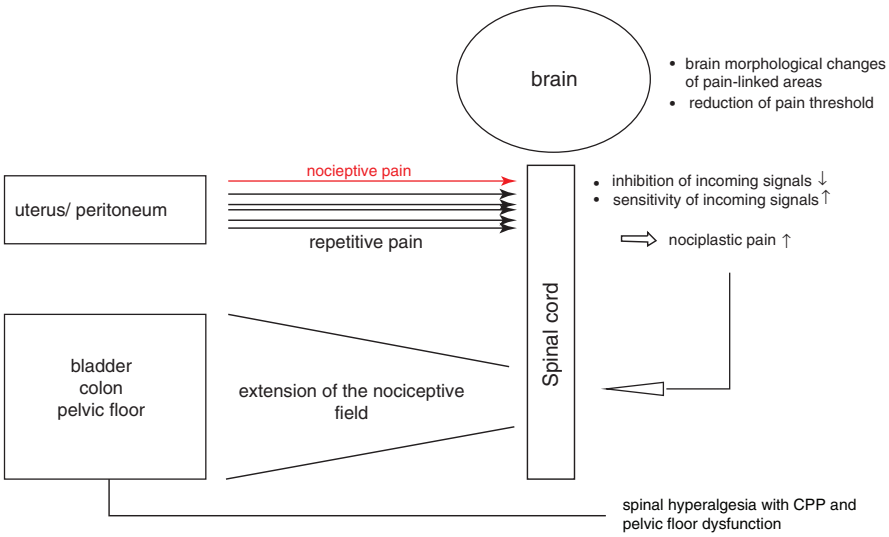

Fig. 15.2 Mechsnisms of central sensitisation and adaption on repetitve pain impulses over years. The modulation on the level of the spinal cord leads to extension of the nociceptive filed. Central changes (nociplasticity) leads to lower paintreshold and normal tough might be painful (spinal hyperalgesia)

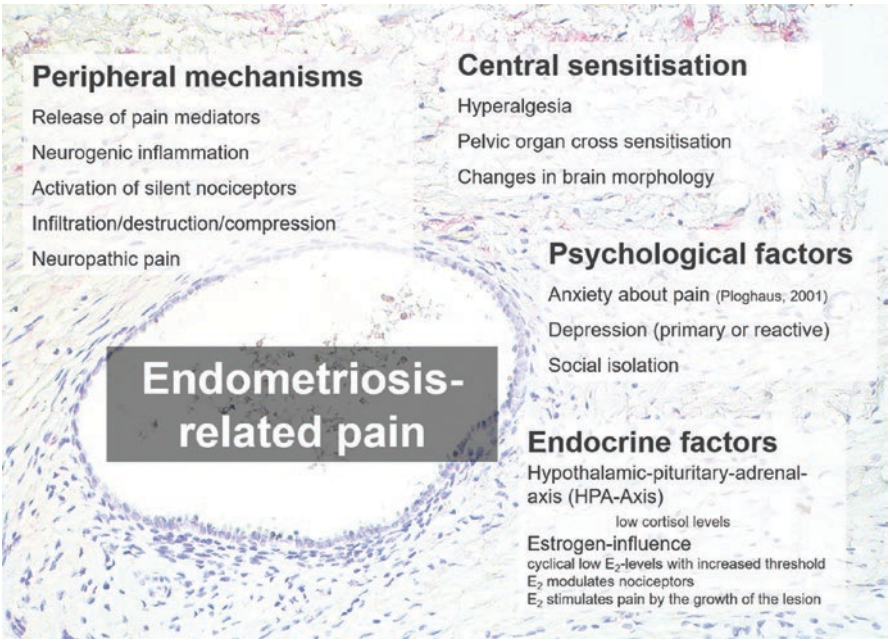

Fig. 15.3 Overview about the different pathomechanisms of pain in endometriosis

[20]. Such patients have an increased risk of developing complex chronic pain syndromes with bladder dysfunction, irritable bowel syndrome and vulvodynia [17]. Taken together, the pathogenesis of endometriosis-associated pain is very complex and certainly not yet fully understood (Fig. 15.3).

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