Chapter

Pain Management for Women with Endometriosis

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Abstract

Endometriosis is a leading cause of chronic pelvic pain in women and requires multidimensional lifelong management strategies. This chapter comprehensively reviews the multidisciplinary approaches to pain management in women with endometriosis, emphasizing both pharmacological and interventional strategies. Medical management includes non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives as the first line of treatment, providing adequate pain relief for many patients. Other pharmacological options include tricyclic and serotonin and norepinephrine reuptake inhibitors (SNRI) antidepressants, calcium channel blockers, GnRH agonists/antagonists, and aromatase inhibitors. Some disadvantages related to pharmacological treatment include inhibition of ovulation, side effects of medications, and high recurrence of pain after discontinuation of treatment. Surgical management is usually delayed due to the risk of pelvic organ damage and postoperative adhesion formation. Physical and behavioral therapy are encouraged as a comprehensive approach to chronic pelvic pain. Interventional pain management techniques have emerged as a therapeutic option providing adequate pain control without impairing fertility. Neuromodulatory techniques such as peripheral nerve stimulation, dorsal root ganglion, and spinal cord stimulation could be a promising line of treatment for patients with refractory pain.

Keywords: chronic pelvic pain, endometriosis, percutaneous neuromodulation therapies, peripheral nerve stimulation, dorsal root ganglion stimulation, spinal cord stimulation

1. Introduction

Endometriosis is a chronic debilitating disease characterized by the formation of endometrial-like tissue outside of the uterine cavity [1, 2]. It affects approximately 10% of reproductive-aged women around the world and it is present in 20–50% of women struggling with infertility and 71–87% of women suffering from chronic pelvic pain [1, 3]. The most common ectopic locations of endometrial glands and stroma are the pelvic peritoneum, the ovaries, and the rectovaginal septum [4].

Unlike eutopic endometrium, endometriosis lesions often contain blood, cysts, and fibrous tissue [5]. It has been proposed that endometriosis is an estrogen-dependent condition and that this aberrant tissue responds to hormonal stimulation and undergoes cyclical growth and shedding [6].

Pain is described as the most debilitating symptom of endometriosis and is usually one of the most challenging symptoms to manage given the presence of both somatic and visceral pain [7]. Presentation of pain most frequently includes dysmenorrhea, cyclic and acyclic pelvic pain, dyspareunia, dyschezia in patients with bowel involvement, dysuria in patients with bladder involvement, and radiating lower back pain [8]. Other nonspecific symptoms include headaches, dizziness, and chronic fatigue. As a result, endometriosis impacts the physical, mental, emotional, and social spheres of life for many women [6].

The precise etiopathogenesis of endometriosis is unclear, involving multiple processes and a combination of genetic and epigenetic factors [9]. There has been described three distinct forms of endometriosis: superficial or peritoneal endometriosis (endometriotic implants on the surface of pelvic peritoneum and ovaries), ovarian endometriomas (ovarian cysts lined by endometrioid mucosa), and deep infiltrative or rectovaginal endometriotic nodules (a solid mass comprising endometriotic tissue mixed with adipose and fibromuscular tissue in the space between the vagina and the rectum) [10]. Recently, nerve entrapment by endometriosis has been proposed as a fourth form of clinical presentation [11].

2. Pathogenesis of pain

Pain secondary to endometriosis has been associated with both inflammatory and neuropathic components that contribute to the severity of symptoms. The International Association for the Study of Pain (IASP) defines neuropathic pain as pain that arises as a direct consequence of a lesion or disease affecting the somatosensory system [12]. It has been proposed that endometriotic lesions growing in the peritoneal cavity stimulate the production of proinflammatory cytokines and growth factors. The resulting inflammation could lead to peripheral nerve sensitization associated with neuropathic pain [13]. The peritoneal fluid of women with endometriosis has shown an increased level of inflammatory cytokines (e.g. IL-1, IL-6, IL-8), leptin, and TNF-α [14–16]. Additionally, the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ) has been correlated with clinical presentation of dysmenorrhea and dyspareunia. Contrarily, treatment regimens that reduce IL-8, PAPP-A, midkin, and progestogen-associated endometrial protein have demonstrated a reduction in pain presentation [17]. Endometriotic lesions usually present a higher nerve density and expression of nerve growth factor, commonly leading to the development of chronic neuropathic pain [18]. It has also been proposed that inflammatory changes interact with the central nervous system leading to chronic pain. In accordance with this theory, structural changes in regional gray matter in women with endometriosis have been found [19, 20]. Moreover, it has been proposed that endometriotic lesions may infiltrate adjacent nerve fibers as they grow, leading to hyperalgesia. Recent studies have linked nerve fiber proximity to increased pain and indicate that pain generation is directly related to the location of the ectopic endometriotic tissue and the involvement of the peripheral nervous system in that region [21]. Therefore, an effective treatment requires a deep understanding of the mechanisms generating pain and a multidisciplinary treatment approach [9].

Endometriosis can also result in neurological symptoms when the central or peripheral nervous system is affected, manifesting as cyclic radiculopathy of the lower limbs, groin and buttocks, leg pain, pelvic pain, and in more severe cases even urinary incontinence and paraplegia [9]. Physical findings that may be present include analgesic gait, gluteal atrophy, groin pain, ankle dorsiflexion weakness, and worsening of pain with hip movement. Abdominal wall endometriosis can appear between 3 months to 10 years after abdominal surgery, presenting as incisional endometriosis at the anterior abdominal wall and often mistaken for other conditions (e.g. hernias, abscesses, granulomas, lipomas) [22]. Endometriosis affecting the sacral plexus is rare and can cause sciatic pain, hip pain, anal pain, pudendal pain, and gluteal atrophy secondary to superior and inferior gluteal nerve involvement [23]. Neuropathic pain is often described as a burning, electrical, and cramping sensation in the compromised region, such as the hypogastrium, perineum, vaginal opening, or anus [24]. **Table 1** summarizes the main types of mechanisms of pain related to endometriosis according to the structures involved.

2.1 Relevant neuroanatomy

A complete medical history and a thorough physical examination are necessary to differentiate between various pain generators properly. Pain related to endometriosis may include a visceral origin from pelvic organs (defined as persistent or recurrent pain that originates from internal organs of the abdominal and pelvic cavities), somatic origin due to muscle and ligament involvement, and neuropathic characteristics in case of nerve infiltration [12]. A clear understanding of pelvic innervation is crucial when stablishing an interventional pain management target.

Mechanism of pain
Endometrial cells that have grown outside the uterus can directly invade or irritate peripheral nerves, impacting the nerve fibers in the pelvic region.
Peripheral and central sensitization.
Scar tissue formation by pressing or pulling on nerves.
Nonspecific bowel and bladder symptoms.
Compression or irritation of the sciatic nerve.
Stretching of the sacral hypogastric fascia.
Pudendal neuropathy (S2, S3, S4).
Involvement of the superior gluteal nerve (L4, S5, S1).
Involvement of the inferior gluteal nerve.
Involvement of the cluneal nerves.
Involvement of posterior femoral cutaneous nerve.
Root nerve involvement.
Abdominal wall nerve entrapment.
Inguinal nerve entrapment.
Trigger points in the iliococcygeus, pubococcygeus, and puborectalis muscles.
Sacral network involvement.

Table 1.
Mechanisms of pain generation in endometriosis.

Afferent sensory roots emerge from the dorsal horn of the spinal cord and travel to the periphery until they collect in a bundle of pseudo-unipolar cell bodies named the dorsal root ganglion (DRG) [25]. Efferent motor roots emerge from the ventral horn of the spinal cord and converge with the dorsal roots to form mixed spinal nerves. As each spinal nerve travels peripherally, it divides into the dorsal and ventral primary rami and forms the peripheral nerves [26].

The ilioinguinal and iliohypogastric nerves (L1), the genitofemoral nerve (L1–L2), and the pudendal nerves (S2, S3, S4) transmit somatic sensory and motor innervation of the pelvis. The pudendal nerves supply mixed innervation to the perineum, the external genital, and the anal region. Visceral or autonomic innervation goes through the sympathetic and parasympathetic systems, with sympathetic trunk fibers having their cell bodies in the thoracolumbar DRG and parasympathetic trunk fibers having their cell bodies in the sacral DRG [26]. The superior hypogastric plexus, inferior hypogastric plexus, the splanchnic nerves, and the impar ganglion carry the sympathetic innervation of the pelvis.

The DRG has gained protagonism in recent years, since now evidence supports its role in neuropathic pain modulation. Previously considered a passive structure that merely connected the central and peripheral nervous systems, it has been shown that stimulation of DRG decreases neuron hyperexcitability secondary to afferent nerve injury [25].

3. Pain management

There is no substantial evidence to determine the superiority of surgical vs. medical management of pain symptoms. A systematic review of 23 studies and 1847 patients reported no statistically significant pain improvement after undergoing surgical treatment compared to medical treatment modalities [27, 28]. Providers are encouraged to consider all modalities, suggesting medical management as the first line of treatment, but understanding that the combination of medical and surgical treatments amounts to the highest success rate [29].

3.1 Surgical management

The surgical approach ranges from excision and/or ablation of the endometriotic lesions to hysterectomy with or without oophorectomy. Ablation of lesions can be performed using monopolar or bipolar cautery, laser, or argon gas. Excision of deeply infiltrating lesions is recommended, and medical therapy following surgical treatment provides a longer symptomatic relief [27]. Furthermore, it has been reported that patients with moderate disease experience a higher improvement of pain symptoms than those with mild or minimal disease. Recurrence of pain occurs in 20–40% of patients who undergo surgical treatment. However, multiple surgical procedures should be avoided due to the risk of adhesions, secondary pelvic pain, and decreased ovarian reserve [30]. Regarding ovarian endometriomas, medical treatment may lead to a temporary reduction of cyst size but has not shown complete resolution of the lesions [31]. Surgery should be the primary option of treatment for large or symptomatic endometriomas. Cyst removal has proven a greater improvement in dysmenorrhea, dyspareunia, and pelvic pain. Simple drainage, fenestration, or ablation of the cyst wall is associated with 80–100% recurrence at 6 months and is not recommended as final treatment [32].

Other ablative techniques are less utilized due to unsatisfactory pain resolution, technical difficulty, and related adverse effects [33]. Laparoscopic uterosacral nerve

ablation or resection targets the efferent fibers within the uterosacral ligaments to disrupt the primary innervation of the cervical sensory fibers. While the rate of complications is low, uterine prolapse and ureter transection have been reported [34]. Presacral neurectomy consists of incising the superior hypogastric nerve plexus 1 cm caudal to the aortic bifurcation. Because of the plexus' location near the venous plexus and major vessels, this procedure is technically challenging and carries a significant risk of bleeding and postoperative complications that include urinary retention and constipation [35]. The rates of recurrent pain were similar to those who underwent conservative surgery, seemingly offering no further benefit over the traditional laparoscopic approach [33].

Regarding hysterectomy with bilateral salpingo-oophorectomy, it should be only considered in patients with advanced and treatment-resistant endometriosis who are satisfied with parity. Debulking of disease and associated menopause leads to atrophy of endometriosis tissue with a lower recurrence of symptoms [27, 36]. The decision to perform salpingo-oophorectomy should consider early menopause and the need for hormone replacement therapy [36].

3.2 Medical management

Medical management for endometriosis includes NSAIDs, oral contraceptives, progestogens, danazol, GnRH-agonists, and anti-progestogens [37]. **Table 2** indicates the recommended treatment regimen for each drug group as stated by the American Academy of Family Physicians [3].

3.2.1 NSAIDS

NSAIDs are commonly employed as the first line of treatment due to availability and manageable side effects. NSAID*s* inhibit prostaglandin production that contributes to inflammation and pain. Anti-prostaglandin agents are effective in the treatment of primary dysmenorrhea, but their effectiveness for endometriosis pain is yet to be established [38, 39]. A 2015 Cochrane review compared NSAIDs to placebo and no recommendation could be established. Even though pain scores were lower for the NSAIDs group, evidence was inconclusive regarding quantifiable data such as quality of life or effect on daily activities [38]. These findings were supported by a more recent 2017 Cochrane review where only two randomized controlled trials (RCT) comparing NSAIDs versus placebo for endometriosis-related pain were found [40, 41]. Results showed a difference between NSAIDs and placebo for overall pain relief, however, unintended effects of treatment or requirement for additional medication remained unclear. No data was provided on other secondary outcomes such as quality of life, the effects on daily activities, work and school absenteeism, the number of women requiring more invasive treatment, and patient's satisfaction with treatment. Additionally, no evidence supports whether an individual NSAID is more effective than another [42]. Both reviews suggested that patients should be informed of secondary effects that could be caused by NSAIDs prior to their prescription [38, 42]. Larger and more recent randomized control trials are needed to update these results.

3.2.2 Neuroleptics

Pelvic pain secondary to endometriosis has been found to encompass a multifaceted neural mechanism that includes nociceptive as well as neuropathic pathways.

Medication	Indication	Dosing
Depot MDA (Depo-Provera)	Pain relief	150 mg intramuscularly every 3 months
MDPA (Provera)	Pain relief	30 to 100 mg daily (orally)
Combined OCPs	Pain relief	0.02 to 0.03 mg ethinyl estradiol and 0.15 mg desogestrel daily for 6 months
Levonorgestrel intrauterine system (Mirena)	Pain relief after surgery	Intrauterine system
Gonadotropin-releasing hormone analogues: • Goserelin (Zoladex) • Leuprolide (Lupron) • Triptorelin (Trelstar Depot)	Pain relief	3.75 mg of leuprolide injected every four weeks or 3.6 mg of goserelin implanted subcutaneously for 6 months
Nafarelin (Synarel)	Pain relief	200 mcg intranasally twice daily for 6 months
Danazol (Danocrine)	Pain relief	200 mg given orally three times daily; 400 mg given orally twice daily for 6 months
Gestrinone	Pain relief	2.5 mg orally twice a week for 6 months

MDPA = medroxyprogesterone acetate; OCPs = oral contraceptive pills (Adapted from Gharaei et Gholampoor).

Table 2.
Medical treatment for endometriosis pain.

For patients who present with significant nerve damage from endometriosis, persistent pain may follow despite excision of the disease, and severity of the disease may not correlate with reported pain. Pregabalin, gabapentin, and calcium channel blockers could be a therapeutic option for these patients by decreasing glutamine uptake, norepinephrine, and substance P and stabilizing central and peripheral membranes. These drugs are conventionally used for neuropathic pain but also for nonspecific pain conditions [43, 44].

Tricyclic antidepressants are another first-line treatment for many neuropathic chronic pain conditions, by increasing available norepinephrine that inhibits descending pain pathways [44]. An RCT in women with chronic pelvic pain comparing the use of amitriptyline, gabapentin, and amitriptyline/gabapentin combined for 24 months reported significantly reduced pain in each group and showed fewer side effects in the gabapentin group [45].

Almeida et al. conducted a systematic review to evaluate the effect of neuromodulatory drugs on the intensity of chronic pelvic pain in women [46]. Among the seven studies included, four showed improvement in pain with the use of neuromodulator drugs for chronic pelvic pain. However, the most powerful and high-quality study did not show pain improvement. Additionally, no studies specifically evaluating pain in women with endometriosis were found. There is still no high-quality evidence to either indicate or avoid the use of neuromodulatory drugs in endometriosis, and further high-quality studies, especially randomized controlled trials, are needed to support the use of these drugs in the treatment of women with endometriosis.

3.2.3 Combined oral contraceptives

The utilization of combined oral contraceptives inhibits the production of gonadal estrogen by suppressing ovarian activity through a negative feedback axis.

Consequently, the release of estrogen-induced release of prostaglandins is reduced and inflammation decreases [47]. In addition, combined hormonal drugs are thought to cause decidualization followed by atrophy of endometrial tissue [48, 49]. When administered for endometriosis, combined hormonal contraceptives should be used continuously in comparison to cyclic administration for symptom control [50].

3.2.4 Progesterones

Norethindrone acetate, depot medroxyprogesterone acetate (MPA), levonorgestrel-releasing intrauterine system (LNG-IUS), and dienogest are some of the most frequently used progestogens in women with endometriosis. Progestogens are proposed to work through several mechanisms [49]:

1. decidualization and consequent endometrial atrophy.

2. progestogen-induced suppression of matrix metalloproteinases, enzymes that influence the growth and ectopic implantation of endometrium.

3. Inhibition of angiogenesis.

Treatment with MPA, dydrogesterone, or norethindrone acetate has been shown to reduce pain scores by 70–100% [1]. MPA has proven to be an effective treatment with combined oral contraceptives, danazol, and GnRH-agonists. Dienogest was reported as significantly better than placebo and as effective as GnRH-agonists with a more favorable side effect profile [51]. Levonorgestrel-releasing intrauterine systems have been proven more effective in reducing dysmenorrhea after laparoscopic surgery when compared to expectant management and have been associated with a significant decrease in the extension of lesions encountered during second-look laparoscopy 6 months later [52].

3.2.5 Gonadotropin-releasing hormone agonists

GnRH agonist analogues have been studied more extensively than other medical lines of treatment [27, 37]. Modified analogues present a longer half-life and bind to the receptors in the pituitary gland, interrupting the pulsatile stimulation of endogenous GnRH [53]. Consequently, downregulation of the pituitary-ovarian axis and hypoestrogenism induce amenorrhea and progressive atrophy of endometrial tissue [49]. Drug presentations include nafarelin acetate calibrated nasal spray, short-acting formulation for daily injection, and depot formulation every *1–3 months* in the form of leuprolide acetate or goserelin acetate [29]. The main side effects reported are related to the induced hypoestrogenic state: hot flushes, vaginal dryness, decreased libido, mood swings, headache, and bone mineral depletion [54].

A Cochrane review demonstrated GnRH-analogues to be more effective for pain than placebo and similarly effective to LNG-IUS and danazol, with one long-term follow-up demonstrating a 53% reduction in recurrence of symptoms at 24 months after six-month treatment with GnRH-agonists [55]. Combined therapy with norethindrone acetate or an estrogen-progestogen regimen has been proposed as an alternative to reduce estrogen deprivation effects and should be started at the same time of GnRH [27]. It has been proposed that the amount of estrogen/progesterone necessary to prevent hypoestrogenism symptoms is less than that which would stimulate endometriotic tissue formation [56].

3.2.6 Gonadotropin-releasing hormone antagonists

GnRH antagonists, such as Elagolix, suppress the gonadotropin hormone production from the pituitary gland and cause a dose-dependent hypoestrogenic state. In contrast to GnRH agonists, they avoid the initial surge in LH and GSH and provide an immediate effect [57]. Side effects may include symptoms of hypoestrogenism such as hot flashes, headaches, insomnia, and higher lipid levels. Elagolix has been recently approved in the USA for moderate to severe pain related to endometriosis, and its studies have shown a significant short-term reduction of dysmenorrhea and non-menstrual pelvic pain with adequate maintenance of response [58, 59].

3.2.7 Danazol

Danazol is a 17 alpha-ethinyltestosterone derivative that inhibits the LH peak and steroidogenesis through the increase of free testosterone levels [49]. Its effectivity for the treatment of endometriosis-related pain has proven to be superior to placebo and comparable to GnRH-agonists [60]. Side effects include hirsutism, acne, weight gain, and deepening of voice. Danazol can be administered orally and through vaginal or intrauterine delivery systems [37].

3.2.8 Experimental treatments: Gestrinone

Ethylnorgestrienone is an antiprogestational steroid that produces a progesterone withdrawal effect at the endometrial cellular level and inhibits ovarian steroidogenesis. It is administered orally from 2.5 to 10 mg daily to weekly basis, showing an effectiveness comparable to danazol and GnRH-agonists [55]. Side effects are associated with its androgenic and anti-estrogenic effects [49]. Gestrinone is not approved for use in the USA, but its use is currently approved for Europe.

3.2.9 Experimental treatments: Aromatase inhibitors

Aromatase inhibitors are still under current investigation, with low-impact studies showing effectiveness in endometriosis-related pelvic pain treatment for women pre- and postmenopause [61]. Endometriotic tissue exhibits a higher level of aromatase activity in comparison to eutopic endometrium. This results in an increase of local estrogen and favors endometriosis formation, explaining the persistence of endometriotic tissue in postmenopausal women and in those patients receiving treatment with GnRH agonists [27]. In women who have not undergone menopause, aromatase inhibitors should be used in combination with an additional agent that down-regulates the ovaries and protects bone density such as progestogens, combined oral contraceptives, or GnRH [62].

3.3 Interventional pain management treatments

Endometriosis-related pain could be treated effectively using interventional pain management strategies. It has been stated that refractory pain due to endometriosis should respond to nerve blocks depending on the site of involvement [63]. The sympathetic nervous system plays an essential role in the transmission of pain from internal organs, independently of its cause [9]. The superior hypogastric plexus block (SHPB) is one commonly used approach in treating persistent pelvic

and rectal pain that does not respond to conservative treatment [64, 65]. Located ventrally to the abdominal aorta, the superior hypogastric plexus innervates hindgut structures like the descendent and sigmoid colon, the proximal rectum, and pelvic organs such as the uterus and ovaries [66]. The SHPB procedure can be performed through either a paravertebral or transdiscal approach and has been reported to significantly improve the quality of life and mental health status of women with endometriosis [67]. The choice of analgesic injectate should be carefully done by the physician considering the maximum analgesic effect while minimizing the side effects experienced by patients. Typical agents used include steroids, bupivacaine, and chemical agents such as (5–10%) and ethanol (50–100%) [68]. The inferior hypogastric plexus block (IHPB) is a less popular technique for the treatment of pelvic, perineal, and genital pain due to its challenging location in the presacral space that conditions a higher risk of nerve damage, vascular puncture, rectal lesion, presacral hematoma, and infection [69].

The ganglion impar block is another useful technique for the treatment of malignant vulvar, rectal, and anal pain; intractable sacral and perineal pain and coccydynia [70]. Other techniques for treating endometriosis-associated pain include performing S3 pulsed radiofrequency in combination with IHPB or botulinum toxin injection and myofascial pain trigger points [71, 72].

Targeting the sympathetic axes has been shown to be useful in controlling visceral pelvic pain. The technique of choice should be based on clinical presentation and the structures that are compromised [73]. SHPB is most effective for pain involving pelvic viscera (e.g. uterus, ovaries, and bladder), the rectum, and hindgut structures [70]. When treating perineal, genital, presacral, and low pelvic pain, an IHPB is most recommended [74, 75]. Ganglion impar block is an option in cases with involvement of the vulva and anal orifice, presence of intractable sacral and/or perineal pain, or coccydynia. Gharaei and Gholampoor proposed an approach to the choice of interventional technique based on location and clinical presentation which is represented in **Figure 1** [9].

3.3.1 Hydrodissection with dextrose for peripheral nerve entrapment

Peripheral nerve entrapment is an underrecognized entity when treating patients with endometriosis and results in the persistence of pain and disability despite the treatment offered. Entrapment of the nerve occurs due to anatomical or pathological structures that cause increased pressure and lead to several mechanisms of nerve damage, producing a segmental injury of the nerve. Symptoms can range from mild discomfort and numbness to debilitating pain and even paralysis. Injury of the nerve is produced by mechanical compression, contraction, and excessive stretching that leads to chronic hypoxia and inflammation. The resulting pain is of neuropathic characteristic which patients may describe as a numbing, tingling, burning, shooting, lancinating, or electric shock sensation [76]. Since central sensibilization can increase pain over time, it is important to perform an early intervention. Hydrodissection consists of a deep perineural injection into the compressing tissue or fascia, releasing the trapped nerves while diluting and washing away the local inflammatory response [77]. Nerve structures are identified under ultrasound and a perineural injection with 5% dextrose is administered. Dextrose reduces neuropathic inflammation and dissects the endometrial tissues. It has been proposed that dextrose delivered to the perineurial soft tissues may aid in nerve recovery by reducing adhesion and damage from chronic contraction and enhancing blood flow [78].

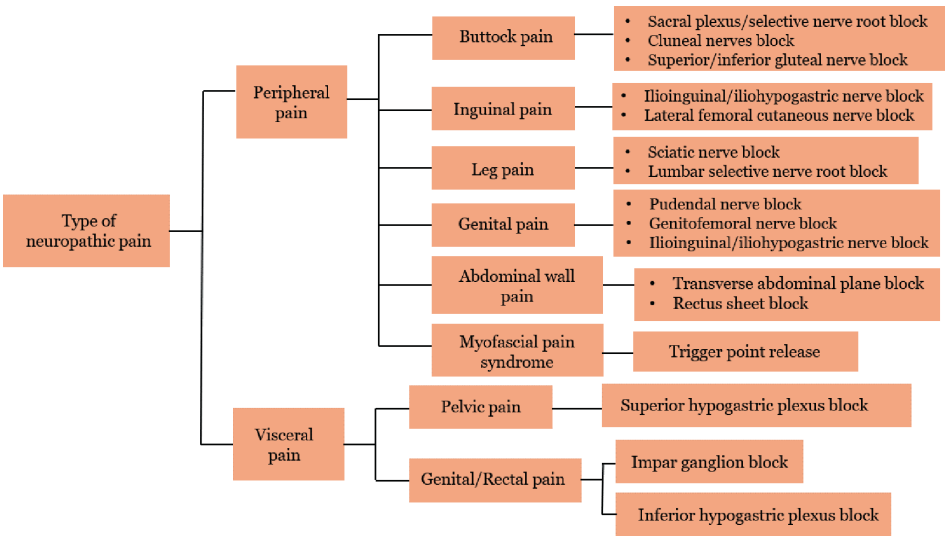

Figure 1.
Algorithmic approach to interventional pain management for neuropathic pain in endometriosis (Adapted from Gharaei et al.).

3.4 Advanced neuromodulation techniques

Neuromodulation consists of electrical stimulation or administration of pharmacological agents that alter and moderate pain signals. Neuromodulation use has been described for the treatment of chronic pelvic pain, including spinal cord stimulation (SCS), dorsal root ganglion (DRG) stimulation, sacral nerve roots stimulation, and peripheral nerve stimulation (PNS) [79].

3.4.1 Spinal cord stimulator

SCS has been proposed as a therapeutical option for refractory pelvic pain and could be effective in endometriosis-related pain management [80]. Case series and prospective studies have been developed with variations in lead placement. Kapural et al. reported the first case series of SCS for refractory visceral pelvic pain in six women using an anterograde approach with lead placement at T11-T12. A significant reduction in the mean visual analog scale (VAS) score was reported, as well as a reduction in pain disability index and opioid use in morphine milligram equivalents (MME) [81]. Buffenior et al. conducted a prospective study evaluating the role of SCS of the conus medullaris applied to 27 patients with refractory pudendal neuralgia. A total of 20 patients had a positive response during the trial period and underwent permanent electrode implantation, remaining long-term responders. At 15-month follow-up, the mean estimated percent improvement (EPI) was 55.5% [82]. A case series conducted by Simopoulous et al. followed three patients who underwent implantation of a high-frequency 10 KHz SCS mediated at the conus medullaris for different clinical presentations of refractory neuropathic pelvic pain, reporting satisfactory pain relief for all patients at long-term follow-up [83]. A prospective, multicenter trial performed by Tate et al. evaluated the efficacy of 10-KHz SCS in patients with chronic pelvic pain. Among the 21 patients who underwent the trial, 17 were positive respondents and 14 of them received a permanent SCS implantation. A total

of 77% of the patients who underwent implantation reported pain relief over 50% and the mean VAS score decreased by 72% [84]. Hunter et al. described lead placement at higher thoracic levels for the management of chronic pelvic pain, with four patients who received SCS lead placement in the mid-thoracic region, two patients with T6 level lead placement, and two patients who underwent T7 level trial. A total of three patients in the series had a positive trial response and received permanent implantation [85]. A prospective chart review completed by De Andres et al. found limited effectiveness of retrograde neurostimulation in the treatment of perineal pain, describing technical limitations and the complex pelvic innervation that does not subscribe to a specific dermatome [86].

3.4.2 Dorsal root ganglion stimulation

Schu et al. reviewed the use of DRG stimulation in patients with groin pain. A total of 29 patients were included and taken to trial with stimulation of the DRG between T12 and L4, resulting in 25 patients who were respondent and eligible for implantation. Among the implanted patients, 82.6% experienced a reduction in pain superior to 50%. These results could indicate that neuromodulation of the DRG is effective in treating pelvic neuropathic pain syndromes, including endometriosis [87]. Hunter et al. conducted the first case series of DRG stimulation in patients with chronic pelvic pain that had not responded to conservative treatment and other interventional pain management techniques. A total of seven patients were trialed successfully and underwent DRG stimulator implants with lead placement over L1 and S2 DRGs bilaterally. Pain relief report was satisfactory at follow-up, opioid consumption decreased, and some of the patients additionally reported improvement in urination and sexual function. The authors proposed that the lead placement generated an upstream and downstream effect through crosstalk between the DRG and the ganglia, and suggested L1 as the most cephalad level in which inferior pain signals get transmitted to the brain. Stimulation of the L1 DRG stops the upper lumbar plexus signaling to the brain and S2 DRG stimulation interrupts pain signals originating from the lower lumbar and sacral plexus [88].

3.4.3 Peripheral nerve stimulation

The main targets for PNS described for chronic pelvic pain include the sacral, pudendal, posterior tibial, genitofemoral, ilioinguinal, and iliohypogastric nerves according to pain localization. PNS leads are aimed to be placed parallel to the peripheral nerve. Among sacral nerves, the most common target is the S3 root. Siegel et al. and Paszkiewicz et al. studied the effectiveness of sacral nerve stimulation in intractable pelvic pain, performing a successful trial in 10 patients with lead placement in S3 or S4 foramen. At a median follow-up time of 19 months, the mean reduction of VAS was superior to 50% [89]. Martelucci et al. included 27 patients with chronic pelvic pain in their study, of which 15 were trialed successfully and underwent implantation, finding sustained pain relief at 60 months follow-up. Additionally, positive response to calcium channel blockers such as pregabalin and gabapentin was found to be a predictor of positive response to sacral neuromodulation, while poorly localized pain was an indicator of poor response [90]. Vancaillie et al. conducted one of the largest studies involving PNS consisting of a case series of 52 patients evaluating sacral neuromodulation for pelvic pain, with promising results indicating that sacral neuromodulation could represent an effective treatment for intractable chronic pelvic pain [91].

Further high-quality research is needed to provide a strong recommendation for the use of advanced neuromodulation techniques in endometriosis-related pain and stablish a consensus on neuromodulatory targets. Decisions on what technique is most convenient should be based on pain location and a thorough medical evaluation. Possible risks and complications, patient's expectations, and the implications of a medical device implantation should be discussed prior to the procedure.

3.5 Adjuvant therapies

3.5.1 Exercise

Physical exercise has been considered an adjuvant treatment for dysmenorrhea for decades, considering that exercise releases anti-inflammatory cytokines and reduces cortisol levels, leading to a reduction in prostaglandin release [92]. Additionally, the skeletal muscle is believed to act as an endocrine organ, releasing myokines with muscular contraction. These myokines are theorized to exert direct effects on the muscle and other distal organs such as the liver, pancreas, and adipose tissue [93]. Carroquino-Garcia et al. concluded in their systematic review that therapeutic exercise for a period of 8 to 12 weeks reduces pain intensity and duration of dysmenorrhea [94]. A recent systematic review by Mira et al. reported an improvement in pain and quality of life when an exercise protocol was added to different pharmacological interventions, however, due to the sample size of individual studies, the evidence was not considered significant [95]. Given the low risk of the intervention and the potential benefits to the patients' overall health, exercise in conjunction with other treatment modalities could be encouraged to alleviate symptoms [96].

3.5.2 Acupuncture

Studies regarding the use of acupuncture in endometriosis-related pain are increasing worldwide. Two randomized trials evaluated specific acupuncture compared to sham acupuncture for endometriosis-related pain finding significantly better pain control with real acupuncture [97, 98]. Xu et al. demonstrated in their systematic review that acupuncture had a beneficial effect on pain reduction compared to other treatments such as traditional Chinese medicine, medication, or placebo [99]. Acupuncture has been suggested to activate peripheral analgesic mechanisms such as the release of endogenous opioids and to participate in the modulation of several anti-inflammatory pathways, and inhibitory control mechanisms [100]. These findings were corroborated by a recent meta-analysis involving the use of acupuncture compared to placebo for women with endometriosis-related pelvic pain [95].

3.5.3 Behavioral health

Chronic pelvic pain has been associated with a higher prevalence of psychologic symptoms such as depression and anxiety, and a significant reduction in work productivity [101]. Most women with endometriosis and pelvic pain present some level of impairment in their mental health and quality of life associated to the chronicity and emotional aspects of the disease [102]. Furthermore, around 67% of women with endometriosis experience problems in the relationship with their partners, mainly due to painful intercourse [103, 104]. This complex interplay of factors, also referred to as the biopsychosocial injuries caused by the disease, could induce a vicious cycle that compromises the base

treatment, whether it is pharmacological or surgical [105]. Buggio et al. described a series of interventions for women with endometriosis, including psychotherapy and sexual therapy, that approach the self-management of physical, psychological, and sexual symptoms obtaining positive outcomes when integrated into the clinical treatment of pain [106]. Practitioners should consider referral to a mental health professional early in the treatment to address the psychological and social factors that contribute to pain.

3.5.4 Pelvic floor physical therapy

Chronic pelvic pain leads to muscle contraction and postural changes that exacerbate musculoskeletal pain. Physical therapy, including heat therapy, has been proposed to enhance the relaxation of abdominal muscles and increase pelvic blood circulation [92]. There is no strong evidence with a well-described methodology for recommending the different forms of physiotherapy that may be most effective in the treatment of endometriosis. Current reviews indicate that transcutaneous electrical nerve stimulation (TENS), pulsed high-intensity laser therapy, pulsed electromagnetic fields, and manual physiotherapy could be of use in reducing pain and improving the quality of life for women with endometriosis [107].

4. Conclusions

- Endometriosis is a challenging, undertreated chronic condition that severely impacts the quality of life of women and adolescents globally.
- Understanding the pathogenesis of the disease and pain mechanism is crucial to offer an integrated and effective treatment strategy.
- A significant proportion of patients respond well to medical therapy; however, hormonal treatment can lead to several secondary effects, and in a great number of patients, symptoms recur once the medication is terminated.
- Interventional pain management strategies have been shown to be effective with fewer adverse effects but require a clear understanding of pelvic anatomy and innervation and a thorough medical evaluation to identify nerve involvement and/or entrapment. The sympathetic nervous system is the focus of analgesic injections for endometriosis-related pelvic pain. Risks and possible complications such as nerve damage, vascular puncture, visceral lesion, and hematoma should be discussed with the patient prior to the procedure.
- Further investigation is required to stablish stronger recommendations and guidelines regarding interventional analgesic procedures.
- Advanced neuromodulatory techniques are promising in the scenario of refractory pelvic pain considering the importance of neuropathic component in endometriosis-related pain. A neuromodulatory target should be accurately determined for the procedure according to the localization of pain.
- Adjuvant therapies are encouraged through the process of diagnosis and treatment to optimize pain control and quality of life. Acupuncture has been

demonstrated to improve pain when compared to placebo, however, no strong recommendation can be provided regarding its use in patients with endometriosis. Other interventions could be incorporated according to the patient's tolerance and best medical judgment.

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Conflict of interest

Dr. Daniela Rangel-Santos, Dr. German William Rangel, and Dr. Sudhir Diwan declare no conflict of interest.

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