Literature Review

The Role of Interventional Pain Management Strategies for Neuropathic Pelvic Pain in Endometriosis

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Background: Endometriosis is a chronic common condition affecting 10% of reproductive-aged women globally. It is caused by the growth of endometrial-like tissue outside the uterine cavity and leads to chronic pelvic pain, affecting various aspects of a woman's physical, mental, emotional, and social well-being. This highlights the importance of an understanding of the potential involvement of the nervous system and involved nerves as well as an effective multidisciplinary pain management.

Objectives: Our aim was to assess the current understanding of pain mechanisms in endometriosis and the effectiveness of different interventional pain management strategies.

Study Design: Literature review.

Methods: A search was conducted using multiple databases, including Google Scholar, MEDLINE (Ovid), PubMed, and Embase. We used keywords such as "endometriosis," "pain," pelvic pain, "management," and "anaesthesia" along with Boolean operators and MeSH terms. The search was limited to English language articles published in the last 15 years.

Results: Nerve involvement is a well-established mechanism for pain generation in patients with endometriosis, through direct invasion, irritation, neuroangiogenesis, peripheral and central sensitization, and scar tissue formation. Endometriosis may also affect nerve fibers in the pelvic region, causing chronic pelvic pain, including sciatic neuropathy and compression of other pelvic nerves. Endometriosis can cause sciatica, often misdiagnosed due to atypical symptoms. Interventional pain management techniques such as superior hypogastric plexus block, impar ganglion block, S3 pulsed radiofrequency, myofascial pain trigger point release, peripheral nerve hydrodissection, and neuromodulation have been used to manage persistent and intractable pain with positive patient outcomes and improved quality of life.

Limitations: The complex and diverse clinical presentations of endometriosis make it challenging to compare the effectiveness of different pain management techniques.

Conclusion: Endometriosis is a complex condition causing various forms of pain including nerve involvement, scar tissue formation, and bowel/bladder symptoms. Interventional pain management techniques are effective for managing endometriosis-related pain.

Key words: Endometriosis, chronic pain, therapeutic interventions, interventional techniques, pain injections, visceral pain, peripheral pain

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Endometriosis is a chronic condition that affects approximately 10% of women of reproductive age worldwide, and is characterized by the growth of endometrial-like tissue outside the uterine cavity (1). The etiopathogenesis of endometriosis involves multifactorial processes. A combination of genetic and epigenetic factors are involved, resulting in a heterogeneous disease (2).

This condition often leads to chronic pelvic pain and can affect individuals' physical, mental, emotional,

and social well-being (3). Recent evidence indicates that pain generation in endometriosis is related to the location of the ectopic endometrial tissue and the extent of which peripheral nervous system is involved in that region. Therefore, effective treatment of this condition requires an understanding of mechanisms behind pain generation and a multidisciplinary pain management approach (4). It is believed that refractory pain due to endometriosis should respond to nerve blocks depending on the site of involvement (5).

This literature review will provide a comprehensive understanding of the pain mechanisms in endometriosis, including nerve involvement and peripheral/central sensitization. It will also outline the types of pain related to endometriosis and their clinical presentations. Additionally, an evaluation of the effectiveness of interventional pain management techniques, such as nerve and plexus blocks, will be discussed.

Methods

The search strategy for this literature review focused on the mechanisms of pain in endometriosis and the role of interventional pain management techniques in treating pain in this condition. The search was conducted using Google Scholar, MEDLINE (Ovid), PubMed, and Embase databases. Boolean operators were utilized to combine relevant keywords and MeSH terms. The key words used were: (Endometriosis OR Endometrioma OR Endometriomas OR Adenomyosis OR Peritoneal Endometriosis) AND (Pelvic Pain OR Pain OR *algia OR nerve) AND (management OR anaesthesia* OR anesthesia* OR Nerve Blocks OR Neural Blockades).

The search was limited to articles published in English and included any studies from the last 15 years. A narrative synthesis was performed to report on findings. The inclusion criteria included any open access research including interventional studies, observational studies, case reports, reviews, or meta-analyses conducted on women experiencing pain secondary to endometriosis. Studies that were conducted in vitro or on children were excluded. For investigating the effectiveness of interventional pain management techniques, papers that focused on patients with co-occurring reproductive conditions were also excluded.

Results and Discussion

An initial total of 330 studies were identified, including 324 through electronic database searches from Google Scholar, MEDLINE (Ovid), PubMed, and Embase databases. An additional 6 studies were identified through other sources, such as those included in other research papers. No filters other than the date of publication were used on the databases; hence no automated exclusion based on study design or other factors was performed. After removing duplicates manually, as well as using automated tools on the databases, 240 studies were screened for eligibility based on their titles and abstracts. At this stage, 193 studies were excluded. The excluded papers at this stage were mainly on other causes of pelvic pain, such as cancer. Finally, 47 studies were found for full-text review and narrative analysis.

Endometriosis: Causes, Symptoms, and Presentations

There are various methods for pain classification; one of the most recognized differentiations is between nociceptive pain and neuropathic pain. Nociceptive pain can be somatic which originates from muscles, tendons, and superficial areas of the body, and is generally acute. However, visceral pain originates from internal organs such as the uterus (6). Nevertheless, both somatic and visceral pain can be nociceptive or neuropathic. Neuropathic pain is a type of neurogenic pain that results from injury to the somatosensory nervous system. In endometriosis, neuropathic pain, which is a kind of neurogenic pain, can occur due to dysfunction in the central or peripheral nervous system in the absence of nociceptor stimulation. Nociceptive pain is different from neuropathic pain in that it is triggered by a specific stimulus in the body, such as the invasion of tissue by endometriosis seeding, whereas neuropathic pain is not. Therefore, it is common for patients to experience both types of pain in endometriosis. The diagnosis of different kinds of pain is primarily based on clinical findings (7,8).

Endometriosis is a chronic condition characterized by the presence of endometrial tissue outside the uterus, leading to functional endometrial glands and stroma lying outside the uterine cavity. This can result in a variety of symptoms that often fluctuate with the menstrual cycle. The symptoms can range from mild to severe and may include abdominal, buttock, perineal, rectal, lumbosacral, and vulvovaginal pain, as well as weakness, loss of bowel and/or bladder control and dyspareunia in some patients (9). Endometriosis can also result in neurological symptoms if the central or peripheral nervous system is affected, including leg pain, pelvic pain, cyclic radiculopathy of the lower limbs, urinary incontinence, and rarely, paraplegia.

The location and extent of compression of nerve elements from the endometrial mass determine the symptoms, which may include cyclic pain in the buttocks radiating to the foot. Symptoms usually worsen with hip movement and analgesic gait, gluteal atrophy, groin pain; ankle dorsiflexion weakness may also be present (10-12). Endometriosis affecting the sacral network is rare and can cause sciatica, hip pain, anal pain, pudendal pain, and gluteal atrophy as a result of superior and inferior gluteal nerves involvement (11).

In some cases, endometriosis can result in genital neurogenic pain due to inferior hypogastric entrapment plexopathy, causing burning, electrical, and cramping sensations in the anus, perineum, vaginal opening, or hypogastric pain (11-13). In rare cases, endometriosis can also present as incisional endometriosis at the anterior abdominal wall. Most reported cases appear after 3 months to 10 years post caesarean delivery and are often clinically mistaken for other conditions such as hernias, abscesses, suture granulomas, or lipomas. It is believed that abdominal wall endometriosis is the result of endometrial tissue seeding during surgery (14).

Logically, refractory abdominal wall pain due to endometriosis should respond to abdominal wall neural blocks, depending on the site of involvement. Inguinal endometriosis is another rare clinical condition, which affects women of childbearing age, with or without pelvic endometriosis. It is characterized by a painful/tender mass in the groin and premenstrual tenderness and/or swelling. Inguinal endometriosis may also develop as a mass in the inguinal region through direct implantation, coelomic metaplasia, tubal regurgitation, or lymphatic spread (15). Evidence from a study on patients with severe lower pelvic pain suggest that ilioinguinal and iliohypogastric nerve blocks could be a choice for managing refractory inguinal pain due to endometriosis (16).

Mechanisms of Pain Generation in Endometriosis

Nerve involvement is a well-established mechanism of pain generation in patients with endometriosis. Endometrial cells that have grown outside the uterus can directly invade or irritate peripheral nerves, causing pain (17). The process of neuroangiogenesis, which involves the formation of new blood vessels around nerves and subsequent inflammation and increased nerve activity, contributes to pain through perineural invasion of endometrial lesions (18). Endometriosis can also lead to peripheral and central sensitization, where nerves surrounding endometrial implants become more sensitive to pain and subsequently, the brain and spinal cord amplify the sensation. Scar tissue formation can cause constant, sharp pain by pressing or pulling on nerves and lead to hyperalgesia (19).

Pain intensity can indicate whether direct nerve involvement is present, with more severe pain indicating a higher possibility of direct nerve involvement (20). In addition, endometriosis may cause other nonspecific bowel and bladder symptoms, including, but not limited to constipation, diarrhea, and dysuria, leading to a delayed diagnosis or misdiagnosis (21). This highlights the complex pain mechanisms of endometriosis and the need for a multidisciplinary approach to manage the associated pain (Fig. 1) (22).

Endometriosis and Nerve Involvement in Chronic Pelvic Pain

Growing evidence suggests that the chronic pain experienced by women with endometriosis is due to nerve fiber involvement in the pelvic region. This principle is supported by the presence of nerve fibers in both the typical endometrium and in endometriotic lesions (23-25). For example, sciatic neuropathy, which is characterized by sharp, electric-like pain in the lower leg and foot, can occur when endometriosis causes compression or irritation of the sciatic nerve (26). This condition is known to stimulate pain throughout the

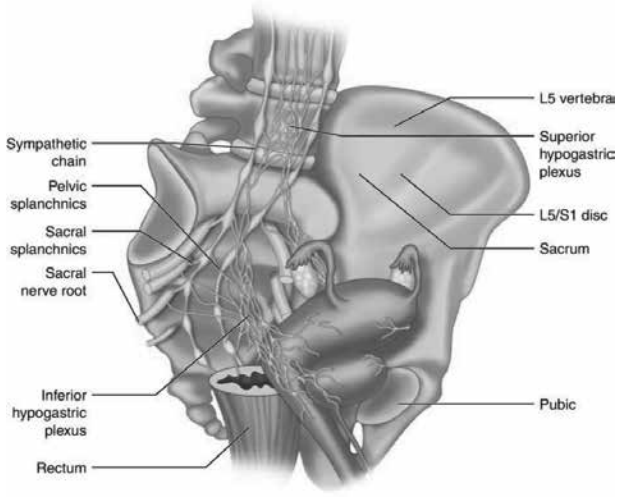

Fig. 1. *The anatomic locations of superior and inferior hypogastric plexus and ganglion impar, courtesy of Springer.*

entire leg even when a Straight Leg Raise test may return negative results. However, endometriosis can cause radiculopathy resulting from root nerve involvement, leading to a positive Straight Leg Raise test, with documented cases where endometriosis has been present within the neural foramen.

Endometriosis and sciatica are often misdiagnosed because of their unusual symptoms of endometriosis and an additional unexplained sciatica. This problem is especially relevant for a woman suffering from dysmenorrhea. Sciatica can persist for years and cause dysfunction in the lower extremities (27). Typically pain attacks are worse during the menstrual period, although in 10% of cases there is no association between pain and menstruation (13).

A difficult-to-diagnose cyclic sciatica lasting over a year is common. The sciatic nerve can be compressed as an endometrial cyst grows larger from internal bleeding and fluid accumulation, leading to pain worsening with shorter painless intervals. Paraesthesia, paresis, and areflexia may also be present in patients (10,11,13). Moreover, endometriosis can cause compression and irritation of pelvic nerves, leading to pain in the buttock area. Trigger points in the iliococcygeus, pubococcygeus, and puborectalis muscles can also contribute to this pain.

Endometriosis affecting the sacral network is relatively uncommon, and is usually observed with the development of severe rectal disease, causing stretching of the sacral hypogastric fascia (26,28,29). Sacral nerve involvement can result in sciatica (S2), hip pain (S3), anal pain (S4), as well as pudendal pain (S2,S3,S4). Furthermore, involvement of the superior gluteal nerve (L4,S5,S1) and the inferior gluteal nerve (L5,S1,S2), which supply the gluteus medius, minimus, and maximus respectively, can lead to gluteal atrophy. Overall, endometriosis can lead to a wide range of symptoms, depending on the amount and location of compression of nerve elements from the mass. It is important for clinicians to consider the potential involvement of the nervous system in endometriosis-associated pain, as this can aid in the diagnosis and management of the condition (23) (Table 1).

Diagnostic Ultrasound of Endometriosis Seeding and Entrapment Neuropathy

It is important for physicians to consider different presentations of endometriosis on ultrasound while diagnosing and managing the condition. Findings suggest that scar endometriosis may present on ultrasound as a solid hypoechoic nodule with hyperechoic spots, or as cystic areas with indistinct margins that are deeply infiltrative compared to the myometrium. There is a possibility that endometriosis may present on an ultrasound screen as a cystic mass with internal septa and hypoechoic content with minimal vascularization (30). It may also present as a hypoechoic, noncompressible, and noncalcified mass without visible flow signals around the peripheral part of the lesion (31).

Endometriosis can also appear in abdominal muscles as nodules or as a heterogeneous, mixed-to-hypoechoic, lobulated mass in the subcutaneous tissue. This mass can be mobile and can clearly separate from the anterior abdominal wall muscles and may display some intrinsic blood flow when evaluated using Doppler ultrasound (32). The ultrasound appearance of nerve entrapment may include an increased cross-section of the nerve, unclear boundaries, a hypoechoic region, an increase in nerve blood flow velocity, and a gradual loss of the normal fascicular echo pattern, leading to the disappearance of the characteristic "honeycomb" appearance (33).

Useful Nerve Blocks for Relieving Endometriosis Pelvic Pain

The sympathetic nervous system is an essential component in transmitting pain from internal organs, regardless of its cause. Endometriosis-associated pain symptoms can effectively be managed through the implementation of interventional pain management techniques. One such approach is the superior hypogastric plexus block (SHPB), which has been shown to be effective in treating persistent or intractable pelvic and rectal pain that has not responded to conservative pain treatment measures (34,35). The SHP, located ventrally to the abdominal aorta, is responsible for innervating hindgut structures such as the descending colon, sigmoid colon, and proximal rectum, as well as pelvic organs such as the uterus, ovaries, prostate, urinary bladder, testes, and seminal vesicles (36). The SHPB is a commonly used technique for managing pelvic visceral pain and has been found to produce positive outcomes for patients with refractory endometriosis (9). Importantly, the SHPB has been shown to significantly improve mental health status and quality of life of premenopausal women with endometriosis (37). The block can be performed using either a paravertebral or transdiscal approach and has been shown to lead to an improvement in quality of life that is sustained over time (34).

The inferior hypogastric plexus block (IHPB) is a less

commonly used technique for managing pelvic, perineal, and genital pain of benign or malignant origin, as accessing it is challenging due to its location in the presacral space. Despite this, an IHPB carries some risks, including nerve damage, vascular penetration, rectal puncture, hematoma, and infection (38).

Another pain management technique is the ganglion impar block, which can be used to treat malignant vulvar, rectal, and anal pain; intractable sacral and perineal pain (e.g., postherpetic neuralgia); and/or coccydynia (39). Additionally, endometriosis-related lumbosacral radiculoplexus neuropathy can be treated with differential neural blockade at the dorsal cutaneous nerve branches of T11, T12, L1, L2, L3, L4, L5, S1, S2, S3, and S4, depending on the clinical presentation (40). Other techniques for treating endometriosis-related pain include the use of S3 pulsed radiofrequency in conjunction with an inferior hypogastric plexus block or botulinum toxin injection, myofascial pain trigger point release, and neuromodulation. Furthermore, pelvic pain and coccydynia arising from endometriosis can respond to an ganglion impar block (41–45).

The most common indication for interrupting the sympathetic axes through a "nerve block" is to control visceral pain from pelvic viscera. The choice of an interventional technique versus the other is based on clinical presentation (46). SHPBs are targeted for pelvic visceral pain, rectal pain, and hindgut structures involved with endometriosis, such as descending colon, sigmoid colon, and proximal rectum, as well as pelvic organs such as the uterus, ovaries, prostate, bladder, testes, and seminal vesicles (47). In the presence of pelvic pain, perineal and genital, and presacral involvement with endometriosis, IHPB is the block of choice (48). When the vulva and anus are involved, and there is intractable sacral and perineal pain or coccydynia with endometriosis implantation, a ganglion impar block is an option (47).

Endometriosis is one of the pathologies that has a significant disease burden throughout the United States and the world. Because the disease presents several different manifestations, it has been relatively rare to focus primarily on pain patterns and therapies that target them. Using evidence-based medicine, according to the experience of expert interventionalists, we can find all the solutions to a problem and then choose the best solution based on the clinical manifestations of pain, collecting data based on our references in the article to provide us with an algorithmic approach. Our goal is to ease decision making for endometriosis interventional pain management by providing guidance for a diagnosis to pain physicians, resident physicians, and physician assistants. We hope this approach provides a template that can minimize unnecessary testing, control medical costs, and ensure the uniform provision of quality care in patient assessment (Fig. 2).

Table 1. *Mechanism of pain generation in endometriosis.*

Mechanism of Pain
Endometrial cells that have grown outside the uterus can directly invade or irritate peripheral nerves, impact the nerve fibres 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 nerve
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

The algorithmic approach to interventional pain management relies heavily on a patient's history, physical examination, and diagnostic ultrasound performed in the clinic. Paraclinical tests, such as magnetic resonance imaging or nerve conduction velocity, may also provide useful information. Currently, sacroiliac joint injections with SHPBs are among the most commonly used treatments, but they only alleviate visceral pelvic pain. Many patients still experience hip and buttock pain due to peripheral nerve entrapments, which may respond to hydrodissection of the peripheral nerves using dextrose (Fig. 3).

Peripheral Nerve Entrapment and Hydrodissection With Dextrose

The presence of entrapped peripheral nerves can cause chronic hypoxia and inflammation, leading to symptoms such as numbness, pain, tingling, and even muscle weakness and atrophy. The increased pressure on the trapped nerve causes disruptions to its microcirculation, including ischemia, impaired nerve conduction, decreased adhesion, increased vascular permeabil-

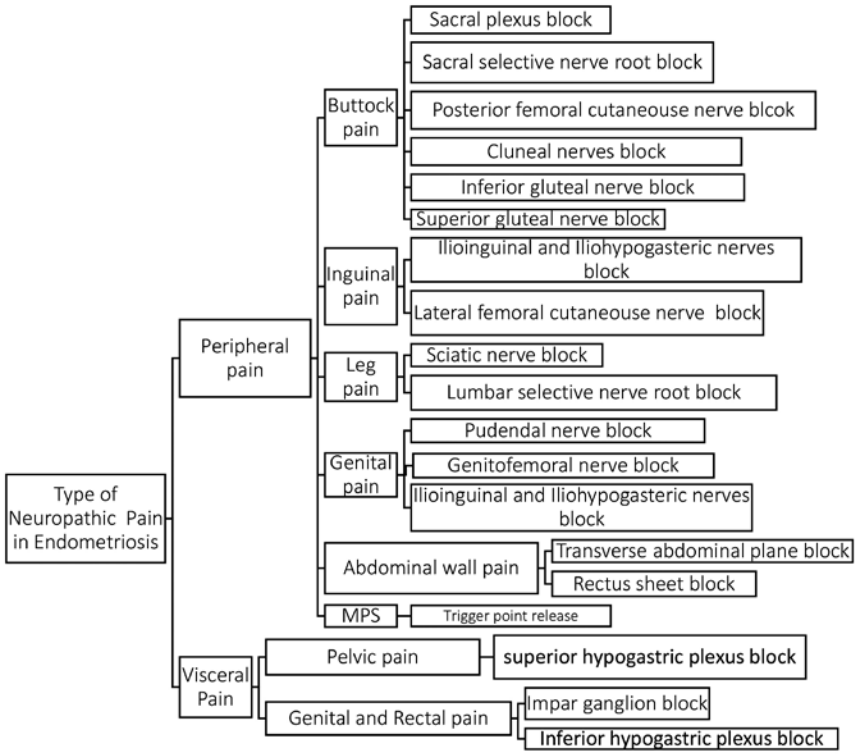

Fig. 2. *An algorithmic approach to interventional pain management for neuropathic pain in endometriosis.*
MPS, myofascial pain syndrome

ity, cessation of axoplasmic flow, and swelling of both the proximal and distal nerves. Hydrodissection using dextrose can separate the compressed and damaged nerve from surrounding soft tissue, reducing adhesion and damage from chronic contraction, and enhancing blood flow and nerve repair. This approach can initially alleviate symptoms and potentially reduce neurogenic inflammation (49-51).

Peripheral nerve entrapment is an unrecognized cause of pain and disability in endometriosis. It is defined as a segmental injury caused by pressure on a peripheral nerve due to an anatomical or pathological structure or process. Nerve entrapment can lead to clinical symptoms ranging from mild discomfort to numbness, paralysis, or debilitating pain. The nerves can be affected by several mechanisms, including mechanical compression, contraction, or excessive stretching. Nerve pain is characteristic ("neuropathic pain") and is often described as burning, shooting, lancinating, or "electric." This pain can increase over time due to "central sensitivity." Therefore, early hydrodissection is necessary, which involves a deep perineural injection into the scar tissue or fascia for releasing trapped nerves and dilution and washing of inflammatory mediators. The hydrodissection technique requires identifying nerves under ultrasound and aiming at the tip of the needle placed on each side of the nerve (perineural) but not within the nerve (intraneural). A low concentration dextrose injection (5%) reduces neuropathic inflammation and dissects the endometrial tissues around the nerve area, mechanically decompressing the nerve. The use of dextrose 5% in water delivers dextrose to the perineurial soft tissues, which may aid in nerve recovery after endometriosis involvement (52).

Limitations

Due to the complex and multifactorial nature of endometriosis, there is a lack of consistency in the clinical presentations of patients in terms of pain severity and associated symptoms, making it challenging to compare and evaluate the effectiveness of different interventional pain management techniques. Ad-

ditionally, our literature search only included studies published in English; this may have excluded important findings in other languages. Despite these limitations, our review provides valuable insights into the complex pain mechanisms of endometriosis and highlights the need for a multidisciplinary approach to manage associated pain effectively.

Conclusion

In conclusion, endometriosis is a complex condition that can result in various pain mechanisms, including nerve involvement, neuroangiogenesis, peripheral and central sensitization, and scar tissue formation. Pain intensity can indicate the extent of nerve involvement. Misdiagnosis can occur due to atypical symptoms, such as sciatica. Interventional pain management approaches, such as SHPBs and IHPBs, have been shown to be effective in managing endometriosis-associated pain. It is crucial for interventional pain management physicians to consider the potential involvement of the peripheral nervous system in endometriosis-associated pain for an accurate diagnosis and effective management of the condition. The goal of interventional pain management is to help patients with endometriosis to control their pain and improve their quality of life, and it should be viewed as a complement to other forms of treatment.

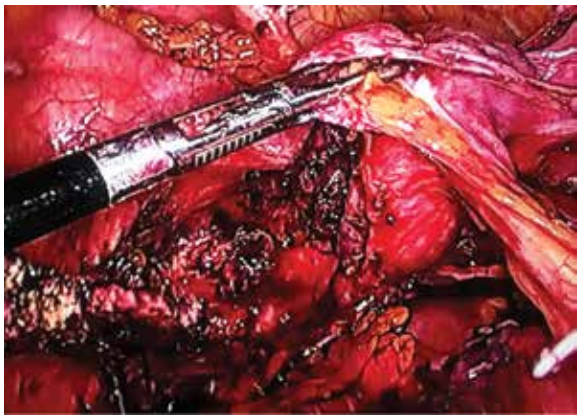

Fig. 3. ***Diffused endometrial seeding into the pelvic viscera can be seen by endoscopic hysterosalpingectomy.***
A 47-year-old woman suffered from chronic right buttock pain for several months, which radiated to her right distal leg and foot. The straight leg raise test was negative. Her pain developed gradually after experiencing menorrhagia and pelvic pain due to endometriosis and was described as constant pain originating in her buttock and intermittently radiating throughout her right leg. Conventional treatments, including endoscopic hysterosalpingectomy, failed to provide relief. With the patient prone, dextrose hydrodissection was performed under real-time ultrasound with a curvilinear probe, resulting in the release of all involved nerves (cluneal nerves, sciatic nerve, sacral plexus, superior and inferior gluteal nerve, pudendal nerve, and posterior cutaneous nerve of the thigh), which led to a dramatic reduction in pain. Injections into endometriosis masses are not recommended to prevent the possibility of seeding (53). (Adapted from the book: Helen Gharaei. (2023) Clinical Pearls in Interventional Pain Management. First Ed. Tehran: Aryateb Publishing).

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