



REVIEW ARTICLE

Endometriosis and unexplained musculoskeletal manifestations in reproductive-age women: A narrative review

Kamel REMITA, Atef DARWISH

ABSTRACT

Classically defined as a chronic, recurrent gynaecological disease characterized by progressive pelvic pain, infertility, and/or abnormal uterine bleeding, endometriosis is increasingly recognized for its systemic manifestations. Emerging evidence links the disease to broad inflammatory and neurobiological processes that may account for symptoms extending beyond the pelvis. Not uncommonly, endometriosis may present solely with musculoskeletal (MSK) manifestations, such as diverse pain patterns, muscle weakness, numbness, gait disturbance, or knee weakness, closely mimicking primary orthopaedic or rheumatological disorders. Pain in endometriosis arises through multiple interconnected mechanisms, including direct lesion infiltration, persistent inflammation, peripheral neuromuscular involvement, and central sensitization. Consequently, its clinical spectrum is broad, encompassing nociceptive MSK pain, neuropathic or radicular symptoms, joint-related pain, mass-forming lesions, and widespread nociplastic pain, often with a characteristic cyclical (catamenial) pattern. This represents a significant clinical gap, as affected patients frequently first seek care in non-gynaecological settings such as orthopaedic or rheumatology clinics. Diagnostic delays are common, averaging 5–10 years, during which patients are often managed symptomatically while the underlying aetiology remains unrecognized. The objective of this narrative review is to raise awareness among clinicians and synthesize evidence-based guidance for diagnosing and managing endometriosis-related MSK manifestations. We propose a stepwise diagnostic approach emphasizing careful history-taking for cyclical symptoms, focused physical examination, judicious use of imaging, and early gynaecological consultation. Management should be multimodal and integrated, combining hormonal therapies, surgical excision for refractory lesions, targeted rehabilitation, and pain neuroscience-informed strategies. Ultimately, optimizing outcomes requires MSK clinicians to serve as sentinels, recognizing red-flag presentations and initiating timely multidisciplinary co-management.

Keywords: Endometriosis, Musculoskeletal Pain, Diagnostic Delay, Extrapelvic Endometriosis, Catamenial Pain, Multidisciplinary Care.

Al Emadi hospital, Doha, Qatar

Received: 15 Dec 2025**Accepted:** 04 Jan 2026**Correspondance to:** Kamel REMITA

E-mail : kremita2001@yahoo.fr

1. INTRODUCTION: BRIDGING THE CLINICAL GAP

Endometriosis is a chronic, recurrent, oestrogen-dependent inflammatory disorder characterized by the presence of endometrial glands and stroma outside the endometrial cavity (1). Its precise aetiology remains incompletely understood, with accumulating evidence suggesting a multifactorial origin involving genetic susceptibility, epigenetic modifications, hyper-oestrogenic states, retrograde menstruation, and dysregulated immune responses (2,3). The condition affects approximately 3–10% of women of

reproductive age, with a substantially higher prevalence among those evaluated for chronic pelvic pain or infertility (4). Despite growing awareness, the interval between symptom onset and diagnosis remains prolonged, often spanning 5–10 years in many healthcare systems (5).

While classically associated with pelvic pain, dysmenorrhea, dyspareunia, infertility, or abnormal uterine bleeding, endometriosis may also manifest through extra-pelvic or referred pain patterns that closely resemble primary musculoskeletal (MSK) disorders. Clinical studies have shown that women with endometriosis may present with low back, hip, buttock, or lower-limb pain, pelvic floor dysfunction, and reduced pressure-pain thresholds (5–8). Consequently, many patients initially seek care from non-gynaecologic specialties, including rheumatology, orthopaedics, neurology, and primary care.

Adding further diagnostic complexity, recent population-based and meta-analytic studies have demonstrated a significant association between endometriosis and several autoimmune conditions, including systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, and autoimmune thyroid disease (9). The clinical overlap with these disorders may obscure the underlying cause of MSK symptoms and further delay accurate diagnosis.

Healthcare utilization studies confirm that a substantial proportion of patients with endometriosis first consult non-gynaecologic clinicians, contributing to fragmented care (5,6). This under-recognition represents a critical clinical gap: MSK practitioners are frequently the first point of contact for women whose symptoms are driven by endometriosis, yet practical guidance on when to suspect the disease remains limited. As has been noted, endometriosis is unlikely to be diagnosed unless it is considered.

Accordingly, this article aims to provide a concise, evidence-based framework to assist non-gynaecologist clinicians in recognizing key “red flags,” initiating an appropriate diagnostic workup, and facilitating timely multidisciplinary co-management in accordance with contemporary guidelines (10,11).

2. METHODOLOGY

This narrative review was designed to synthesize current evidence into a practical framework for clinicians evaluating musculoskeletal manifestations of endometriosis. We conducted a focused, concept-driven search of PubMed, Embase, and the Cochrane Library for publications from January 2000 to March 2025, using terms such as endometriosis, extrapelvic, musculoskeletal, neuropathic pain, catamenial, diagnosis, and management. Eligible sources included peer-reviewed original studies, systematic reviews, meta-analyses, clinical guidelines, and clinically informative case series. Non-English articles without accessible abstracts, duplicate publications, and studies lacking direct clinical relevance to musculoskeletal or neuropathic manifestations were excluded. Reference lists of key papers were manually reviewed. Given the heterogeneity of study designs and the exploratory nature of this topic, no formal quality scoring or predefined hierarchy of evidence was applied; instead, studies were selected and interpreted based on clinical relevance, methodological soundness, and consistency of reported patterns. Extracted information was organized thematically into four domains: (1) underlying mechanisms; (2) the spectrum of musculoskeletal presentations; (3) a stepwise diagnostic approach; and (4) integrative treatment considerations.

3. POSSIBLE UNDERLYING AETIOLOGY OF ENDOMETRIOSIS

The exact aetiology of endometriosis remains unknown and is likely multifactorial, with genetic susceptibility and environmental influences each contributing significantly to disease risk (12). Among proposed mechanisms, retrograde menstruation is thought to play a central role, though it does not fully explain the wide clinical spectrum. As illustrated in Figure 1 (Source: Adapted from Cousins et al., 2023), advances in research methodologies continue to generate new concepts regarding pathogenesis (13).

Recent genomic research increasingly supports the concept that endometriosis is not merely a localized pelvic disorder, but a systemic inflammatory disease with multi-organ involvement (14). Using an integrated genomics strategy, investigators have identified key molecular pathways, including phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and oestrogen receptor 1 (ESR1) signalling, which are current therapeutic targets in clinical trials (14–16). Cross-disease mapping has revealed substantial genetic overlap with immune-mediated disorders, supporting the potential repurposing of immunomodulatory therapies such as TNF inhibitors, IL-6/IL-6R blockade, and JAK inhibitors (14,17).

Notably, genes uniquely enriched in endometriosis point to disease-specific mechanisms like neutrophil degranulation, which may contribute to distant inflammatory effects and help explain extra-pelvic manifestations (14,18,19).

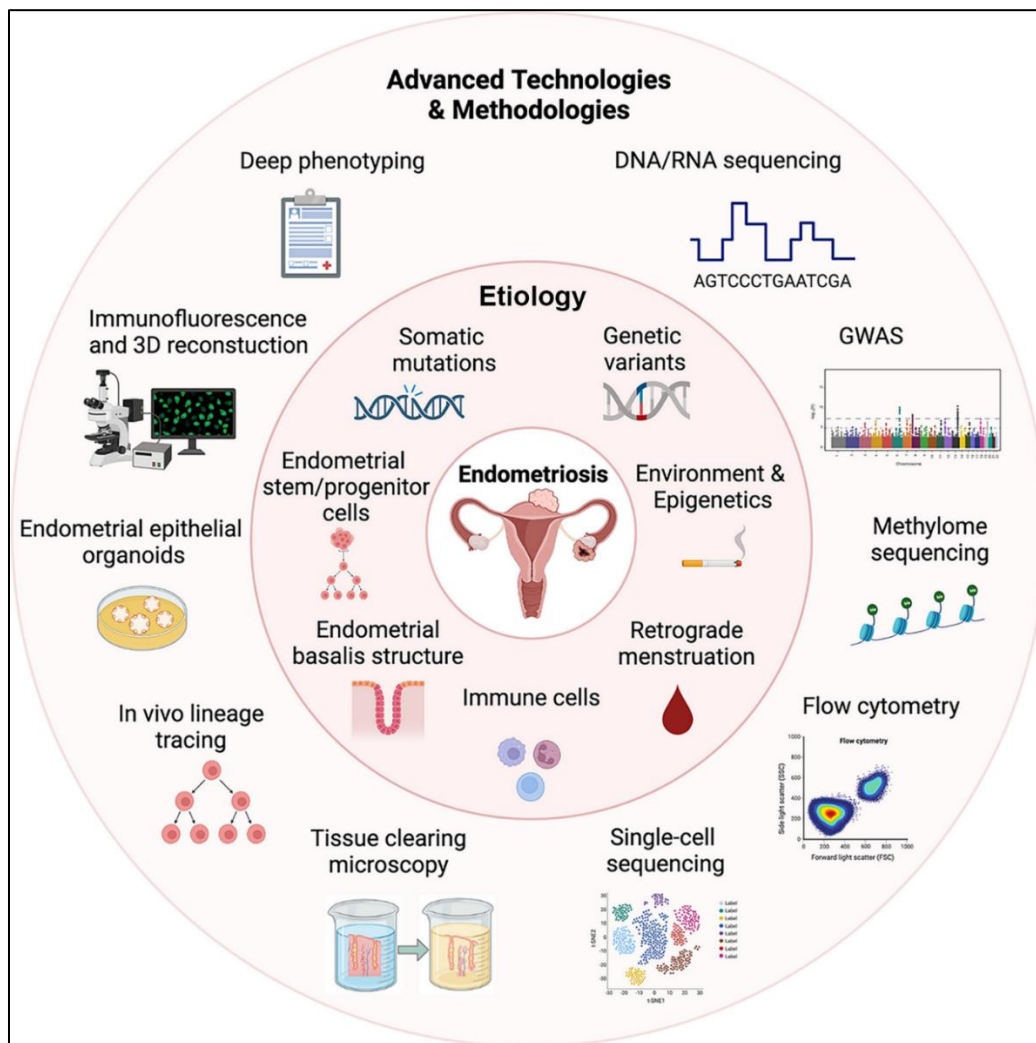


Figure 1. Advanced technologies and methodologies are enabling the generation of new concepts on the aetiology of endometriosis. (Source: Adapted from Cousins et.al., 2023).

4. PATHOPHYSIOLOGICAL MECHANISMS OF ENDOMETRIOSIS-INDUCED MSK MANIFESTATIONS

The musculoskeletal impact of endometriosis stems from a dynamic interplay between mechanical disruption, sustained inflammation, peripheral neural remodeling, and central nervous system amplification (20,21). These mechanisms frequently converge, producing pain patterns that extend beyond the pelvis and mimic primary musculoskeletal or neurological disorders (22) (See Table 1).

1. **Direct infiltration and mass effect:** Deep infiltrating endometriosis (DIE) may invade or compress major pelvic nerves—including the sciatic, pudendal, and gluteal branches, or involve supporting ligaments and soft tissues (23). Such mechanical involvement can result in focal neuropathic or radicular pain and may be accompanied by sensory or motor deficits (23). Figure 2 summarizes the potential neuromuscular effects attributable to endometriotic involvement.
2. **Inflammatory pathways:** Endometriotic lesions function as active inflammatory foci, recruiting immune cells and releasing cytokines (e.g., IL-1 β , IL-6, TNF- α) and neurotrophins like nerve growth factor (NGF) that sensitize nociceptors (20). This milieu contributes to localized pain and systemic features such as arthralgia, fatigue, and generalized pain hypersensitivity.
3. **Peripheral and central neuromuscular sequelae:** Sustained nociceptive input can trigger maladaptive musculoskeletal responses, including pelvic floor hypertonicity, myofascial trigger points, and altered gait (24). Cross-sensitization between pelvic viscera and surrounding musculature can further amplify symptoms.

4. **Central sensitization and comorbidity:** Persistent peripheral input can induce neuroplastic changes within the central nervous system, resulting in nociplastic pain characterized by heightened sensory gain and impaired descending inhibition (22). This helps explain the frequent coexistence of fibromyalgia-like symptoms and pain persistence after surgical excision (24).

Table 1. Pathophysiological mechanisms of musculoskeletal pain in endometriosis.

Mechanism	Key biological processes & mediators
Direct infiltration & Mass effect	Physical invasion/compression of nerves, ligaments, muscle, or fascia by deep-infiltrating endometriosis (DIE) lesions.
Inflammatory pathways	• Lesions act as inflammatory hubs secreting cytokines (IL-1β, IL-6, TNF-α) and neurotrophins (NGF). • Recruitment of macrophages/mast cells. • Peripheral sensitization of nociceptors.
Peripheral & Central neuromuscular sequelae	• Chronic pain $\rightarrow$ guarding reflexes, muscle hypertonia, and altered posture/gait. • Development of myofascial trigger points. • Cross-sensitization between pelvic viscera and surrounding musculature.
Central sensitization	• Prolonged nociceptive input $\rightarrow$ neuroplastic changes in the central nervous system. • Impaired descending inhibition, amplified pain processing.

Abbreviations: DIE, deep-infiltrating endometriosis; IL, interleukin; TNF- α , tumour necrosis factor-alpha; NGF, nerve growth factor; MSK, musculoskeletal.

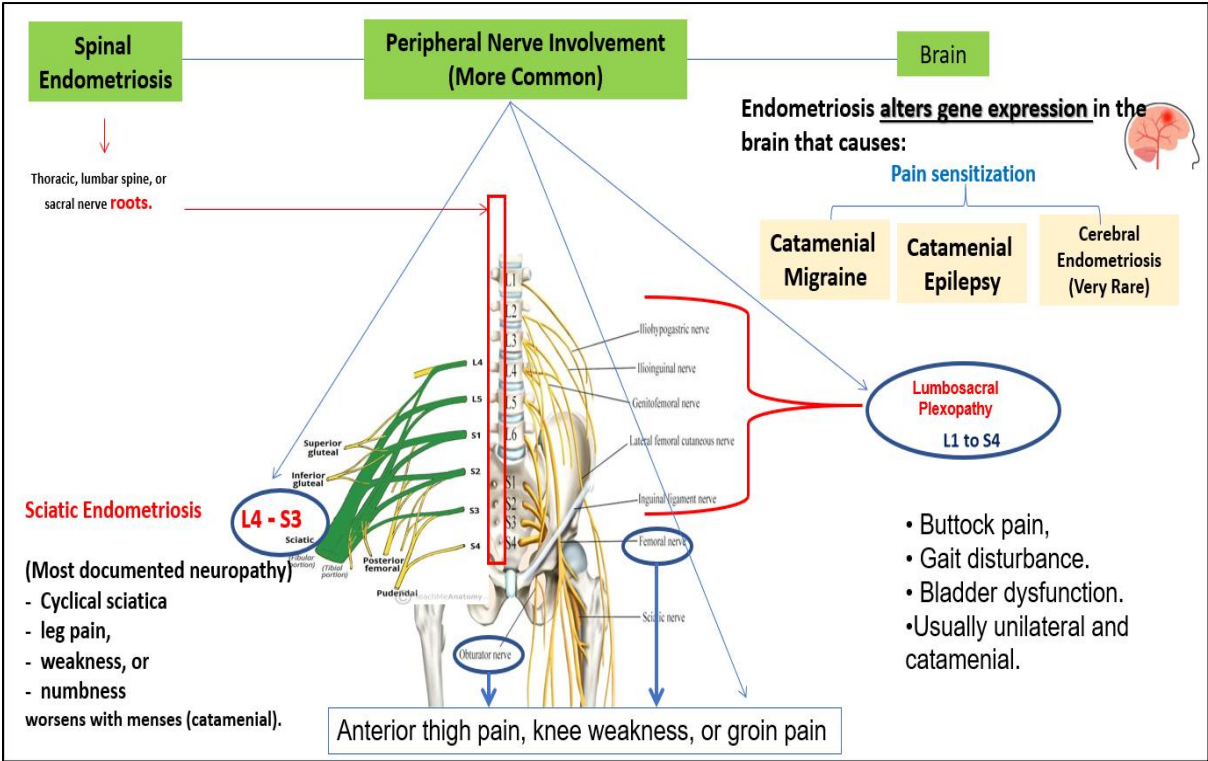


Figure 2. Potential neuromuscular effects of endometriosis.

5. CLINICAL SPECTRUM

Endometriosis may affect muscles, fascia, peripheral nerves, joints, and periarticular soft tissues through overlapping nociceptive, neuropathic, inflammatory, and nociplastic mechanisms. The resulting clinical picture is heterogeneous and often indistinguishable from primary musculoskeletal disease (25) (See Table 2).

Table 2. The clinical spectrum of musculoskeletal endometriosis: a guide for differential diagnosis.

Pain Phenotype & Primary Driver	Key Characteristics & Classic Locations	Common MSK/Rheumatologic Mimics
Nociceptive Pain (Local inflammation, tissue irritation)	Deep, aching pain. Pelvis, lower back, abdominal wall. Clear catamenial pattern.	Mechanical low back pain, myofascial pain syndrome, abdominal wall strain.
Neuropathic/Radicular Pain (Direct nerve infiltration/compression)	Burning, shooting, radiating pain ± paresthesia. Sciatic, femoral, pudendal distributions. Cyclical exacerbation.	Lumbar radiculopathy, piriformis syndrome, peripheral neuropathy.
Joint-Related Pain (Peri-articular inflammation, cytokines)	Pain/stiffness in hips, knees, shoulders. May be cyclic or persistent. RF/anti-CCP normal.	Inflammatory arthritis (RA, SpA), osteoarthritis, polymyalgia rheumatica.
Mass-Forming Lesion (Fibrotic reaction around ectopic tissue)	Palpable tender nodule. Abdominal wall scars, gluteals, thigh. May swell with menses.	Soft-tissue sarcoma, lipoma, hematoma, hernia, neuroma.
Widespread/Nociplastic Pain (Central sensitization)	Diffuse myalgia, hyperalgesia, fatigue, poor sleep. Catamenial pattern may be lost.	Fibromyalgia, chronic fatigue syndrome, central sensitization syndromes.

Abbreviations: MSK, musculoskeletal; RA, rheumatoid arthritis; SpA, spondyloarthritis; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies.

A key diagnostic clue is a catamenial pattern, characterized by cyclical symptom fluctuation with the menstrual cycle, typically intensifying in the perimenstrual period (26,27). Although timing and severity vary, recognizing this pattern markedly increases the likelihood of an endometriotic aetiology. Diagnostic delay remains substantial, often exceeding 5–7 years, highlighting the need for early cross-disciplinary recognition of menstrual-related symptom patterns (28). Clinicians should routinely inquire about cyclical exacerbation when evaluating reproductive-age patients with unexplained MSK complaints (25,29).

The clinical manifestations may be categorized into the following domains:

- Nociceptive musculoskeletal pain:** Patients often describe deep, aching pain in the pelvis, abdominal wall, lumbar region, or proximal limbs, with a characteristic catamenial pattern (30,31). These symptoms are often mistaken for mechanical back pain or myofascial pain (33).
- Neuropathic and radicular symptoms:** Neuropathic pain arises from lesion infiltration or compression of peripheral nerves, plexuses, or nerve roots, leading to paraesthesia, radiating pain, or weakness (35). Presentations like catamenial sciatica or femoral neuropathy are increasingly recognized (36). In one cohort, 44.1% of symptomatic patients had positive neuropathic pain scores (37).
- Joint-Related pain and arthropathy:** Joint-related manifestations can occur through peri-articular soft-tissue involvement or inflammatory signalling, despite direct synovial invasion being rare (40). Patients may develop pain in the hips, knees, or shoulders, sometimes with menstrual exacerbation (41). This can resemble inflammatory arthritis or osteoarthritis (42).
- Mass-Forming lesions and structural abnormalities:** Ectopic tissue may form discrete nodules within skeletal muscle, fascia, or peri-articular structures, commonly in the abdominal wall, rectus abdominis, or gluteal muscles (44,45). Such masses are frequently mistaken for hernias, lipomas, or soft-tissue tumours (47). MRI is the preferred modality for evaluation (48).
- Widespread, nociplastic, or mixed pain syndromes:** Chronic input can induce central sensitization, resulting in widespread myalgia, hyperalgesia, and fatigue (49). This phenotype frequently overlaps with chronic widespread pain or fibromyalgia (50). Cyclical worsening of generalized pain remains a key diagnostic clue (52).

6. A PRAGMATIC DIAGNOSTIC FRAMEWORK FOR THE MSK CLINICIAN

Diagnosing musculoskeletal endometriosis requires a systematic assessment anchored in a menstrual-focused history, targeted examination, and stepwise imaging strategy (30,31).

1. **Red-Flag history and symptom patterns:** A careful history is the most informative tool. Key elements include cyclical/perimenstrual pain exacerbation; pain location (e.g., deep buttock/hip); abdominal wall pain near surgical scars; diffuse symptoms; associated gynaecologic symptoms (dysmenorrhea, dyspareunia); and poor response to standard MSK therapies (30,31,35,40,44,45). Practical note: Record the specific temporal relationship between pain intensity and the menstrual cycle.
2. **Focused physical examination:** Non-gynecologic clinicians can identify reproducible signs. This includes palpating abdominal wall scars for nodules; assessing pelvic floor and adjacent musculature (gluteals, adductors) for hypertonia/trigger points; and performing a basic neurologic screen for radicular features (30,35,36,44,45). Clinical tip: Document whether findings vary with the menstrual cycle.
3. **Imaging and laboratory workup:** Imaging complements history and examination.
 - *Ultrasound:* Transvaginal ultrasound is first line for suspected pelvic lesions. Targeted abdominal-wall ultrasound is appropriate for scar or subcutaneous masses (44,47).
 - *Magnetic Resonance Imaging (MRI):* Pelvic/regional MRI is preferred for evaluating deep infiltrating disease, muscular involvement, neural pathways, or complex soft-tissue masses, especially when ultrasound is negative (32,45).
 - *Limitations:* Normal imaging does not exclude peritoneal, microscopic, or early deep disease (32).
 - *Laboratory testing:* CBC, CRP, and ESR help exclude other inflammatory processes but are not diagnostic for endometriosis (40).
4. **Stepwise diagnostic pathway and collaboration:** A structured approach minimizes delay. After screening and examination, appropriate imaging should be obtained. Patients with persistent symptoms or inconclusive findings should be referred to gynaecology or a multidisciplinary team for consideration of diagnostic laparoscopy, which with histopathology remains the gold standard (30,35,44,47). Figure 3 outlines a proposed diagnostic pathway.

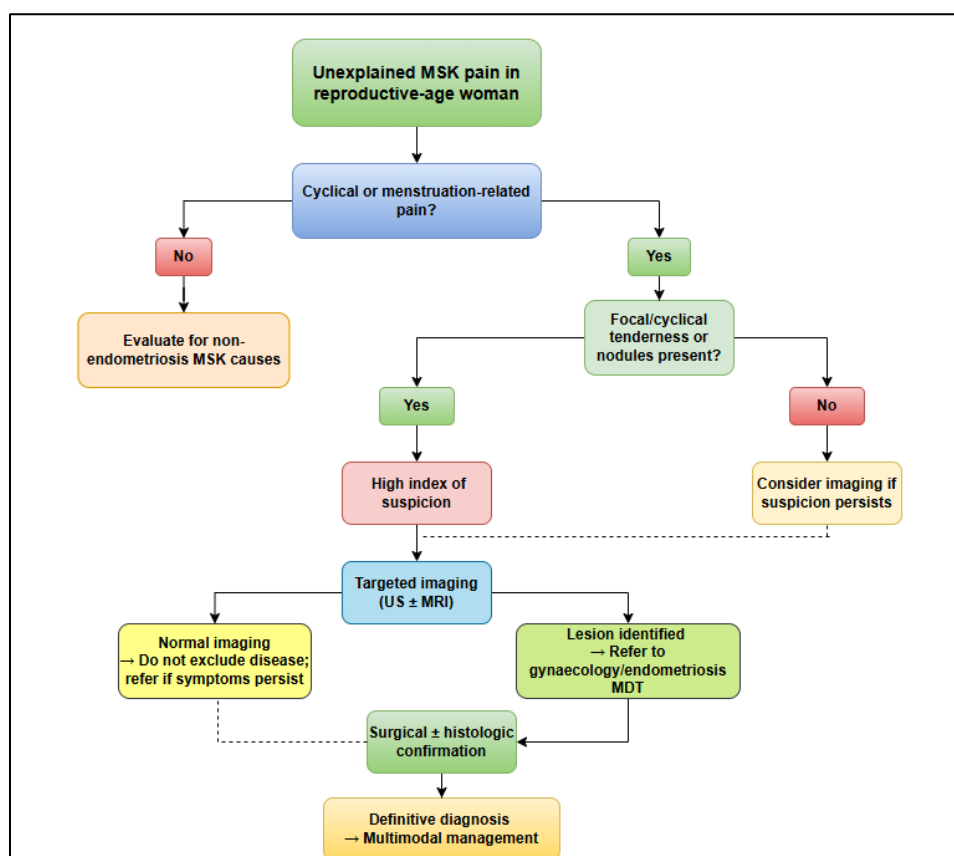


Figure 3. Proposed Conceptual Diagnostic Framework for Suspected Musculoskeletal Endometriosis

Abbreviations: MSK – Musculoskeletal; MDT – Multidisciplinary Team; MRI – Magnetic Resonance Imaging; US – Ultrasound; CBC – Complete Blood Count; CRP – C-reactive Protein; ESR – Erythrocyte Sedimentation Rate.

7. INTEGRATED MANAGEMENT PRINCIPLES

Management requires an integrated strategy addressing hormonal responsiveness, structural pathology, and pain-processing mechanisms (53-55).

1. **Medical treatment:** Medical treatment: Systemic hormonal therapies, including combined oral contraceptives, progestogens, and GnRH agonists or antagonists, are commonly used first-line options to reduce cyclical activation of ectopic tissue and alleviate pain (52,53). However, tolerability, patient adherence, and long-term acceptability may be limited by adverse effects such as breakthrough bleeding, mood changes, hypoestrogenic symptoms, and concerns regarding prolonged use. Treatment response is heterogeneous, and sustained benefit must be weighed against potential risks, underscoring the need for individualized decision-making and multidisciplinary follow-up. NSAIDs may provide adjunctive analgesia but do not modify disease progression (53,56).
2. **Surgical considerations:** Surgical excision is the mainstay for focal extrapelvic or deeply infiltrating lesions causing persistent pain, neurologic deficits, or mass effect unresponsive to medical therapy (56,57). Complete excision with careful attention to margins provides the best chance for durable relief (56,57). Multidisciplinary surgical planning optimizes outcomes (56,57).
3. **The essential role of rehabilitation:** Rehabilitation should be integrated early. Pelvic-floor physiotherapy (manual therapy, biofeedback, graded training) reduces focal pain (60). Core stabilization, biomechanical correction, and individualized exercise programs address secondary dysfunction (61).
4. **Pain management strategies:** For central sensitization, multimodal strategies are key. Neuromodulatory agents (e.g., TCAs, SNRIs, gabapentinoids) can alleviate neuropathic features (62,63). Non-pharmacologic interventions like cognitive behavioural therapy (CBT), pain neuroscience education, and mindfulness support pain modulation and coping (63-65). A biopsychosocial, multidisciplinary model yields optimal outcomes (53,60,64).

8. DISCUSSION

This review addresses the under-recognition of endometriosis in MSK medicine, rheumatology, orthopaedics, and primary care. Our analysis confirms that endometriosis is a systemic inflammatory condition capable of producing diverse musculoskeletal and neuropathic symptoms (14,33,51). Mounting epidemiological evidence underscores this systemic nature, revealing a significant association with autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus (65-67), highlighting a shared dysregulated immune milieu (68).

The pathophysiological triad of direct infiltration, sustained inflammation, and neuroplastic remodelling provides a coherent biological explanation for pain that transcends pelvic boundaries (20-22). The central clinical insight is that a cyclical, catamenial pain pattern is the most potent historical clue, yet it is frequently overlooked (27,28,30).

The pragmatic framework proposed here redefines the role of the MSK clinician as an essential sentinel. By systematically screening for red flags, clinicians can interrupt the cycle of misdiagnosis (6,8,29). This stepwise approach is designed to be efficient, acknowledging that normal imaging does not exclude the diagnosis (32,48).

Effective care requires a phenotype-matched strategy. While hormonal suppression and surgery are cornerstones (52,54,56,57), the high prevalence of central sensitization necessitates concurrent integration of rehabilitation and neuromodulation (37,50,62). Physical therapy must address specific pain mechanisms (60,61), and pain management should target nociplastic pain (49,63,64). Several limitations of the current evidence base must be acknowledged. High-quality prospective studies quantifying the prevalence of specific extrapelvic manifestations are needed. The diagnostic accuracy of proposed "red flags" requires formal validation. Research into optimal integrated treatment pathways for musculoskeletal endometriosis is still nascent.

Implementing this framework faces barriers, including time constraints and lack of awareness. Overcoming these requires efforts in continuing medical education, streamlined referral pathways, and a fundamental shift in perspective when evaluating chronic pain in reproductive-age women.

9. CONCLUSION

Endometriosis is a systemic inflammatory disease capable of producing a complex array of musculoskeletal symptoms that extend far beyond the pelvis. For a reproductive-age woman presenting with unexplained lower back, hip, buttock, or abdominal wall pain, endometriosis must be a key diagnostic consideration. This review consolidates the evidence linking ectopic endometrial tissue to

diverse pain phenotypes via genetic, inflammatory, and neuropathic mechanisms. The consistent finding of a catamenial symptom pattern serves as the most vital, yet frequently missed, clinical clue. The provided pragmatic framework empowers the MSK clinician to screen effectively, perform targeted assessment, utilize imaging judiciously, and initiate collaborative referral.

Closing the diagnostic gap requires a fundamental shift in perspective. MSK clinicians are essential sentinels in identifying endometriosis earlier. By incorporating targeted questions about menstrual cyclicity, clinicians can disrupt the cycle of misdiagnosis. Effective management is inherently multidisciplinary, demanding collaboration to address the hormonal, structural, biomechanical, and central nervous system components of the disease. Future efforts must focus on validating diagnostic screening tools, developing evidence-based integrated care pathways, and enhancing interdisciplinary education. By raising awareness and equipping clinicians with a structured approach, we can significantly shorten the diagnostic odyssey and improve the quality of life for the millions of women whose endometriosis pain has been hiding in plain sight.

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