Inflammation Beyond the Lesion

A Multi-System Framework for Endometriosis Pain Management

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A B S T R A C T

Endometriosis pain frequently persists or recurs despite appropriate surgical and hormonal treatment. This paper presents evidence that chronic inflammation—operating through neuroangiogenesis, central sensitization, gut-immune dysregulation, and progesterone resistance—drives pain independent of lesion presence. I propose a multi-system inflammatory framework that complements surgical excision and pelvic floor therapy across the care continuum: pre-operative optimization, post-operative support, non-surgical management, and long-term maintenance. This approach targets the systemic dysfunction that influences surgical outcomes, recovery trajectories, and disease recurrence. Clinical indications for referral and patient selection criteria are provided for excision surgeons, pelvic floor physical therapists, and other specialists seeking coordinated care options for complex endometriosis patients.

1. Introduction: The Clinical Challenge

Endometriosis affects approximately 10% of reproductive-age women worldwide, including nearly 9 million in the United States. Despite its prevalence, the average diagnostic delay remains 5 to 12 years from symptom onset to diagnosis, with most women consulting three or more clinicians before receiving answers. [1]

The conventional treatment paradigm offers two primary options: hormonal suppression or surgical excision. Both are evidence-based and appropriate for many patients. However, their limitations are increasingly documented. In a network meta-analysis of 1,680 women from 15 clinical trials, hormonal medications produced clinically significant pain reduction, yet 11–19% of individuals experience no pain reduction with hormonal therapy, and 25–34% experience recurrent pelvic pain within 12 months of discontinuing treatment. [1] Surgical outcomes present a similarly complex picture. Taylor et al. reported that 40–45% of women experience pain recurrence after surgery, with a 15–20% probability of requiring repeat surgery within two years, reaching 50% within five to seven years. [2] A 2025 JAMA systematic review offers more granular data: among 25 studies (n = 2,652) of women who underwent surgical removal of lesions without postoperative hormone treatment, 25% reported persistent pain at a median follow-up of 24 months, while 15.8% experienced recurrent pain specifically attributable to endometriosis. [1] The discrepancy likely reflects differences in study populations, definitions of recurrence, and whether postoperative hormonal suppression was used—underscoring that surgical outcomes depend heavily on the broader management context. Among patients who undergo hysterectomy for endometriosis, approximately 25% experience recurrent pelvic pain and 10% undergo additional surgery—and notably, nearly 50% of patients with a history of

endometriosis who undergo hysterectomy for recurrent pelvic pain do not have evidence of recurrent endometriosis lesions at the time of surgery. [1]

These statistics do not reflect surgical failure—they reflect the multi-system nature of the disease. Endometriosis is not merely ectopic tissue; it is a chronic inflammatory condition with hormonal, immunological, neurological, and metabolic dimensions. Addressing only the anatomical component, while essential, leaves other disease drivers untreated.

This paper proposes a complementary framework: systematic attention to the inflammatory drivers that influence surgical outcomes, recovery trajectories, and long-term disease management—whether a patient is preparing for surgery, recovering from it, managing non-surgically, or maintaining remission.

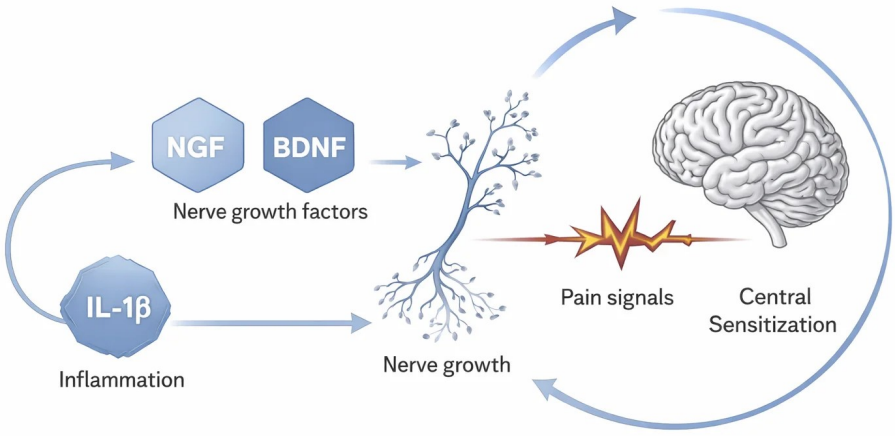
2. Mechanisms: How Inflammation Perpetuates Pain

2.1 Neuroangiogenesis and Central Sensitization

Endometriosis actively recruits nerve fibers into lesions and surrounding tissue through neuroangiogenesis. Inflammatory cytokines—particularly interleukin-1β (IL-1β)—stimulate production of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), promoting aberrant nerve proliferation. [3,4] Critically, **this nerve growth can persist even after surgical removal of lesions**. The inflammatory microenvironment and continued neurotrophin production maintain pain signaling independent of the original tissue. [5]

As peripheral pain signals persist, the central nervous system undergoes maladaptive changes—central sensitization—in which the spinal cord and brain become hyperresponsive to pain signals. [6,7] Studies find that 74.8% of women with chronic pelvic pain show evidence of central sensitization on validated screening tools. [8] This explains why pain severity often correlates poorly with lesion burden, why some patients develop widespread pain beyond the pelvis, and why treating lesions alone may not resolve symptoms.

Figure 1: The Inflammation-Pain Cycle



Inflammation (IL-1β) triggers nerve growth factors, promoting aberrant nerve proliferation. Pain signals feed back to central sensitization, which amplifies inflammation—creating a self-perpetuating cycle that can persist after lesion removal.

2.2 Gut-Immune Dysregulation

The gut microbiome plays a critical role in estrogen metabolism through bacterial genes collectively termed the estrobolome. [10] These bacteria produce β-glucuronidase and related enzymes that deconjugate and reactivate estrogen, influencing circulating levels. Studies demonstrate altered gut microbiota composition in endometriosis patients, with changes in bacterial populations regulating estrogen metabolism. [11,12] Animal models show that endometriosis-associated dysbiosis promotes systemic inflammation and altered immune metabolism.

Given that endometriosis is fundamentally an inflammatory disease—characterized by elevated cytokines, macrophage infiltration, and immune dysfunction—addressing gut health becomes relevant for modulating inflammatory drivers. [13]

2.3 Progesterone Resistance

While endometriosis is appropriately characterized as estrogen-dependent, the hormonal picture is more nuanced. Endometriotic lesions express abnormally high aromatase levels, creating local estrogen production independent of ovarian function. Simultaneously, progesterone resistance—in which tissue fails to respond appropriately to progesterone despite adequate circulating levels—prevents normal anti-proliferative and anti-inflammatory effects. [2,14] This resistance stems from decreased progesterone receptor B expression, epigenetic silencing, and chronic inflammation interfering with progesterone signaling. [15]

Progesterone resistance explains why some patients fail to respond to progestin therapy and why symptoms may persist despite hormonal suppression—the tissue itself cannot respond appropriately.

3. A Multi-System Approach Across the Care Continuum

The mechanisms above share a common thread: chronic inflammation operating through multiple systems simultaneously. Effective comprehensive care therefore requires attention to these inflammatory drivers—not as a replacement for surgery or pelvic floor therapy, but as a complement that can improve outcomes at every stage of treatment.

Table 1: Multi-System Support Across the Care Continuum

Stage	Clinical Goal	Multi-System Interventions
Pre-Surgical Optimization	Reduce systemic inflammation, optimize healing capacity, address gut dysfunction pre-op	Anti-inflammatory protocols, gut restoration, sleep/stress optimization, metabolic support
Post-Surgical Support	Support recovery, address persistent symptoms, prevent recurrence	Central sensitization treatment, hormonal optimization, ongoing inflammation management
Non-Surgical Management	Comprehensive symptom control for patients not pursuing or not candidates for surgery	Full protocol: hormonal, gut-immune, nervous system, metabolic interventions

Long-Term Maintenance	Sustain remission, prevent recurrence, optimize overall health	Maintenance protocols, periodic reassessment, lifestyle optimization

Table 2: Multi-System Treatment Targets

System	Mechanism	Clinical Interventions
Hormonal	Estrogen dominance, local aromatase activity, progesterone resistance	Bioidentical progesterone support, estrogen metabolism optimization, aromatase modulation
Gut-Immune	Estrobolome dysregulation, SIBO/IMO, intestinal permeability, systemic inflammation	Targeted antimicrobials, microbiome restoration, gut barrier support, anti-inflammatory protocols
Nervous System	Central sensitization, neuroplastic pain, autonomic dysregulation	Pain Reprocessing Therapy, somatic tracking, vagal tone optimization, sleep/circadian restoration
Metabolic	Mitochondrial dysfunction, oxidative stress, metabolic inflammation	Targeted supplementation, anti-inflammatory nutrition, movement optimization

3.1 Pain Reprocessing Therapy: Evidence Base

Pain Reprocessing Therapy (PRT) is a psychological treatment targeting central sensitization by helping patients reconceptualize chronic pain as arising from learned neural pathways rather than ongoing tissue damage. In a randomized controlled trial of chronic back pain, 66% of patients receiving PRT were pain-free or nearly pain-free at post-treatment, compared to 20% receiving placebo and 10% receiving usual care. At five-year follow-up, 55% of PRT participants remained pain-free or nearly pain-free, compared to 26% receiving placebo and 36% receiving usual care—demonstrating durable, long-term benefits. [16,17]

While PRT has not yet been studied specifically in endometriosis, the mechanisms it targets are highly relevant to persistent endometriosis pain, particularly for patients whose pain is disproportionate to lesion burden or persists despite appropriate surgical treatment.

4. Clinical Vignettes

The following cases illustrate clinical presentations that benefit from multi-system inflammatory treatment.

Case 1: Post-Surgical Persistent Pain

Presentation: 34-year-old woman, 8 months post-excision with an experienced surgeon. Pathology confirmed complete excision of stage III endometriosis. Pre-operative pain was 8/10; current pain remains 6/10. She reports “the character of the pain is different—less sharp, more diffuse” but functionally she remains limited. She has completed 12 sessions of pelvic floor PT with modest improvement in muscle tension but no significant change in overall pain.

Clinical reasoning: The shift from localized to diffuse pain suggests central sensitization. Persistent pain despite complete excision and adequate PT indicates inflammatory and nervous system drivers operating independently of remaining lesions.

Multi-system approach: Pain Reprocessing Therapy for central sensitization, gut assessment (she also reports significant bloating), inflammatory marker evaluation, and hormonal optimization to support the surgical outcome.

Case 2: Pre-Surgical Optimization

Presentation: 29-year-old woman scheduled for excision surgery in 10 weeks. Imaging suggests deep infiltrating endometriosis with bowel involvement. She reports significant fatigue, chronic constipation alternating with diarrhea, brain fog, and sleep disruption in addition to pelvic pain. She asks: “Is there anything I can do before surgery to improve my chances of a good outcome?”

Clinical reasoning: Her systemic symptoms suggest significant inflammatory burden and gut dysfunction. Addressing these pre-operatively may improve surgical healing, reduce post-operative complications, and decrease the likelihood of persistent symptoms after anatomically successful surgery.

Multi-system approach: 10-week pre-surgical protocol focusing on gut restoration (SIBO assessment, microbiome support), anti-inflammatory interventions, sleep optimization, and metabolic support to optimize her physiological state before surgery.

5. Clinical Decision Guide: When to Refer

Figure 2: Referral Decision Algorithm

Clinical Presentation	Referral Indication
Pre-surgical patient (any stage)	Optimization: gut restoration, anti-inflammatory protocols, metabolic support
Post-surgical persistent pain (6+ months, clean margins)	Central sensitization assessment, inflammatory driver workup
Pain disproportionate to lesion burden	Central sensitization screening, nervous system evaluation
Significant GI dysfunction (endo belly, IBS-type symptoms, suspected SIBO)	Gut-immune workup, estrobolome assessment
Failed progestin therapy	Progesterone resistance evaluation, alternative hormonal approaches
PT plateau despite good manual work	Underlying inflammatory and hormonal driver assessment
Non-surgical management desired with comprehensive approach needed	Full multi-system protocol

6. Patient Selection

Appropriate candidates for multi-system inflammatory treatment demonstrate:

- Motivation to engage in a comprehensive, 4-month protocol
- Willingness to examine diet, stress, and lifestyle factors
- Capacity for active participation in treatment
- Financial ability to invest in cash-pay care ($3,499 program + labs/supplements)

Patients who may not be appropriate include:

- Those in acute crisis requiring surgical intervention
- Patients seeking a quick fix or single-modality treatment
- Those unwilling to modify diet or lifestyle factors
- Patients who require insurance-based care

7. Collaborative Care Model

This approach is designed to complement—not replace—surgical excision and pelvic floor physical therapy.

For surgeons: I address the systemic inflammatory environment that influences surgical outcomes and recurrence risk. Pre-operative optimization may improve healing; post-operative support addresses persistent symptoms that are not surgical failures but rather reflect ongoing inflammatory and nervous system dysfunction.

For pelvic floor PTs: I address the inflammatory and hormonal factors that may be causing muscle guarding to return despite good manual work. When patients plateau, underlying systemic drivers often explain the stall.

For GI specialists: I address the functional gut dysfunction and estrobolome dysregulation common in endometriosis after structural pathology has been ruled out.

I am happy to provide progress notes and coordinate care (with patient consent). Direct communication improves outcomes.

8. Conclusion

Endometriosis is a multi-system inflammatory disease that extends beyond ectopic lesions. Current evidence demonstrates that neuroangiogenesis, central sensitization, gut-immune dysregulation, and progesterone resistance perpetuate pain independent of lesion presence—and influence outcomes across the treatment continuum.

A multi-system approach addressing these inflammatory pathways offers a logical complement to surgical and pelvic floor interventions—whether optimizing patients before surgery, supporting recovery afterward, managing non-surgically, or maintaining long-term remission.

For patients who are stuck, who plateau in PT, who have systemic symptoms beyond pelvic pain, or who want to optimize their chances of a good surgical outcome, systematic attention to these drivers may provide the missing piece.

I welcome the opportunity to discuss specific cases or explore collaborative referral relationships.

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