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ADVANCING ENDOMETRIOSIS CLINICAL RESEARCH THROUGH INTEGRATED EXPERTISE

Author: Dr. Maxime Jeljeli, MD, PhD, Medical Director, Immunology, Allergies & Inflammatory Diseases

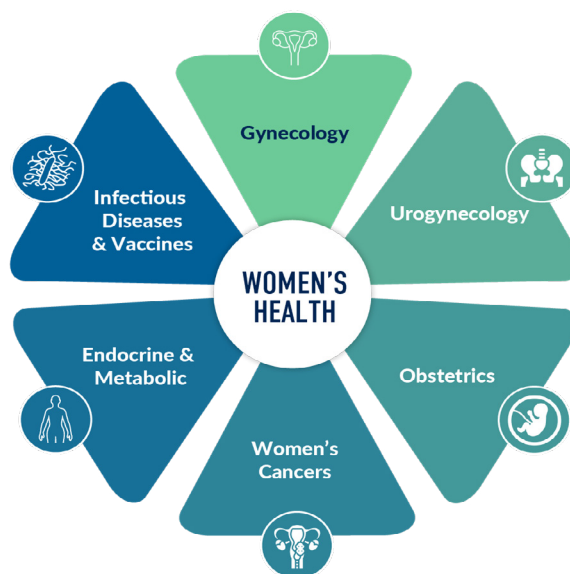
Despite affecting millions of women globally, endometriosis has suffered from a prolonged unmet clinical need characterized by delayed diagnoses, limited non-invasive biomarker options, and a lack of non-hormonal disease-modifying therapies. However, endometriosis research is now entering a transformative era such as advanced genomic mapping, single-cell sequencing, growing immunotherapeutic pipelines, and patient-centric advocacy converge to overcome these historical barriers. This scientific shift is fueled by growing investment from biotech and pharmaceutical companies looking to capture an underserved women's health market through novel oral therapeutics and targeted anti-inflammatory pathways.

Crucial clinical momentum was highlighted at the Society of Endometriosis and Uterine Disorders (SEUD) 2026 annual congress, where global data highlighted systemic endometriosis comorbidities, including autoimmune disorders, cardiovascular risks, and chronic pain. The frequency of inflammatory comorbidities is redefining the condition as a systemic, whole-body illness rather than an isolated pelvic disease.

Ultimately, the key takeaway is that endometriosis remains a deeply complex, multifactorial disease that defies simplistic, uniform interventions, and requires looking toward a multi-disciplinary approach that unites women's health, immunology, and integrative pain management.

THE CURRENT LANDSCAPE

Endometriosis affects roughly 10% -13% (about 200 million) of reproductive-aged women globally.¹ This statistic is heavily underestimated due to systemic underdiagnosis and a multi-year lag in identification. As a chronic inflammatory disease with highly heterogeneous manifestations, its presentation varies drastically between individual patients. Mechanistically, ectopic endometrial-like tissue implants secrete pro-inflammatory cytokines, such as Interleukin-6 (IL-6) and Tumor Necrosis Factor (TNF) which actively recruit local macrophages and drive a state of persistent pelvic neuroinflammation. This dysregulated immune response with sustained inflammation fuels pelvic chronic pain and promotes infertility. It directly stimulates local nerve endings to cause debilitating dysmenorrhea and non-cyclical pelvic pain, while simultaneously altering peritoneal fluid chemistry and creating pelvic adhesions that compromise oocyte quality and fallopian tube anatomy.²



Unfortunately, current therapeutic paradigms remain severely limited. Patients are forced to rely on hormone suppression and repetitive surgery, both of which feature high recurrence rates, frequently reaching 50% within five years. Surgery often misses microscopic implants, and hormone therapies only provide temporary suppression. Consequently, the disease persists by utilizing complex molecular mechanisms that allow ectopic cells to create an immune-privileged shield.^{3,4} Dormant lesions inevitably reactivate once these conventional treatments are stopped.

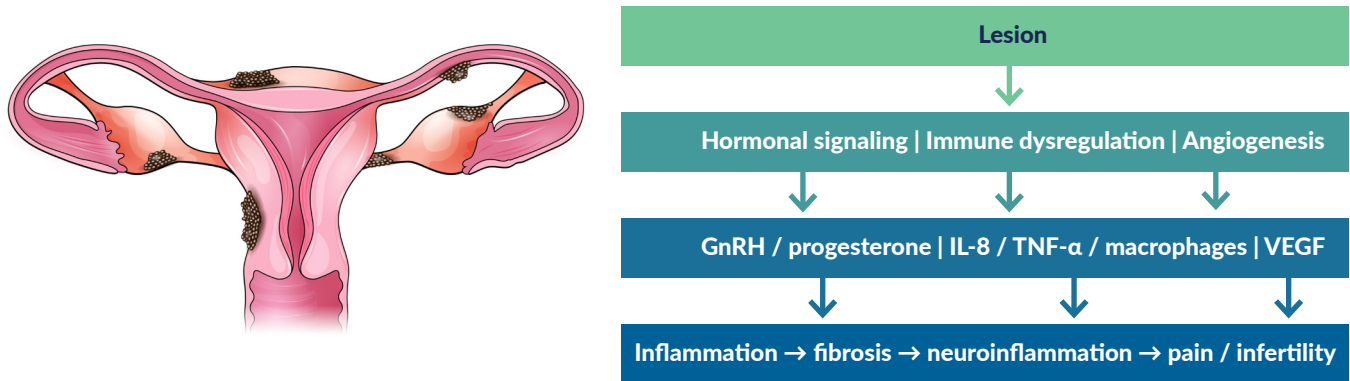


Figure 1: Endometriosis: A Complex Pathogenesis

WHAT EMERGING THERAPIES ARE BEING DEVELOPED FOR ENDOMETRIOSIS?

The emerging therapeutic pipeline for endometriosis is expanding rapidly, with new approaches focused on precise hormonal modulation and non-hormonal immunomodulatory strategies. These next-generation therapies aim to target endometriotic lesions and the underlying mechanisms of disease while minimizing systemic side effects.

- **Hormonal Therapies**

- Modern endocrine research is introducing next-generation hormone receptor modulators that target lesion growth with potentially fewer systemic side effects. For example, GnRH antagonists such as Elagolix offer precise estrogen suppression to decrease pelvic pain and menstrual cramps with significantly lower bone density risks.⁵
- Selective progesterone receptor modulators (SPRMs) are synthetic compounds with mixed agonist and antagonist effects on progesterone receptors. They offer an alternative treatment for endometriosis pain by suppressing endometrial growth and lowering local prostaglandins without inducing low estrogen levels or bone loss. Selective progesterone receptor modulators (SPRMs) that suppress tissue proliferation directly at the lesion site. Concurrently, to move entirely away from endocrine side effects, researchers are targeting non-hormonal, pathogenic pathways.⁶

- **Non-Hormonal and Immunomodulatory Therapies**

- Researchers are also investigating non-hormonal therapies that target the pathogenic pathways involved in endometriosis. Immunomodulatory approaches include macrophage-targeting agents and cytokine inhibitors designed to disrupt local inflammatory pathways that promote lesion survival and immune evasion. For instance, recent preclinical studies have shown that a small molecule inhibitor can act as an epigenetic modulator to selectively suppress pathogenic macrophages responsible for the establishment and the progression of endometriotic lesions.⁷
- IL-8 expression is highly up-regulated in endometriotic tissues and closely correlates with disease progression.⁸ Non-clinical and early clinical studies from Chugai Pharmaceuticals demonstrated neutralizing IL-8 through an innovative recycling antibody technology successfully reduces the size of endometriotic lesions, ameliorates fibrosis, and prevents pelvic adhesions without suppressing normal menstrual cycles.^{9,10}



- Similarly, tumor necrosis factor-alpha (TNF- α), a proinflammatory cytokine is highly expressed in the peritoneal fluid of endometriotic patients and has been shown to actively drive cell adhesion, lesion vascularization and pelvic nerve sensitization.¹¹ Repurposed rheumatologic biologics neutralizing TNF- α , such as adalimumab, infliximab, and etanercept have shown efficacy in reducing lesion size and preventing postoperative pelvic adhesions in preclinical models.¹² Emerging data suggest these anti-TNF- α therapies may also counteract the embryotoxic effects of pelvic inflammation, potentially improving IVF pregnancy rates and alleviating pain.^{13,14}
- Endometriotic lesions rely on angiogenesis and fibrosis to survive, grow, and achieve pelvic adhesion. To disrupt this process, researchers are evaluating the inhibition of Vascular Endothelial Growth Factor (VEGF), a crucial signaling protein that promotes angiogenesis, including monoclonal antibodies and decoy receptors, to starve lesions of their blood supply.¹⁵ Emerging pipelines are also developing approaches to target Transforming Growth Factor-beta 1 (TGF- β 1) signaling pathways that drive myofibroblast transformation, with the goal of disrupting the severe, deep tissue scarring characteristic of deep infiltrating endometriosis.¹⁶

CLINICAL DEVELOPMENT CHALLENGES IN ENDOMETRIOSIS

The clinical development landscape for endometriosis therapies is severely restricted by multiple trial design challenges. These challenges include:

1. Evolving Diagnostic Complexity

- Diagnostic delay has long plagued clinical management of endometriosis. Several organizations in the USA, EU and Australia recently updated their endometriosis guidelines to recommend “that a clinical diagnosis of endometriosis is sufficient to initiate empiric medical treatment.”¹⁷ in the effort to combat diagnostic delay.¹⁸
- For a systemic, heterogeneous condition with symptoms that overlap with several other disorders, relying solely on clinical diagnosis for recruitment risks enrolling patients without endometriosis, potentially affecting efficacy data.
 - While laparoscopy remains the “golden standard”, this requirement carries enrollment challenges as laparoscopy is an invasive and costly surgical procedure.¹⁹

2. Recruitment Challenges

- Endometriosis trials have some of the highest screen-failure rates among women’s health studies, often exceeding 50%. This rate is driven by several factors such as the requirement for a hormonal washout period or a lengthy screening period that encompasses multiple menstrual cycles and can last up to 100 days.
- Surgical/histologic diagnosis requirement excludes symptomatic patients who lack a qualifying surgical history.

3. Strong Competition from Overlapping Academic Studies

- Historical underfunding of endometriosis research has restricted scientific expertise to a small number of elite academic medical centers, preventing its integration into broader healthcare systems. This severe concentration of resources isolates vital medical advances within a few hubs. This creates significant geographic and financial barriers for patients who must travel for specialized care. Furthermore, because local clinics and general practitioners lack access to this centralized knowledge, patients suffer from fragmented care and average diagnostic delays of seven to ten years, while a lack of diverse grants continues to constitute an obstacle to smaller institutions from developing novel treatments.^{20,21}



THE PATH FORWARD: TRANSLATING SCIENTIFIC INNOVATION INTO CLINICAL DEVELOPMENT

Endometriosis research is entering a new era, driven by a growing understanding of the disease as a complex, systemic inflammatory condition rather than an isolated pelvic disorder. Advances in genomics, immunology, biomarker research, and targeted therapeutics are creating new opportunities to address the underlying mechanisms of disease and move beyond temporary symptom suppression.

However, translating these scientific advances into successful clinical development remains challenging. Diagnostic complexity, heterogeneous disease presentation, high screen failure rates, and limitations in current clinical trial endpoints can complicate patient identification, recruitment, and study execution. Addressing these challenges requires clinical development strategies that account for the complexity of the disease while incorporating emerging scientific insights.

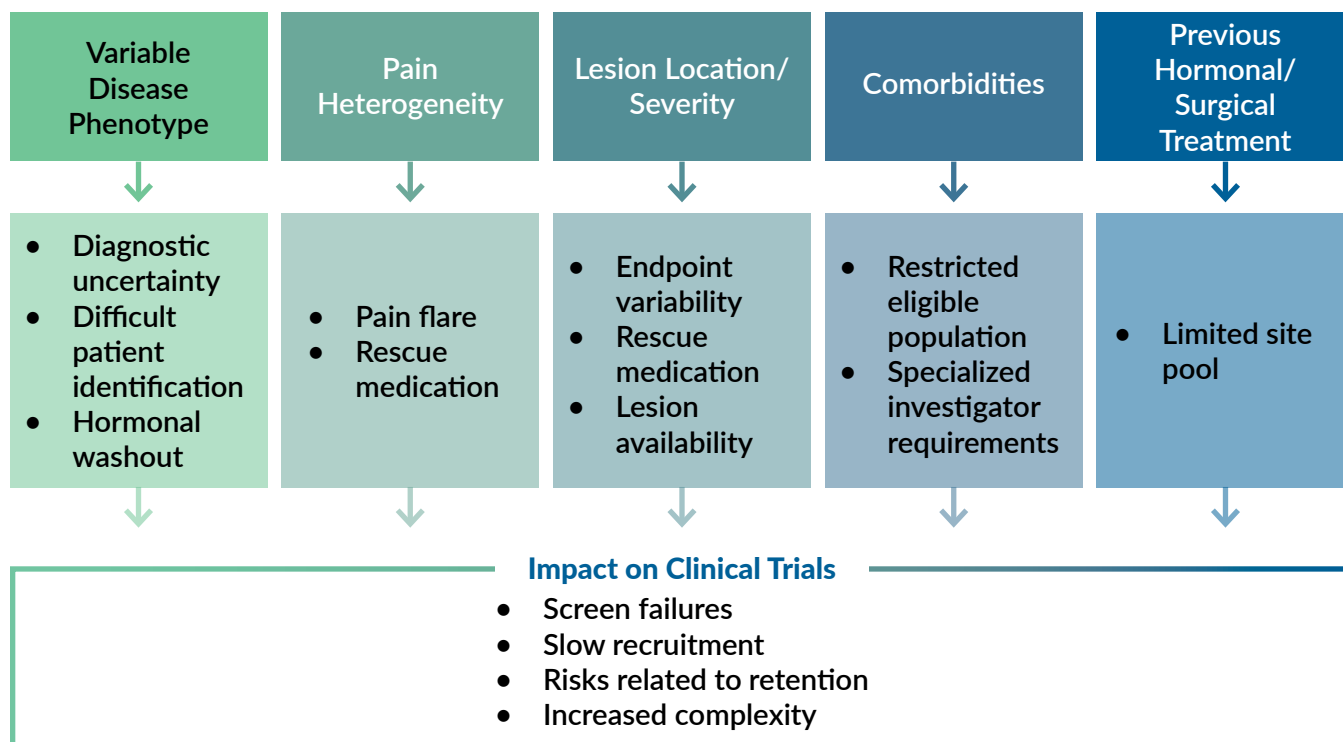
As therapeutic approaches move beyond broad hormonal suppression toward targeted immunomodulation and disease modification, clinical trials must evolve accordingly. Patient identification, endpoint selection, biomarker strategy, investigator selection, and operational execution must be planned as connected components of the same development strategy.

This shift is also reflected in the regulatory landscape: the FDA's July 2026 CDER guidance agenda include planned draft guidance on establishing the effectiveness and safety of drugs for endometriosis-associated pain.²²

Against this backdrop, the path forward depends on integrated expertise across women's health, immunology, translational research, pain management, clinical operations, patient recruitment biostatistics and regulatory strategies from the earliest stages of development. By connecting advances in disease biology with thoughtful trial design and patient-centered execution, the industry can help accelerate the development of more targeted and meaningful therapies for the millions of women worldwide affected by endometriosis.



Heterogeneous Endometriosis



Integrated Clinical Development Strategy

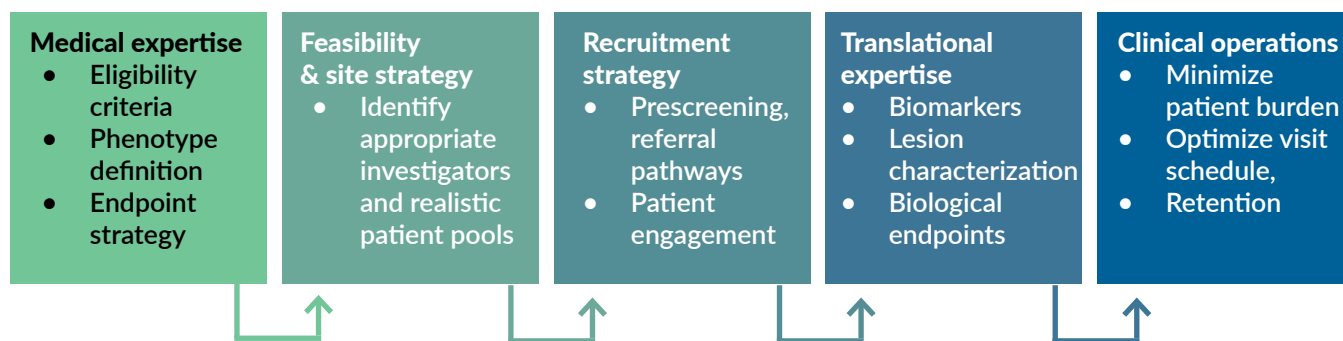


Figure 2: Integrated Expertise Simplifies Endometriosis Clinical Trials

YOUR NEXT BREAKTHROUGH STARTS HERE

Bringing the next generation of endometriosis therapies to market requires a partner with scientific depth, regulatory insight, and operational scale. Medpace brings a full-service approach to women's health clinical development, combining medical expertise, regulatory insight, scientific rigor, and global operational capabilities.

Our Women's Health Leadership Team draws on decades of experience in women's health research ensuring that study designs are both scientifically sound and operationally feasible.

Your next breakthrough in women's health starts here. Connect with our Women's Health Leadership Team today.



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