



A Translational Therapeutic Framework Combining Mesenchymal Stem Cell Therapy and Targeted Immunomodulation for Disease Modification in Endometriosis

Ulduz Jafarova¹; Khayala Alakbarli Guliyeva²; Pritam Majumdar^{3*}

¹Consultant Gynaecologist and Obstetrician, Functional GynoModulation, Nurax Clinics, Turkey, Azerbaijan and UAE.

²Consultant Gynaecologist and Obstetrician, VM Medical Park Pendik, Istanbul, Turkey.

³Consultant Functional Neurology and Neuromodulation, Nurax Clinics, India, UAE and USA.

*Corresponding Author(s): Pritam Majumdar

Consultant Functional Neurology and Neuromodulation,
Nurax Clinics, India, UAE and USA.

Email: drx.pritam@gmail.com

Abstract

Background: Endometriosis is a chronic inflammatory and fibrotic disorder characterized by ectopic endometrial tissue survival, immune dysfunction, neurogenic inflammation, and persistent pain. Current therapies rely heavily on hormonal suppression or surgical excision, both of which have high recurrence rates and notable side effects.

Objective: We propose a novel translational study design that combines Mesenchymal Stem/Stromal Cell (MSC) therapy with targeted immunomodulation to address the immune, fibrotic, and neuro-inflammatory aspects of endometriosis.

Methods: This preclinical framework integrates three complementary models: (i) ex vivo human endometriosis microenvironment models, (ii) immunocompetent rodent endometriosis models, and (iii) GLP-compliant safety and toxicology studies. The strategy combines allogeneic umbilical cord-derived MSCs or MSC-derived exosomes with selective cytokine pathway inhibition (IL-33 or IL-6). Primary outcomes include immune phenotype reprogramming, reduction in inflammatory and neurogenic mediators, suppression of fibrosis and angiogenesis, and lesion regression.

Expected outcomes: We hypothesize that the combined therapy will outperform monotherapies by restoring immune surveillance, reducing fibrosis, and attenuating neurogenic inflammation.

Conclusion: This study design provides a comprehensive roadmap for developing non-hormonal, fertility-preserving therapies for endometriosis and lays the groundwork for first-in-human trials.

Received: Sep 10, 2026

Accepted: Sep 29, 2026

Published Online: Oct 06, 2026

Journal: Journal of Gynecology Case Reports

Publisher: MedDocs Publishers LLC

Online edition: <http://meddocsonline.org/>

Copyright: © Majumdar P (2026). *This Article is distributed under the terms of Creative Commons Attribution 4.0 International License*

Keywords: Endometriosis; Mesenchymal stem cells; Immunomodulation; IL-33; Fibrosis; Neurogenic inflammation; Translational research.



Introduction

Endometriosis affects 10–15% of women of reproductive age, causing chronic pelvic pain, infertility, and diminished quality of life [1,2]. Traditionally considered an estrogen-dependent disorder, it is increasingly recognized as a chronic immune-mediated inflammatory disease with prominent neurogenic and fibrotic features [3,4].

Current treatments, including surgical excision and hormonal suppression, provide only temporary relief. Recurrence remains high, and no therapy effectively targets the underlying disease mechanisms [5,6]. Immune dysfunction—manifested as impaired Natural Killer (NK) cell activity, macrophage M1 polarization, and elevated pro-inflammatory cytokines—plays a central role in lesion persistence. This evidence suggests that combining regenerative therapy with immune modulation may offer a transformative approach [7].

This manuscript presents a novel translational study design integrating MSC therapy with targeted immunomodulation to overcome these limitations.

Scientific rationale

Immune dysregulation in endometriosis (Figure 1)

Endometriotic lesions persist due to:

- Elevated pro-inflammatory cytokines (IL-6, IL-8, TNF- α , IL-33)
- Impaired cytotoxic immune clearance
- Dominance of pro-inflammatory (M1) macrophages
- Aberrant angiogenesis and nerve growth

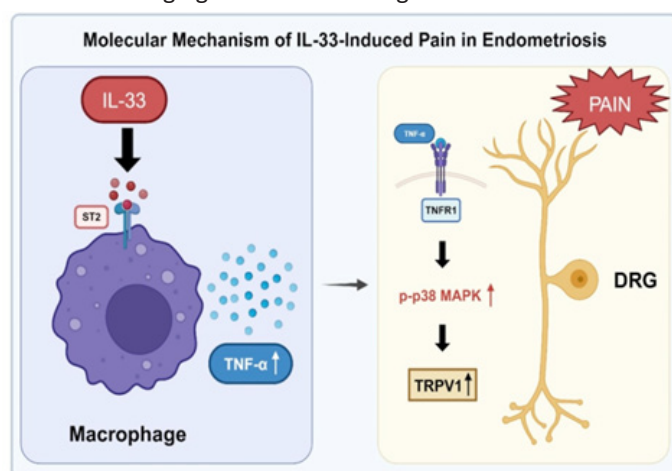


Figure 1: Immune dysregulation and neuro inflammatory microenvironment driving endometriosis lesion persistence.

Therapeutic potential of MSCs

MSCs offer immunomodulatory, anti-fibrotic, and regenerative effects, largely through paracrine signalling. However, their activity is limited in highly inflammatory environments, highlighting the need for immune priming [8].

Rationale for targeted immunomodulation

IL-33 and IL-6 are key drivers of stromal inflammation, fibrosis, and neuro-immune signalling. Targeted inhibition can normalize the lesion microenvironment, enhancing MSC efficacy [9].

Synergistic strategy

Combining MSCs or MSC-derived exosomes with immunomodulation:

- Reprograms immune cells (M1 $\rightarrow$ M2 macrophages, enhanced NK activity)
- Repairs tissue and reduces fibrosis
- Attenuates neurogenic inflammation

This approach addresses disease biology rather than merely alleviating symptoms.

Study design overview

We propose a three-tiered translational framework:

1. Ex vivo human endometriosis microenvironment models
2. Immunocompetent rodent endometriosis models
3. GLP-compliant safety and toxicology studies

Experimental framework

Human ex vivo model

Fresh endometriotic tissue from laparoscopic surgery will be co-cultured with PBMCs, stromal fibroblasts, and nerve growth factor-conditioned media to mimic the native lesion environment [10].

Therapeutic groups (Figure 2)

1. Control (untreated)
2. Immunomodulator alone
3. MSCs alone
4. MSC-derived exosomes alone
5. MSCs + immunomodulator
6. Exosomes + immunomodulatory

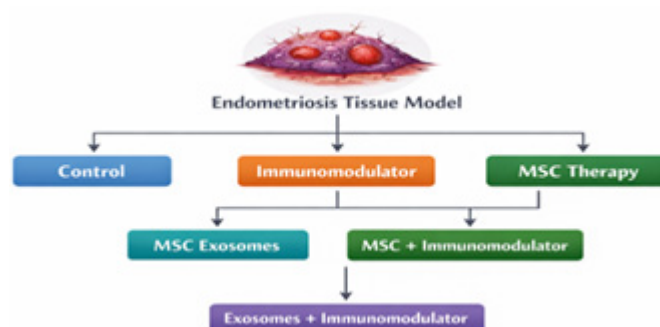


Figure 2: Experimental groups in the endometriosis translational model control, immunomodulation, MSC therapy and combination treatment strategies.

Outcome Measures (Figure 3)

- Cytokine levels (IL-6, IL-8, TNF- α , IL-1 β)
- Macrophage phenotype (M1 $\rightarrow$ M2)
- NK cell activity
- Fibrosis and angiogenesis markers
- Neurogenic inflammation markers (NGF, substance P)

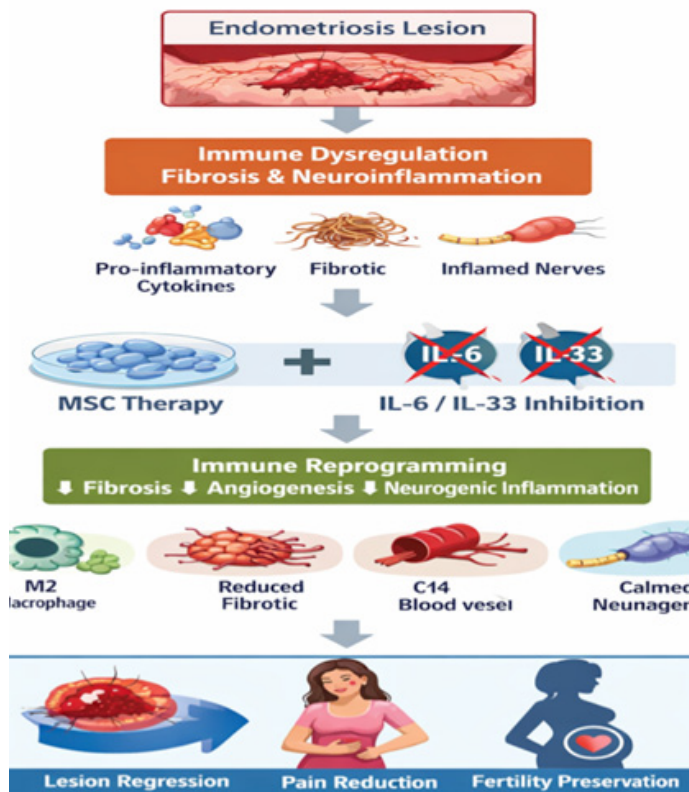


Figure 3: Mechanistic overview of MSC-based immunomodulation in endometriosis. Endometriotic lesions drive immune dysregulation, fibrosis, and neuroinflammation. Combined Mesenchymal Stem Cell (MSC) therapy and cytokine pathway inhibition (IL-6/IL-33) may restore immune balance, reduce fibrosis and angiogenesis, suppress neurogenic inflammation, and ultimately promote lesion regression, pain reduction, and fertility preservation.

In vivo validation

Rodent models will evaluate:

- Lesion regression
- Immune modulation
- Fibrosis reduction
- Pain-related behavioural outcomes

Safety and translational readiness

GLP-compliant toxicology studies in rabbits will assess:

- Biodistribution
- Immunogenicity
- Tumorigenicity
- Repeat-dose safety

These data provide the foundation for first-in-human trials.

Expected impact and innovation

This design offers a non-hormonal, disease-modifying strategy. By integrating regenerative medicine with immunotherapy, it preserves fertility, reduces recurrence, and allows personalized, biomarker-guided therapy (Figure 4).

Significance & novelty

This is a novel translational framework for combining MSC therapy with targeted immunomodulation in endometriosis.

Experimental Groups		
Group	Treatment	Purpose
Group 1	Control	Baseline disease activity
Group 2	Immunomodulator (IL-6 or IL-33 inhibitor)	Assess immune pathway blockade
Group 3	MSC therapy	Evaluate regenerative immunomodulation
Group 4	MSC-derived exosomes	Assess cell-free therapeutic effect
Group 5	MSC + Immunomodulator	Test synergistic therapy
Group 6	Exosomes + Immunomodulator	Test cell-free combination therapy

Figure 4: Overview of experimental treatment groups investigating MSC based immunomodulation in Endometriosis.

It simultaneously addresses immune dysfunction, fibrosis, and neurogenic inflammation. The multi-tiered preclinical approach ensures clinically relevant data and accelerates translation to human trials. By targeting the underlying disease mechanisms rather than just symptoms, this strategy represents a paradigm shift in endometriosis treatment [11,12].

Limitations

While the proposed framework integrates multiple experimental platforms, it remains a conceptual translational design. The therapeutic hypotheses require validation in controlled experimental models and clinical trials. Additionally, the complex immunological heterogeneity of endometriosis may influence therapeutic responsiveness across patient populations.

Conclusion

Endometriosis remains a complex, chronic disease with limited treatment options. This study design—combining MSC therapy with targeted immunomodulation—directly addresses the key drivers of lesion persistence, pain, and fibrosis. It provides a non-hormonal, fertility-preserving, and disease-modifying strategy. If successful, it could transform the clinical management of endometriosis by reducing recurrence, restoring tissue homeostasis, and improving reproductive outcomes. The proposed framework represents a scientifically robust, clinically relevant, and highly novel contribution, offering a roadmap for next-generation therapies and justifying its publication in a journal.

Translational clinical trial roadmap

Following successful completion of preclinical validation, the proposed therapeutic strategy may progress to early-phase clinical trials. A phase I study would primarily evaluate safety, tolerability, and immunological responses following administration of MSCs combined with cytokine pathway inhibition in patients with moderate-to-severe endometriosis. Biomarker profiling—including circulating cytokines, macrophage phenotype markers, and neuro-inflammatory mediators—would be used to assess biological activity. Subsequent phase II trials could investigate clinical efficacy, focusing on pain reduction, lesion regression assessed by imaging, and fertility outcomes. Patient stratification using immunological biomarkers may enable personalized therapy approaches. This translational roadmap provides a practical pathway for moving from mechanistic discovery to clinical implementation.

Author declarations

Ethical approval

Nurax Clinics ethical committee approval has been taken, IRB Protocol ID: NRX-IRB-CTI-2026-001 Clinical Study Registry ID: NRX-REG-2026-014 Approval Date: 10-02-26 (Its institutional ethical clearance number for the study to conduct).

Consent to participate

Informed consent was prepared for all individual participants and will be obtained from all individual participants who are included in this study.

Human ethics and consent to participate declaration

This study was designed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was prepared to obtain from all individual participants who will be included in this study.

Written consent for publication

Written informed consent for publication was obtained from all participants included in this study. Patients were informed about this purposes of the research, nature of the intervention and using for clinical data's for publications.

Availbalaty of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability

No custom code or software was used in this study. Standard validated statistical methods were utilized for this study.

Authors contribution

U.J: Manuscript Review and Clinical Analysis; **K.A.G:** Manuscript Review and Clinical Analysis; **P.M:** Clinical study design, Original manuscript drafting, and Analysis.

References

1. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N Engl J Med*. 2020; 382: 1244-1256.
2. Bulun SE, Yilmaz BD, Sison C, et al. Endometriosis. *Endocr Rev*. 2019; 40: 1048-1079.
3. Chen S, Zhong Z, Wei C, Liu Y, Zhu X. Peritoneal immune micro-environment of endometriosis: role and therapeutic perspectives. *Front Immunol*. 2023; 14: 1134663.
4. Interleukin 6 as a useful predictor of endometriosis associated infertility: a systematic review. *J Reprod Immunol*. 2023. PMID: 37577903.
5. Miller JE, et al. Interleukin 33 modulates inflammation in endometriosis. *Sci Rep*. 2017; 7: 18224.
6. IL 33 ST2 axis promotes epithelial-mesenchymal transition in endometriosis. *Cell Commun Signal*. 2024; 22: 1483.
7. Interleukin 33 derived from endometriotic lesions promotes fibrogenesis through regulatory T cell cytokine release. *J Immunol*. 2024. PMID: 36428461.
8. Zha H, Yan J, et al. Exosomes from the uterine cavity mediate immune dysregulation in endometriosis by inhibiting the JNK signaling pathway. *J Immunol Res*. 2023. PMCID: PMC9775046.
9. Anti-inflammatory cytokines in endometriosis. *Cytokine*. 2020. PMID: 30826860.
10. Endometriosis with infertility: a comprehensive review on immune deregulation and immunomodulation therapy. *Hum Reprod Update*. 2020; 26: 78-98.
11. Exosomes from the uterine cavity influence macrophage polarization and contribute to endometriosis pathogenesis. PMCID: PMC9775046.
12. Evaluation of microecological therapy in endometriosis through modulation of gut microbiota. *Eur J Med Res*. 2025; 30: 1084.