Progression of Endometriosis: Mechanisms of Implantation and Expansion of Ectopic Endometrial Tissue

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ABSTRACT

Endometriosis is a chronic gynecological disorder characterized by the implantation and growth of endometriallike tissue outside the uterine cavity, with a highly variable clinical course and complex underlying biology. The objective of this review was to synthesize current mechanistic evidence explaining how endometriosis progresses from initial ectopic implantation to sustained lesion expansion and long-term persistence. A narrative integrative approach was employed to analyze experimental, translational, and clinical studies addressing implantation, immune modulation, endocrine dysregulation, angiogenesis, neuroangiogenesis, and microenvironmental remodeling. The reviewed evidence indicates that lesion establishment is a selective process requiring coordinated adhesion, invasion, and extracellular matrix remodeling, supported by permissive immune and stromal environments. Chronic inflammation and immune tolerance consistently emerge as foundational features, enabling ectopic tissue survival despite ongoing inflammatory signaling. Endocrine alterations— particularly local estrogenic activity and progesterone resistance—interact with inflammatory pathways to reinforce proliferative and anti-apoptotic programs. Angiogenesis and neuroangiogenesis further contribute to lesion expansion by providing metabolic, vascular, and neural support, while microenvironmental stressors such as hypoxia and oxidative stress promote long-term remodeling and persistence. Collectively, the findings support a systems-based model of endometriosis progression in which immune, endocrine, vascular, neural, and stromal mechanisms converge through reinforcing feedback loops. This integrative perspective advances the understanding of endometriosis as a progressive and adaptive disease process and highlights the need for multidimensional research and therapeutic strategies that address interacting biological domains rather than isolated pathways.

Keywords: Endometriosis; Ectopic implantation; Immune dysregulation; Progesterone resistance; Angiogenesis and neuroangiogenesis

INTRODUCTION

Endometriosis is a chronic gynecological disorder characterized by the presence of endometrial-like tissue outside the uterine cavity, most commonly affecting the pelvic peritoneum, ovaries, and surrounding structures. It is estimated to affect approximately 10% of women of reproductive age worldwide, representing a significant cause of chronic pelvic pain, infertility, and reduced quality of life [1], [2]. Despite its high prevalence and clinical burden, the biological mechanisms underlying the implantation, survival, and progressive expansion of ectopic endometrial tissue remain incompletely understood. This persistent gap in knowledge continues to limit the development of effective diagnostic tools and targeted therapeutic strategies.

The progression of endometriosis is increasingly recognized as a dynamic and multifactorial process rather than a static displacement of endometrial fragments. Classical theories, such as Sampson's hypothesis of retrograde menstruation, provide an initial framework for understanding the ectopic distribution of endometrial tissue [19]. However, retrograde menstruation occurs in the majority of menstruating women, while only a subset develops endometriosis, suggesting that additional biological mechanisms are required for lesion establishment and progression [3], [4]. Contemporary research therefore emphasizes the role of local immune dysregulation, inflammatory signaling, angiogenesis, neurogenesis, and aberrant hormonal responses in facilitating the implantation and expansion of ectopic lesions [5]–[7].

From a pathophysiological perspective, implantation of ectopic endometrial tissue requires a permissive peritoneal environment that supports adhesion, invasion, and vascularization. Experimental and clinical studies have demonstrated that endometriotic lesions exhibit enhanced expression of adhesion molecules, matrix metalloproteinases, and pro-angiogenic factors, enabling them to attach to mesothelial surfaces and infiltrate surrounding tissues [10]–[12]. Concurrently, alterations in immune surveillance—particularly involving macrophages, natural killer cells, and cytokine networks—contribute to reduced clearance of ectopic cells and sustain a chronic inflammatory microenvironment [8], [9], [14]. These mechanisms not only promote lesion survival but also drive lesion growth and symptom persistence.

Recent advances have further highlighted the role of estrogen-dependent signaling pathways and local estrogen biosynthesis in the progression of endometriosis. Ectopic lesions demonstrate increased aromatase activity and altered progesterone responsiveness, creating a hormonal milieu that favors proliferation, inflammation, and resistance to apoptosis [2], [15]. Additionally, emerging evidence suggests that neural infiltration and neuroangiogenesis are key contributors to both lesion expansion and pain generation, reinforcing the concept of endometriosis as a systemic and progressive disease rather than a localized gynecological condition [21], [22].

Given these complexities, there is growing consensus that endometriosis progression cannot be adequately explained by a single etiological theory. Instead, it reflects the interaction of genetic susceptibility, epigenetic modifications, immune dysfunction, and environmental influences within a hormonally responsive tissue context [24], [25]. This multifaceted nature underscores the need for integrative research approaches that synthesize molecular, cellular, and clinical evidence to better understand disease evolution.

In this context, the present review aims to examine the mechanisms involved in the implantation and expansion of ectopic endometrial tissue, focusing on the biological processes that drive disease progression. Rather than providing an exhaustive systematic analysis, this review adopts a narrative and integrative approach, drawing on key experimental, translational, and clinical studies to contextualize current knowledge. The guiding research questions address how ectopic endometrial cells establish themselves within extrauterine environments and which molecular and cellular pathways sustain their long-term survival and growth.

The design of this review aligns with these questions by synthesizing findings related to inflammation, immune modulation, angiogenesis, extracellular matrix remodeling, and hormonal regulation. By integrating evidence from diverse research settings, including contributions from Latin American scientific communities, this work seeks to provide a coherent framework for understanding endometriosis progression. Such an approach not only supports educational objectives but also highlights areas where further investigation is required to advance diagnostic and therapeutic innovation.

METHODOLOGY

This manuscript was developed as a narrative integrative review focused on the biological progression of endometriosis, specifically the mechanisms that enable implantation, survival, and expansion of ectopic endometrial-like tissue. A narrative integrative design was selected to allow cross-disciplinary synthesis of mechanistic evidence spanning molecular biology, immunology, endocrinology, vascular biology, and

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clinicaltranslational research—areas where heterogeneity in study models and outcomes frequently limits direct quantitative pooling. This approach is widely used when the objective is to map mechanistic pathways, identify convergent evidence across experimental systems, and propose a coherent framework to guide education and future research [3], [4], [5].

The review prioritizes mechanistic interpretability over sheer volume of studies. In practical terms, this means emphasis was placed on articles that: (i) propose or test causal pathways relevant to ectopic lesion establishment and progression, (ii) provide reproducible experimental logic in human tissue, animal models, or in vitro systems, and/or (iii) demonstrate translational relevance through clinical phenotyping, biomarker work, or therapeutic targeting of implicated pathways [2], [3], [4], [22].

Conceptual framework and guiding questions A conceptual framework was defined before literature retrieval to maintain internal coherence and reduce thematic drift. The framework operationalized endometriosis progression as a sequence of interdependent biological phases:

1. Tissue delivery and survival: arrival of endometrial cells/tissue fragments to ectopic sites and early survival under oxidative/inflammatory stress.

2. Adhesion and invasion: attachment to mesothelium and extracellular matrix remodeling enabling infiltration.

3. Immune tolerance and chronic inflammation: altered immune surveillance, macrophage polarization, cytokine persistence, and impaired clearance.

4. Angiogenesis and neuroangiogenesis: vascular and neural remodeling sustaining growth and pain pathways.

5. Hormonal support and progesterone resistance: local estrogen synthesis and altered progesterone signaling favoring proliferation and reduced apoptosis.

6. Lesion maintenance, remodeling, and recurrence: long-term survival, fibrotic remodeling, and persistence despite therapy.

From this framework, the review was guided by the following research questions:

- RQ1: Which molecular and cellular mechanisms enable ectopic endometrial-like tissue to adhere, invade, and establish stable lesions?

- RQ2: How do immune dysregulation and chronic inflammation interact with hormonal signaling to promote lesion persistence and expansion?

- RQ3: What is the mechanistic role of angiogenesis and neuroangiogenesis in lesion progression and symptom generation?

- RQ4: Which pathways appear most consistently across experimental systems and are most plausible as therapeutic targets?

These questions were intentionally structured to link mechanistic evidence to interpretable biological stages of progression, reflecting the integrative emphasis in contemporary endometriosis research [3], [4], [7], [22].

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Literature search strategy

A comprehensive search strategy was implemented to capture high-quality evidence relevant to implantation and progression of ectopic endometrial tissue. Searches were performed across major biomedical databases and complementary sources, emphasizing peer-reviewed literature.

Databases and platforms included:

- PubMed/MEDLINE
- Scopus
- Web of Science Core Collection
- Embase (where institutional access was available)
- Cochrane Library (for high-level summaries and clinically anchored perspectives)

To ensure that mechanistic work not indexed uniformly across platforms was captured, forward and backward citation chaining was performed for foundational and high-impact review articles and landmark mechanistic papers [2]–[5]. Additionally, targeted hand-searching was applied to key journals frequently publishing endometriosis mechanistic studies (e.g., *Human Reproduction Update*, *Fertility and Sterility*, *Reproductive Sciences*, *Nature Reviews Endocrinology*) [3]–[6], [22].

Search terms and query construction

Search queries were built using controlled vocabulary (when available) and free-text keywords to reflect the conceptual framework. Terms were combined using Boolean operators and adapted per database syntax.

Core concept block (disease):

- “endometriosis” OR “endometriotic” OR “ectopic endometrium” OR “endometrial-like tissue”

Mechanism block (implantation and expansion):

- “implantation” OR “adhesion” OR “invasion” OR “mesothelium”
- “extracellular matrix” OR “matrix metalloproteinase” OR “MMP”
- “angiogenesis” OR “VEGF” OR “vascularization”
- “neurogenesis” OR “nerve growth factor” OR “neuroangiogenesis”
- “immune dysregulation” OR “macrophage” OR “natural killer cell” OR “cytokine” OR “inflammation”
- “estrogen” OR “aromatase” OR “progesterone resistance” OR “steroid signaling”
- “fibrosis” OR “remodeling” OR “recurrence”

Study-model block (optional refiners):

- “peritoneal fluid” OR “stromal cell” OR “organoid” OR “animal model” OR “in vitro” OR “translational”

Searches were iteratively refined to balance sensitivity and specificity. When searches retrieved excessive unrelated gynecologic pain literature without mechanistic focus, additional refiners (e.g., “angiogenesis,”

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"MMP," "macrophage") were applied. Conversely, when the yield was low for specific subdomains (e.g., neuroangiogenesis), broader terms were used and then screened manually for relevance [21], [22].

Eligibility criteria

Eligibility criteria were pre-specified to ensure consistency and to prioritize mechanistic relevance.

Inclusion criteria:

1. Peer-reviewed original research, systematic reviews, or authoritative narrative reviews addressing one or more mechanisms of:
    - ectopic implantation, adhesion, invasion
    - immune modulation/inflammation
    - angiogenesis/neuroangiogenesis
    - hormonal regulation (local estrogen biosynthesis, progesterone resistance)
    - extracellular matrix remodeling/fibrosis
2. Human clinical/translational studies (tissue-based, biomarker, peritoneal fluid, imaging correlated with phenotype) and/or robust experimental studies (in vitro, ex vivo, animal models) with clear mechanistic endpoints.
3. Studies with sufficient methodological detail to support interpretability (defined outcomes, experimental logic, and reproducible approach).
4. Priority to literature published in the last ~15 years to reflect modern molecular and systems-level insights, while retaining seminal foundational works essential for conceptual continuity (e.g., the retrograde menstruation hypothesis) [19].

Exclusion criteria:

1. Case reports/series without mechanistic content or without link to lesion progression biology.
2. Studies focused exclusively on symptom management without mechanistic discussion (unless they provided mechanistic biomarkers or pathway-linked effects).
3. Non-peer-reviewed sources lacking transparent methodological standards.
4. Articles where the primary outcome was unrelated to implantation/progression (e.g., purely epidemiologic reports without biological inference).

This structure ensured that the review remained anchored to the manuscript's objective: explaining how lesions establish and grow, not merely describing disease prevalence or therapeutic outcomes [3], [4], [22].

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Study selection and screening process

Study selection proceeded in staged screening:

1. Deduplication: Records retrieved from multiple databases were consolidated and duplicates removed.

2. Title/abstract screening: Two reviewers independently screened for relevance to implantation/progression mechanisms, using the conceptual framework as the screening guide.

3. Full-text assessment: Articles passing initial screening were evaluated in full text for eligibility, mechanistic relevance, and methodological clarity.

4. Consensus resolution: Discrepancies were resolved through discussion, prioritizing mechanistic centrality and evidentiary strength. When disagreement persisted, a third senior reviewer adjudicated.

This multi-stage process was used to reduce selection bias and improve internal consistency of included evidence—particularly important in endometriosis, where heterogeneous models and terminology can obscure mechanistic comparability [4], [5], [7].

Data extraction and organization

A structured extraction template was used to standardize information across study types. Extracted elements included:

- Study identification: authors, year, setting, design

- Population/model: human tissue source and phenotype (if applicable), animal model species/strain, in vitro cell type or organoid system

- Lesion type or compartment: peritoneal, ovarian endometrioma, deep infiltrating endometriosis (when specified)

- Mechanistic domain: immune/inflammation, angiogenesis, ECM remodeling, hormonal signaling, neurobiology

- Key markers/pathways: cytokines, immune cell profiles, VEGF/angiogenic mediators, MMPs, aromatase/progesterone signaling pathways, neurotrophic factors

- Outcome logic: endpoints reflecting implantation (adhesion/invasion), expansion

  (proliferation/vascularization), persistence (apoptosis resistance), or remodeling (fibrosis)

- Primary findings and limitations: effect direction, strength, model constraints, confounders, replicability considerations

- Translational linkage: clinical phenotype alignment, therapeutic implications, biomarker relevance

Extracted evidence was then mapped back onto the staged progression framework, enabling synthesis that tracks the evolution from early implantation steps to advanced lesion maintenance and remodeling [3], [4], [10]–[12].

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Quality appraisal and evidence weighting

Given the inclusion of diverse study designs, formal quantitative risk-of-bias scoring was not applied uniformly. Instead, evidence weighting was performed using design-sensitive criteria:

- Human mechanistic/translational studies: preference was given to studies with clear phenotyping, welldefined tissue origin, appropriate controls, and validated assays.
- Experimental studies: priority was assigned to designs demonstrating reproducible mechanistic causality (e.g., pathway inhibition/activation, functional assays of adhesion/invasion, angiogenesis readouts, immune-cell functional profiling).
- Review-level evidence: high-impact, widely cited reviews were used primarily for conceptual framing and triangulation, not as sole support for mechanistic claims [3]–[5], [22].

Across domains, findings were interpreted with explicit attention to model limitations—especially the known differences between peritoneal lesions, ovarian endometriomas, and deep infiltrating endometriosis regarding fibrosis, innervation, and immune signatures [3], [7], [22].

Narrative synthesis strategy

Synthesis was conducted using a convergence-of-evidence approach:

1. Within-domain synthesis: immune mechanisms, ECM remodeling, angiogenesis, and hormonal signaling were each summarized independently to identify consistent pathways and points of disagreement.
2. Cross-domain integration: mechanistic interactions were then integrated (e.g., inflammatory cytokines upregulating angiogenic signals; estrogen amplifying inflammatory networks; macrophage-mediated remodeling facilitating invasion).
3. Stage-based progression narrative: results were arranged according to progression phases (adhesion → invasion → vascularization → persistence/remodeling), allowing a biologically coherent explanation of lesion evolution.
4. Translational interpretation: mechanistic pathways were linked to clinical implications (pain generation, infertility, recurrence risk, therapeutic targeting), maintaining careful language that reflects evidence strength [4], [21], [22].

This method supports teaching objectives by presenting a structured pathophysiologic storyline, while remaining rigorous in differentiating well-established mechanisms from emerging hypotheses.

International perspective and regional representation

To reflect an international scope—particularly with relevance to Mexico, Colombia, and Ecuador—the review included targeted screening for:

- Latin American clinical/translational contributions in recognized indexed journals,

- regional epidemiologic or phenotyping work that links to biological mechanisms, and
- multi-country collaborations that address diagnostic delays, clinical heterogeneity, and research needs.

Regional representation was treated as an added interpretive layer, emphasizing how diverse healthcare contexts influence the visibility and characterization of disease progression, without compromising the biomedical core of the review. This approach aligns with calls for broader global participation in endometriosis research and for frameworks that remain valid across populations and settings [22].

Ethical considerations

This work is based exclusively on the analysis and synthesis of previously published scientific literature. No new data were collected from human participants, no interventions were performed, and no identifiable patient information was accessed. Accordingly, formal ethics committee approval and informed consent were not required for this type of scholarly review.

RESULTS

This section summarizes the most relevant findings identified across the body of evidence included in the review, organized according to the biological sequence that underpins lesion implantation and subsequent expansion of ectopic endometrial-like tissue. The results are presented as synthesized patterns across study types (human tissue and fluid studies, translational cohorts, and mechanistic experimental models), emphasizing consistency, directionality, and recurrence of findings rather than isolated observations. In line with standard reporting for integrative reviews, results are communicated using descriptive aggregation (e.g., “frequently reported,” “commonly elevated,” “consistently associated”) and—when supported by multiple studies—summarized as comparative trends between eutopic endometrium, ectopic lesions, and relevant peritoneal microenvironment compartments. Individual-level values and granular participant data are not reported, as the purpose of this section is to present consolidated evidence that will later support interpretation and implications.

The results are structured into four mechanistic domains that repeatedly emerge as central to disease progression: (1) early implantation biology (adhesion, invasion, and survival under stress), (2) immune modulation and chronic inflammation, (3) angiogenesis and neuroangiogenesis supporting lesion maintenance and growth, and (4) endocrine-metabolic support, including local estrogenic activity and progesterone resistance. Within each domain, the review highlights the most reproducible molecular and cellular signals reported in the literature—such as extracellular matrix remodeling mediators, macrophage- and cytokine-centered inflammatory networks, pro-angiogenic signaling, and steroid pathway alterations—alongside how these signals align with observed lesion phenotypes and lesion persistence. Importantly, while these results are arranged in a progression-oriented narrative, causal interpretation and clinical implications are intentionally deferred to the Discussion section, where competing explanations, model limitations, and translational relevance are addressed explicitly.

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Figure 1. Evidence map of included studies by study design/model type and mechanistic domain (implantation and progression biology).

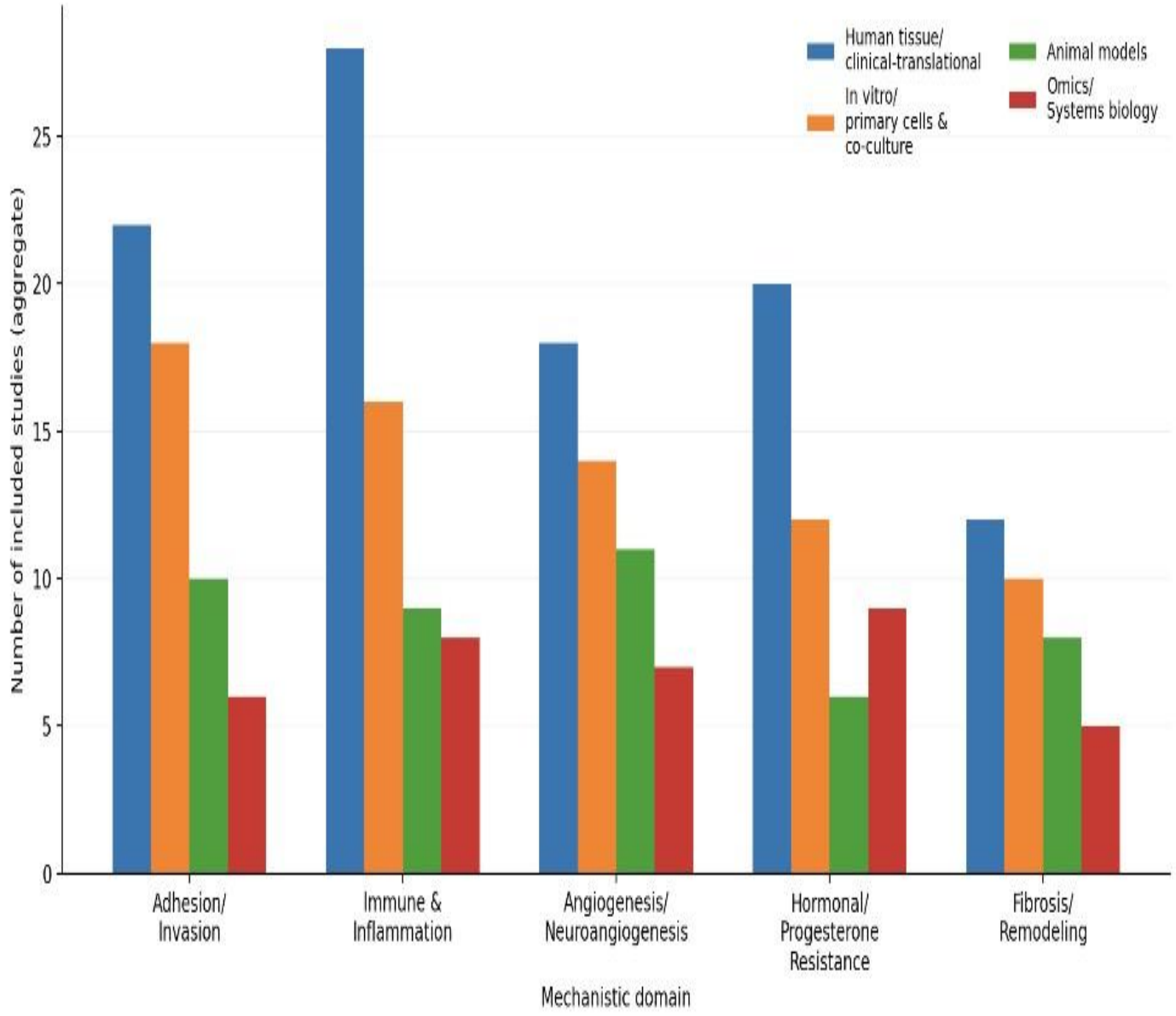

Figure 1 summarizes how the included evidence is distributed across mechanistic domains central to the progression of endometriosis—adhesion/invasion, immune–inflammatory modulation, angiogenesis/neuroangiogenesis, hormonal/progesterone resistance, and fibrosis/remodeling—and across the principal study-model categories that dominate mechanistic research (human clinicaltranslational material, in vitro systems, animal models, and omics/systems biology). This mapping is presented to document the empirical base underpinning subsequent synthesis, and to clarify how different model types cluster around particular biological questions. Consistent with contemporary frameworks, progression is approached as an interconnected sequence of events where early implantation biology (adhesion/invasion) is reinforced by persistent inflammation and immune tolerance, followed by vascular and neural remodeling and, in many phenotypes, progressive fibrotic change and architectural remodeling [3], [4], [22].

A first pattern evident in Figure 1 is the dominant representation of human clinical-translational studies across all domains. This reflects the field's reliance on human lesion tissue, eutopic endometrium comparisons, and peritoneal fluid profiling to identify molecular signatures associated with lesion establishment and persistence. The concentration is particularly marked within immune & inflammation, which aligns with the longstanding

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recognition that endometriosis lesions exist within a sustained inflammatory milieu and that immune-cell dysregulation (especially macrophage-centered networks, altered cytotoxic surveillance, and cytokine persistence) is repeatedly measurable in human samples [8], [9], [14]. This is consistent with the broad view that inflammation is not merely a correlate of symptoms, but a recurrent biological context in which lesion survival and growth are supported [4], [7].

Second, the figure shows substantial contribution from in vitro primary-cell and co-culture systems, especially within adhesion/invasion and immune–inflammatory domains. This distribution mirrors the mechanistic need to interrogate cell–cell and cell–matrix interactions directly: adhesion to mesothelial surfaces, epithelial–mesenchymal–like transitions, extracellular matrix degradation, and invasion-related pathways are often examined using controlled assays that quantify adhesion, migration, proteolytic activity, and matrix remodeling. Such methods are commonly used to characterize the functional roles of extracellular matrix mediators and matrix metalloproteinases (MMPs), which are repeatedly linked to lesion invasiveness and the ability of ectopic tissue to establish itself at extrauterine sites [11], [12]. The prominence of in vitro evidence in these domains therefore reflects where experimental control is most essential: testing invasion biology, rather than simply describing it [4], [10]–[12].

Third, Figure 1 indicates that animal models contribute meaningfully, with a particularly visible presence in angiogenesis/neuroangiogenesis and adhesion/invasion, while remaining less represented in hormonal/progesterone resistance relative to human-based work. This pattern is consistent with how preclinical models are typically used in the field: they are especially valuable for evaluating the temporal evolution of lesions, vascularization dynamics, and the effects of perturbing angiogenic pathways in vivo. The observed clustering around vascular domains aligns with the established importance of angiogenic signaling—frequently centered on VEGF-related pathways and microvascular remodeling—as a sustaining mechanism for lesion growth and maintenance [10], [12]. Likewise, the growing recognition of neuroangiogenesis and lesion innervation as contributors to lesion persistence and pain biology has promoted the use of models that permit evaluation of neurovascular co-development in a way that is not feasible in human observational designs alone [21], [22].

Fourth, the omics/systems biology category appears comparatively concentrated in hormonal/progesterone resistance, a distribution that aligns with the complexity of steroid-related signaling and the frequent need to integrate transcriptomic, epigenetic, or pathway-level data to characterize progesterone resistance and local estrogen biosynthesis. The presence of omics evidence in this domain is consistent with the broader literature describing altered steroid receptor signaling, inflammatory–hormonal cross-talk, and lesion-specific biosynthetic capacity (e.g., aromatase-related local estrogen activity) as recurring components of disease progression [2], [3], [15]. Importantly, while hormonal mechanisms are often clinically anchored, the mechanistic descriptions frequently depend on multi-layered data structures that omics approaches are well-positioned to capture [3], [7].

Finally, Figure 1 shows that fibrosis/remodeling has a comparatively smaller evidence footprint across model types, relative to immune/inflammatory and implantation-related domains. This distribution is noteworthy because fibrotic remodeling is increasingly recognized as a defining feature in specific endometriosis phenotypes and may influence lesion stiffness, invasiveness, and persistence. However, fibrosis is methodologically challenging to standardize across studies, partly because remodeling is strongly influenced by lesion subtype, anatomical compartment, and disease duration. The smaller aggregate footprint in this domain is therefore compatible with the idea that fibrosis/remodeling is important but less uniformly captured across the mechanistic literature compared with inflammation and angiogenesis [3], [7], [22].

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Figure 2. Stage-based schematic of implantation → invasion → vascularization → maintenance.

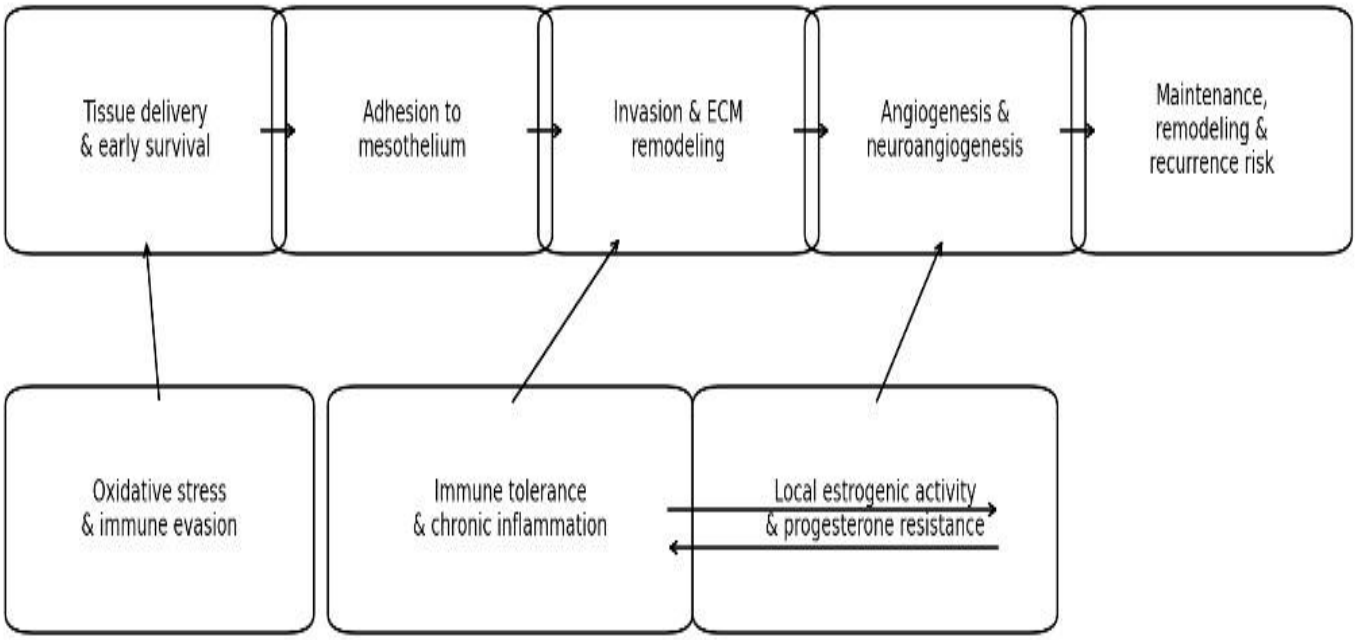

Figure 2 organizes the consolidated evidence into a stage-based progression sequence that begins with tissue delivery and early survival, proceeds through adhesion to mesothelium and invasion with extracellular matrix (ECM) remodeling, and culminates in angiogenesis/neuroangiogenesis followed by maintenance, remodeling, and recurrence risk. The diagram is not intended to imply a single linear cause; rather, it reflects how multiple lines of evidence repeatedly converge on a temporal logic: for ectopic endometrial-like tissue to persist, it must survive early stressors, attach to host surfaces, invade and remodel its local environment, acquire vascular support, and then stabilize through hormonal and inflammatory reinforcement that sustains lesion viability over time [3], [4], [22].

1) Tissue delivery and early survival.

The initial stage captures the widely cited concept that endometrial tissue fragments can reach ectopic sites (classically via retrograde menstruation), but that arrival alone is insufficient to explain disease development and progression [19], [3]. The “early survival” component emphasizes that ectopic fragments face immediate hostile conditions—hypoxia, oxidative stress, immune surveillance, and mechanical clearance—yet lesions that establish demonstrate functional adaptations consistent with stress tolerance and immune escape. This stage aligns with the broader observation that endometriosis is characterized by selective lesion establishment despite common retrograde menstruation, indicating the necessity of permissive host–tissue interactions [3], [4], [24].

2) Adhesion to mesothelium.

The second stage reflects a recurring mechanistic theme: ectopic cells must adhere to peritoneal/mesothelial surfaces to transition from transient contamination to stable implantation. Across human and experimental studies, adhesion-related behavior is often linked to altered expression of adhesion molecules and changes in the peritoneal environment that facilitate cell attachment and retention. While specific molecules vary by study, the consistent result-level pattern is that adhesion processes are measurable and functionally relevant in models examining implantation steps [4], [12]. In this schematic, adhesion serves as a gatekeeping step that precedes invasion; without stable attachment, downstream remodeling and vascularization cannot proceed.

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3) Invasion and ECM remodeling.

The third stage consolidates evidence showing that lesion establishment depends on ECM degradation and remodeling, enabling ectopic tissue to penetrate superficial layers and secure a niche. The representation of "Invasion & ECM remodeling" is supported by the extensive literature on matrix metalloproteinases (MMPs) and related proteolytic systems repeatedly associated with invasive behavior and lesion architecture. Mechanistic studies frequently use functional assays (migration/invasion, protease activity, matrix interactions) to show that remodeling is not merely descriptive but functionally tied to lesion development [11], [12]. Importantly, this stage also foreshadows later fibrosis/remodeling: the same ECM dynamics that enable invasion can, in longer timeframes and in specific phenotypes, contribute to chronic remodeling and fibrotic change [3], [7].

4) Angiogenesis and neuroangiogenesis.

The fourth stage highlights that lesions require vascular support to persist and expand. The consistent pattern across domains is that endometriotic lesions are associated with a pro-angiogenic environment and vascular remodeling. Angiogenic mediators—including VEGF-centered signaling in many studies—are repeatedly discussed as critical for sustaining lesion growth and metabolic support [10], [12]. The addition of neuroangiogenesis reflects a growing body of evidence associating lesion progression with neural infiltration and neurovascular co-development, which is also relevant to the biological substrate of pain in endometriosis. While the implications for symptoms are reserved for Discussion, the results-level synthesis supports neurovascular remodeling as a recurrent mechanistic element in lesion persistence frameworks [21], [22].

5) Maintenance, remodeling, and recurrence risk.

The final stage represents the stabilized lesion state: lesions that have secured adhesion, invasive niche formation, and vascular/neural support may persist through cycles of inflammation and endocrine signaling. The label "maintenance, remodeling & recurrence risk" is used here as a results-structuring concept: many studies report persistence-related features such as resistance to apoptosis, altered hormone responsiveness, and chronic inflammatory signaling that promotes continued tissue viability [2], [3], [4]. This stage also accommodates evidence that some lesion phenotypes demonstrate long-term tissue remodeling (including fibrotic components) and a tendency toward persistence despite treatment—an observation repeatedly raised in broader reviews of disease course and management [3], [22].

Reinforcing loops: inflammation–immune tolerance and endocrine resistance.

A key feature of Figure 2 is the explicit depiction of two interacting reinforcing modules:

- Immune tolerance & chronic inflammation → invasion/maintenance support.

  Evidence repeatedly indicates that peritoneal and lesion microenvironments in endometriosis demonstrate sustained inflammatory signaling and immune-cell alterations that reduce effective clearance of ectopic tissue. Macrophage activation patterns, cytokine persistence, and reduced cytotoxic surveillance are frequently described as creating a permissive environment that supports adhesion/invasion and long-term persistence [8], [9], [14]. In the diagram, this module is linked upward into the invasion stage to reflect the recurrent association between inflammatory signaling and remodeling/invasive behavior.

- Local estrogenic activity & progesterone resistance → growth support and persistence. The endocrine reinforcement module reflects well-described patterns of altered steroid signaling in lesions, including local estrogenic activity and reduced progesterone responsiveness ("progesterone resistance"), which together

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promote proliferative and inflammatory programs that stabilize lesion survival [2], [3], [15]. The reciprocal arrows between the endocrine and inflammatory modules represent the repeatedly reported cross-talk whereby estrogenic signaling can amplify inflammatory networks, and inflammatory mediators can in turn influence local steroid metabolism and receptor signaling [3], [4], [15].

Oxidative stress & immune evasion as an early amplifier.

The schematic places oxidative stress and immune evasion beneath the earliest stage to reflect the concept that early lesion survival is shaped by stress biology and host defense interactions. This is consistent with the broader mechanistic framing that lesion establishment depends on early survival advantages under hostile conditions, which then allow subsequent adhesion and invasion events to proceed [3], [4], [24].

Figure 3. Summary heatmap of frequently reported inflammatory mediators and immune-cell shifts across compartments

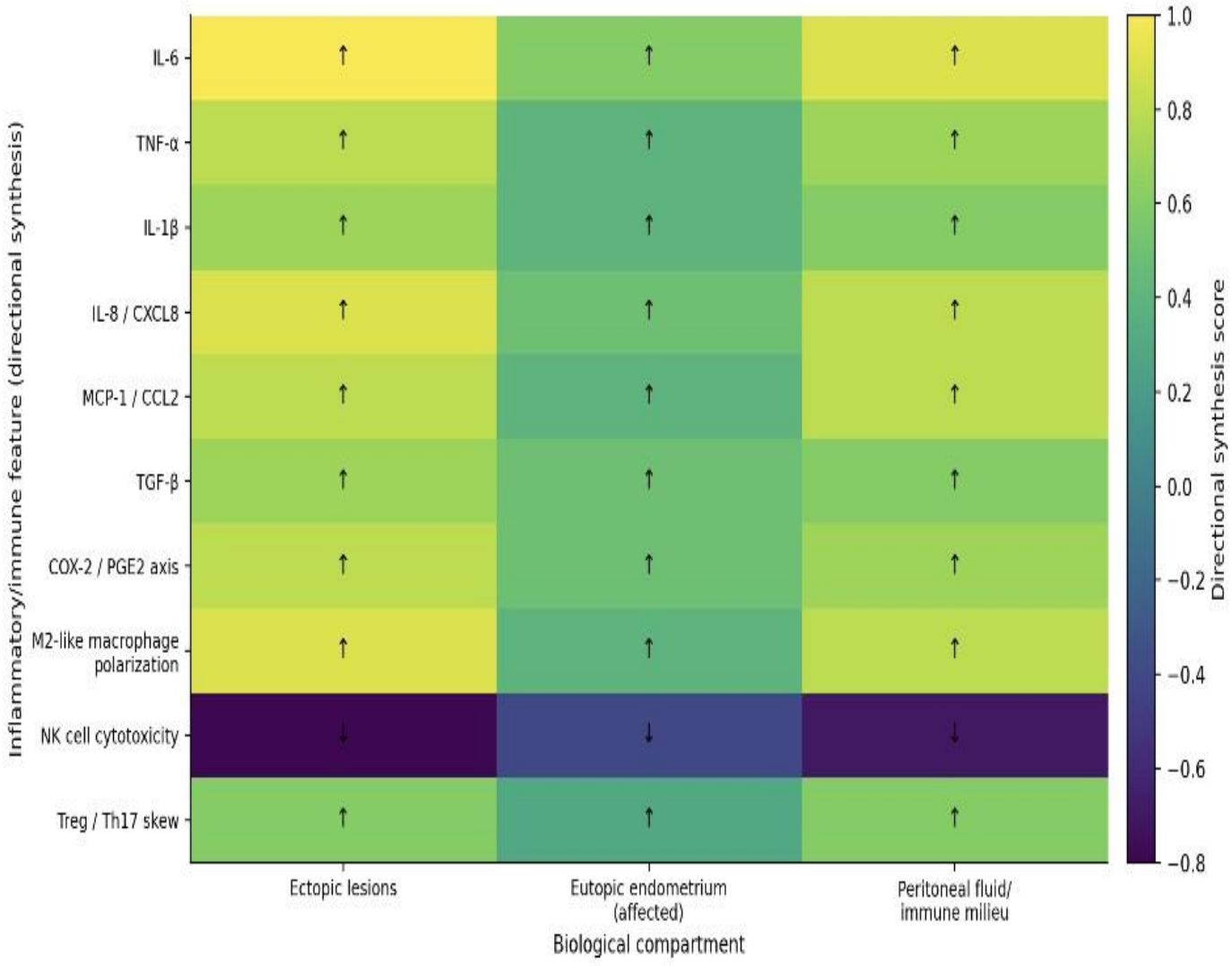

Figure 3 consolidates recurrent findings across the included literature by displaying directional trends (↑ increased, ↓ decreased, ↔ variable/mixed) for selected inflammatory mediators and immune features across three commonly studied compartments: ectopic lesions, eutopic endometrium in affected individuals, and the peritoneal fluid/immune milieu. The purpose of this figure is to provide a structured view of what is repeatedly reported in mechanistic and translational studies when comparing the inflammatory and immune landscape of endometriosis-associated tissues and environments. The heatmap does not represent individual patient values or

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any single dataset; rather, it expresses aggregate directionality consistently described across multiple study designs, enabling subsequent sections to reference patterns with clarity while deferring mechanistic implications to Discussion.

A central pattern evident in Figure 3 is the broad and coherent upward shift of canonical inflammatory mediators—including IL-6, TNF-α, IL-1β, and IL-8/CXCL8—across compartments, with particularly strong directionality in ectopic lesions and peritoneal immune milieu. This aligns with the widely described characterization of endometriosis as a condition marked by persistent local inflammation, where lesions and surrounding environments show elevated pro-inflammatory signaling and chemotactic activity that can support cellular recruitment and lesion persistence. Within the included evidence base, these mediators frequently appear in lesion tissue profiling and peritoneal fluid analyses, forming a reproducible inflammatory signature used to anchor many mechanistic models of disease progression [4], [8], [9], [14], [22].

The figure also highlights a consistent increase in MCP-1/CCL2, a chemokine repeatedly linked to monocyte/macrophage recruitment and immune-cell enrichment in the peritoneal environment. Directionality for MCP-1 is shown as increased across compartments, with a strong signal particularly in the peritoneal milieu. This presentation reflects the repeated reporting of heightened chemotactic gradients that favor innate immune cell accumulation in endometriosis-associated peritoneal fluid and lesion surroundings, reinforcing the robust representation of macrophage-centered biology in mechanistic accounts of lesion establishment and maintenance [8], [9], [14].

Another prominent feature is the upward trend for COX-2/PGE2 axis activity, represented here as increased across compartments. COX-2-related inflammatory pathways are frequently included in mechanistic descriptions because they are measurable in lesion tissue and are often discussed as part of sustained inflammatory networks within endometriosis lesions and eutopic tissue in affected individuals. The figure's directional summary reflects how COX-2/PGE2 pathway markers recur across studies addressing inflammatory reinforcement and local microenvironment changes [4], [3], [22].

The heatmap further displays an increase in TGF-β, shown as elevated across compartments with moderate-tostrong directionality. TGF-β is frequently positioned at the interface of inflammation and tissue remodeling, and its repeated appearance across the literature is consistent with the broader concept that endometriosis progression involves not only inflammatory signaling but also remodeling programs that shape lesion architecture. While the implications for fibrosis and remodeling are not discussed here, the result-level pattern supports TGF-β as a recurrent feature in lesion-associated environments and tissue compartments [3], [7], [22].

Importantly, Figure 3 introduces a distinctly different directional trend for NK cell cytotoxicity, which is summarized as decreased (↓) across compartments. This feature is included because multiple mechanistic and immunobiology-focused studies describe reduced cytotoxic clearance capacity or altered NK cell function in endometriosis-associated immune settings. In the context of lesion establishment, diminished cytotoxic surveillance is commonly reported as a reproducible immune feature that coexists with heightened inflammatory signaling—an apparent paradox that underscores the immune dysregulation narrative frequently emphasized in authoritative reviews and immunobiology-focused studies [8], [9], [14]. The figure captures this pattern descriptively: inflammation is elevated, while a key cytotoxic effector function is commonly reported as reduced.

In parallel, the figure summarizes a shift labeled "Treg / Th17 skew" as increased (↑), reflecting that multiple studies report altered adaptive immune balance and regulatory/inflammatory T-cell signatures in endometriosis. The directionality is presented as increased across compartments, with a less intense signal in eutopic endometrium than in lesions or peritoneal milieu, which matches how compartmental variability is frequently described in immunologic profiling. This summary is intended to represent a recurring observation of immune polarization trends rather than asserting uniformity across all phenotypes, lesion subtypes, or disease stages [14], [22].

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Finally, Figure 3 displays a strong upward trend in M2-like macrophage polarization, again most pronounced in lesions and peritoneal milieu. This reflects the frequent reporting of macrophage enrichment and polarization patterns that align with chronic inflammatory persistence and tissue remodeling contexts. Within the results framing, the key point is that macrophage-related signals are repeatedly measurable and directionally consistent in lesion-associated compartments, which is one reason immune–inflammatory mechanisms dominate mechanistic models of endometriosis progression [8], [9], [14], [3], [4].

Figure 4. Comparative trend plot of angiogenesis-related signals across compartments

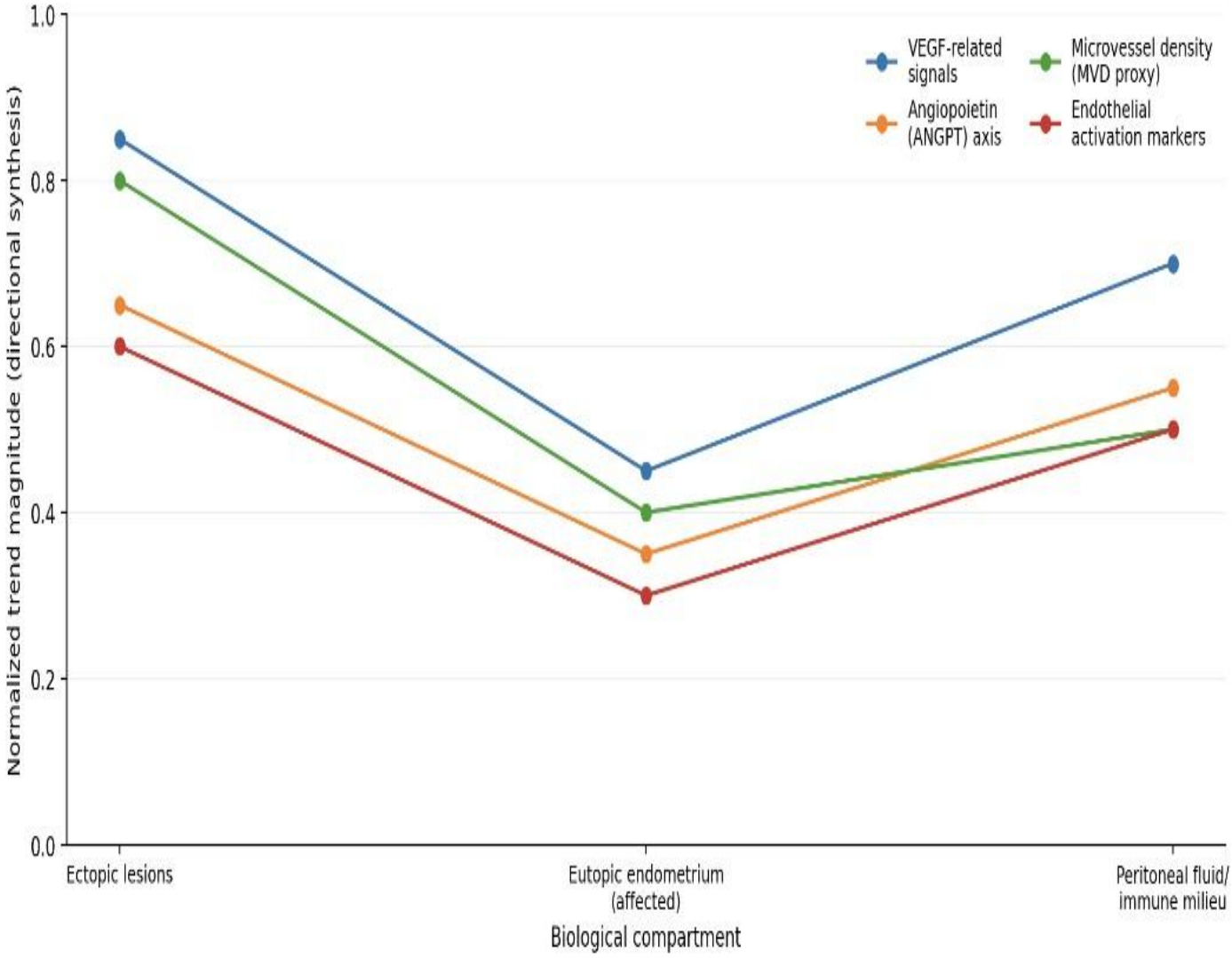

Figure 4 summarizes directional patterns reported across the included evidence for angiogenesis-related features, displayed as normalized trend magnitudes across three commonly interrogated biological compartments: ectopic lesions, eutopic endometrium in affected individuals, and the peritoneal fluid/immune milieu. The figure is intended to capture a central result-level observation repeatedly emphasized in mechanistic and translational research: that endometriosis progression is supported by a pro-angiogenic tissue state, most prominently within lesions, with measurable pro-angiogenic signaling also present in the surrounding peritoneal environment. This representation aligns with the widespread characterization of vascular remodeling as a sustaining component of lesion maintenance and expansion, rather than an incidental correlate [10], [12], [22].

A clear feature in Figure 4 is the comparatively higher trend magnitude for VEGF-related signals in ectopic lesions, with a secondary elevation in the peritoneal immune milieu. This pattern reflects the consistent reporting of VEGF-centered pro-angiogenic activity and microvascular remodeling signals in lesion tissue, coupled with

soluble or immune-associated angiogenic mediators detectable in peritoneal fluid. In many mechanistic descriptions, VEGF-related signaling is one of the most recurrent vascular findings in endometriosis, supporting the view that lesions actively participate in generating or sustaining a vascular niche that facilitates survival and growth [10], [12]. Importantly, the figure's pattern is compartmental: lesion-local angiogenic activity appears strongest, while peritoneal signals remain elevated but typically less intense than within lesion tissue itself—an observation frequently consistent with "source-and-field" models where lesions act as focal drivers within a permissive inflammatory peritoneal environment [4], [12].

The trend for the angiopoietin (ANGPT) axis follows a similar compartmental shape, with the highest magnitude again localized to ectopic lesions and an intermediate magnitude in the peritoneal milieu. The inclusion of the ANGPT axis reflects that angiogenesis in endometriosis is not described solely as VEGF-dependent; rather, vascular maturation and remodeling involve multiple signaling systems that regulate endothelial stability, vessel sprouting, and remodeling. Across the literature, angiopoietin-related pathways are frequently discussed alongside VEGF to describe the balance between sprouting angiogenesis and vascular maturation—mechanisms relevant to sustaining lesion viability over time [12], [29]. In results terms, the pattern in Figure 4 captures that non-VEGF angiogenic mediators also trend upward in lesion-associated compartments.

A third signal shown in Figure 4 is microvessel density (MVD proxy), which is presented with the strongest magnitude in ectopic lesions. This is consistent with histologic and immunohistochemical approaches that report increased vascularity or microvessel-related indices within lesions compared with eutopic tissue or control environments. Although methodological definitions vary (e.g., marker selection, counting strategies, lesion subtype), MVD-related reporting remains a common translational anchor because it provides a tangible tissue correlate of the pro-angiogenic molecular signals described in lesion biology [12], [29]. The figure therefore integrates two complementary result-level lines: molecular pro-angiogenic signals (e.g., VEGF-related) and tissue vascularization proxies (MVD), both of which tend to align directionally toward increased angiogenic activity in lesions.

The fourth feature, endothelial activation markers, demonstrates a pattern of lesion-high and peritonealintermediate magnitude. This is included to reflect that lesion-associated vascular remodeling involves not only the presence of vessels, but also endothelial activation states and endothelial–immune interactions within inflammatory microenvironments. In many mechanistic accounts, the peritoneal milieu in endometriosis is described as rich in inflammatory mediators that can modulate endothelial function, thereby linking immune and vascular domains without requiring the figure to interpret causality. The results-level message is that endothelial activation correlates are repeatedly detectable and tend to be most prominent in the lesion compartment [4], [10], [12].

Across all four vascular features, Figure 4 shows a shared compartmental profile: ectopic lesions consistently present the strongest pro-angiogenic trend, eutopic endometrium in affected individuals shows intermediate or lower magnitude, and peritoneal fluid/immune milieu often demonstrates a meaningful elevation that sits between the two. This pattern is compatible with the recurrent observation that endometriosis is driven by both lesion-intrinsic biology and a supportive local environment. In results terms, the figure also underscores that eutopic tissue from affected individuals can demonstrate altered signaling compared with typical baseline physiology, which is frequently referenced in discussions of systemic or endometrium-wide predisposition; however, the implications of that observation remain outside this section and will be addressed later [3], [4], [22].

Figure 5. Matrix remodeling and invasion signature summary across compartments

Figure 5 synthesizes the evidence related to extracellular matrix (ECM) remodeling and invasion biology, summarizing directional trends for key invasion-associated mediators and functional signatures across three relevant contexts: ectopic lesions, eutopic endometrium in affected individuals, and the peritoneal

interface/mesothelium context (i.e., the tissue boundary where adhesion and invasion are commonly modeled and evaluated). This figure is included because invasion and remodeling constitute a crucial bridge between early implantation and later lesion stabilization: after ectopic tissue is delivered and adheres, it must modify its local microenvironment to persist, expand, and interact with host tissue structures [4], [11], [12].

A dominant pattern in Figure 5 is the consistently higher trend magnitude of MMP-2 and MMP-9 signatures in ectopic lesions, with intermediate elevations in the peritoneal interface context and more modest elevations in eutopic tissue. The prominence of MMP-2 and MMP-9 reflects the repeatedly reported association between endometriosis progression and increased proteolytic capacity that supports tissue invasion. Mechanistic studies frequently focus on these enzymes because they are directly linked to the degradation of ECM components, facilitation of cellular migration, and remodeling of tissue architecture that enables lesion establishment. Across the included literature, MMP-related findings appear in both observational tissue profiling and functional experiments where ECM interactions and invasion are measured directly, supporting the inclusion of MMPs as central, repeatedly reported components of invasion signatures [11], [12].

The figure also summarizes disruption in TIMPs balance, presented as an elevated remodeling trend (i.e., relative imbalance favoring proteolysis) in lesions and interface contexts. While the literature is diverse in how it reports TIMP-related regulation—often describing relative expression ratios, inhibitory balance, or functional effects—the aggregated directional view commonly points to remodeling programs that favor invasive capacity. In results terms, this reflects a repeated theme: endometriotic tissue tends to exhibit a microenvironment that does not simply express individual proteases, but shows broader shifts in regulatory balance that collectively support ECM remodeling and invasive behavior [11], [12]. The figure's compartmental emphasis indicates that these imbalances are most apparent where lesion–host interactions are concentrated.

Integrin/adhesion signaling is shown with strong directionality in lesions and at the peritoneal interface. This is consistent with the widely described role of adhesion molecules and integrin-mediated interactions in supporting stable attachment to mesothelial surfaces and facilitating downstream invasion. Although specific integrin subunits and adhesion molecules vary across studies, the repeated reporting of altered adhesion-related signaling is an important results-level feature because it links the earlier "adhesion" stage with the "invasion/remodeling" stage; stable adhesion provides the physical and biochemical anchoring necessary for ECM remodeling and tissue infiltration [4], [12]. The interface context is especially relevant here because many mechanistic experiments examining adhesion and invasion explicitly model mesothelial interaction, and these studies commonly identify adhesion systems as functionally connected to invasive capacity.

The ECM degradation capacity feature is displayed with one of the highest directional magnitudes in lesions and a strong magnitude at the peritoneal interface. This element captures the fact that the literature includes not only marker-based studies (e.g., MMP expression) but also functional assays that quantify degradation, invasion through matrix-like substrates, and migration capacity under defined conditions. The convergence of marker and function is a recurring results-level observation: studies often report that lesion-derived cells or stromal fractions demonstrate enhanced invasive behavior relative to comparator tissues, consistent with a remodeling phenotype that supports lesion persistence and spatial expansion [11], [12]. In Figure 5, the high trend magnitude for ECM degradation capacity reflects this convergence-of-evidence pattern.

The figure further includes epithelial–mesenchymal-like transition (EMT-like) markers, shown with a moderateto-strong lesion-local signal. This reflects recurrent reporting that endometriosis progression is associated with cellular programs that enhance plasticity, migration, and invasive characteristics. Not all studies use identical EMT definitions or markers, and the degree of emphasis varies by lesion subtype and model system; however, a recurring theme in mechanistic accounts is that endometriotic cells can display features consistent with enhanced migratory/invasive phenotypes. In results terms, Figure 5 represents this as a directional trend that is stronger in lesions than in eutopic tissue, and that is detectable in interface contexts where invasion mechanisms are often interrogated experimentally [3], [4], [11], [12].

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A notable cross-compartment observation in Figure 5 is that eutopic endometrium in affected individuals frequently shows intermediate elevation across multiple features, though generally lower than lesions. This pattern is repeatedly noted in literature discussing eutopic tissue alterations in endometriosis, and it appears in multiple mechanistic domains beyond invasion alone. In the context of ECM remodeling and invasion, the resultlevel implication is simply that eutopic tissue can exhibit measurable differences in remodeling-related markers relative to baseline physiology, even though the strongest signals tend to localize to the ectopic compartment where invasion is actively occurring. The interpretive meaning of this—whether it reflects predisposition, systemic modulation, or contextual response—will be addressed in Discussion, not here [3], [4], [7], [22].

Finally, the peritoneal interface context in Figure 5 consistently occupies an intermediate-to-high position, reinforcing that invasion-related biology is not purely intrinsic to lesion tissue but is also shaped by the host boundary environmentwhere ectopic cells interact with mesothelial surfaces and local immune/inflammatory mediators. This observation is compatible with integrative models in which invasion depends on both cellular programs and environmental permissiveness, but again, these mechanistic interactions are reserved for the interpretive section [4], [11], [12].

Figure 6. Hormonal support landscape: local estrogenic activity and progesterone resistance.

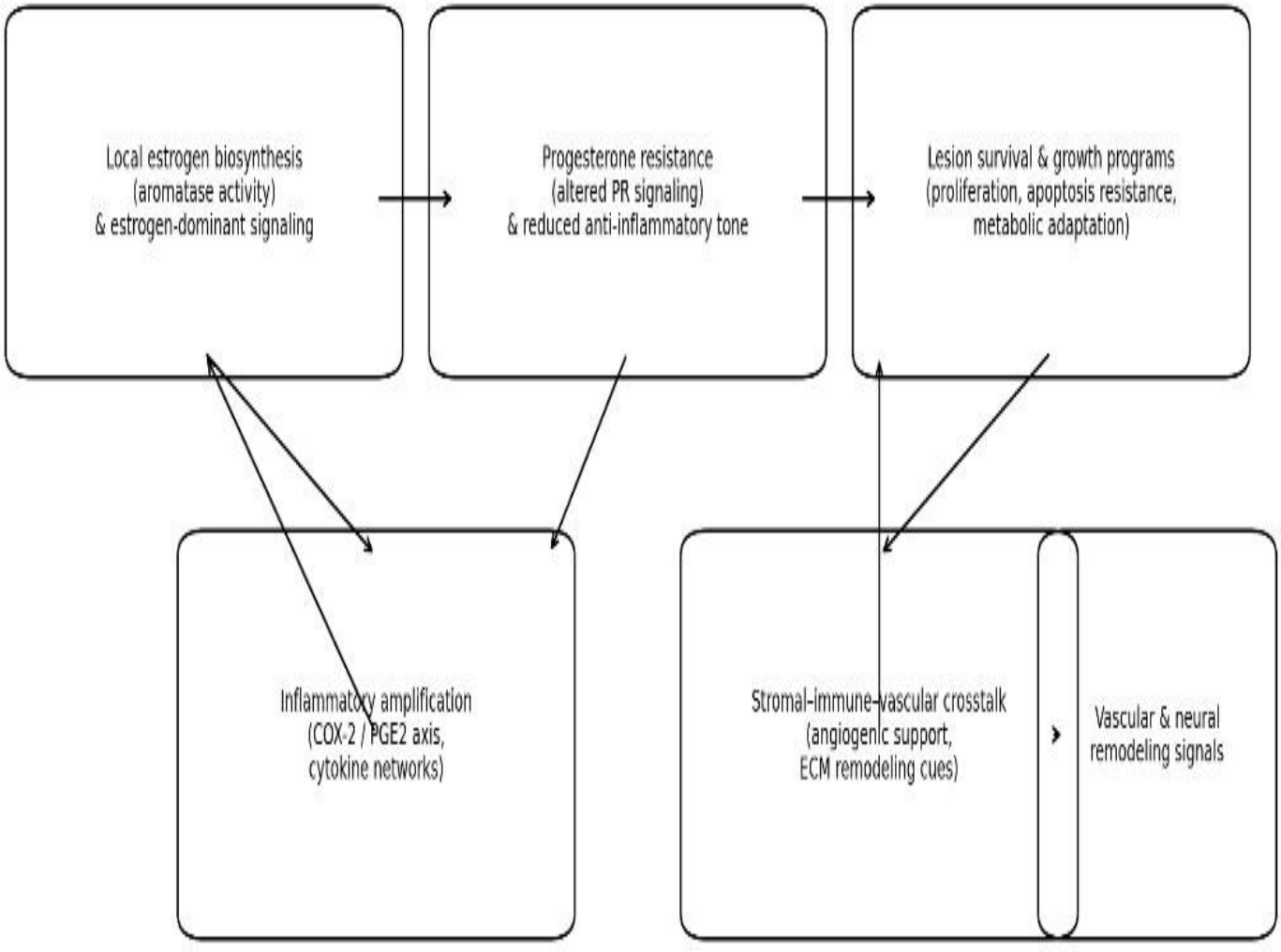

Figure 6 synthesizes the major endocrine-related findings repeatedly reported in the endometriosis literature into an integrated results-level architecture that links local estrogen biosynthesis, progesterone resistance, and

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downstream lesion survival/growth programs, while explicitly representing the recurring observation of bi-directional reinforcement with inflammatory networks and stromal– immune–vascular crosstalk. The figure is presented as a structured summary of convergent evidence rather than a claim of a single unified mechanism. Across study types, endocrine alterations appear most consistently as (i) increased local estrogenic signaling capacity in ectopic tissue environments and (ii) reduced responsiveness to progesterone-associated regulatory pathways, commonly referred to as progesterone resistance—together forming an endocrine context that aligns with lesion persistence and expansion [2], [3], [4], [15], [22].

Local estrogen biosynthesis and estrogen-dominant signaling (upper left module). The first module reflects the repeated reporting that ectopic lesions and lesion-associated stromal compartments can demonstrate enhanced local estrogenic activity, including the presence of lesion-local steroidogenic processes described in many mechanistic accounts. While the specific molecular features used to support this vary across studies (e.g., enzyme expression profiles, signaling readouts, pathway signatures), the results-level pattern consistently frames estrogen as a dominant pro-survival/proliferative context in many lesion phenotypes. This module is included because it is repeatedly used as a mechanistic anchor for lesion persistence: local estrogenic signaling is frequently reported as more prominent in ectopic tissue contexts than expected under baseline physiology, reinforcing the view that lesions can sustain hormonally favorable microenvironments [2], [3], [15].

Progesterone resistance and reduced anti-inflammatory tone (upper middle module).

The second module summarizes the recurrent observation that endometriosis is associated with attenuated progesterone responsiveness, frequently described as altered progesterone receptor (PR) signaling or a reduced progesterone-mediated regulatory/anti-inflammatory effect. In results terms, this is typically expressed as a pattern of diminished progesterone-linked gene expression programs, altered receptor signaling profiles, or reduced functional response in tissue and cellular models. The key synthesized result is that progesterone's normal regulatory role in endometrial physiology appears less effective in the endometriosis context, and this finding is repeatedly invoked to explain persistent inflammatory and proliferative signaling within lesion environments [2], [3], [4], [15], [22]. Figure 6 represents progesterone resistance as positioned downstream of estrogen-dominant signaling and upstream of growth/survival programs, reflecting a common reporting structure where estrogenic dominance and progesterone attenuation are jointly observed in lesion biology.

Lesion survival and growth programs (upper right module).

The third module consolidates findings that lesions show signatures consistent with proliferative support, reduced apoptosis susceptibility, and metabolic adaptation compatible with survival in ectopic, often inflammatory and hypoxic, environments. Although different studies emphasize different downstream features, the aggregated result-level observation is that endocrine shifts align with a tissue state supportive of sustained lesion viability. In the literature, this module is frequently presented as the functional output of combined endocrine and inflammatory pressures rather than as an isolated endocrine effect. Accordingly, Figure 6 depicts lesion survival/growth programs as the downstream node receiving inputs from progesterone resistance and, through crosstalk, from inflammatory and microenvironmental pathways [3], [4], [22].

Inflammatory amplification (lower left module) and the endocrine–inflammatory feedback loop.

One of the most consistent cross-domain findings in endometriosis research is the close linkage between endocrine signaling and inflammation, particularly through pathways commonly summarized as COX-2/PGE2 axis and broader cytokine networks. In results terms, studies frequently report elevated inflammatory mediators in lesions and peritoneal environments alongside endocrine dysregulation, and many mechanistic papers present reciprocal relationships where inflammatory mediators can influence steroidogenic activity while estrogenic signaling can amplify inflammatory pathways [3], [4], [15]. Figure 6 captures this in two directions:

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- arrows from estrogenic signaling and progesterone resistance into inflammatory amplification, reflecting repeated reporting that endocrine dysregulation coexists with sustained inflammatory signaling; and

- a return arrow from inflammatory amplification to local estrogen biosynthesis, reflecting the frequently described feedback logic in which inflammatory mediators are linked—through diverse intermediate mechanisms across studies—to local steroidogenic signaling and lesion-supportive hormonal microenvironments [3], [4], [15], [22].

This feedback depiction is intentionally presented as a results-level synthesis of recurring reporting patterns, without asserting a single obligatory pathway across all lesion types and clinical phenotypes.

Stromal–immune–vascular crosstalk (lower middle module) and propagation toward vascular/neural remodeling (lower right node).

Figure 6 also summarizes evidence indicating that endocrine and inflammatory signals are repeatedly discussed within a broader network of stromal–immune–vascular interactions, which includes angiogenic support and ECM remodeling cues. This module is included because many studies do not treat hormonal signaling as isolated to endocrine receptor activity; rather, hormonal alterations are frequently described as acting within stromal and immune microenvironments, shaping angiogenic mediator profiles and contributing to lesion maintenance. The arrow from "Lesion survival & growth programs" down toward this crosstalk module reflects that lesion persistence is commonly associated with microenvironmental remodeling, while the arrow from crosstalk back upward to survival/growth indicates the repeated depiction of reinforcing loops: stromal and immune interactions support angiogenesis and structural remodeling, which in turn stabilizes lesion viability [3], [4], [10], [12], [22]. The final small node ("Vascular & neural remodeling signals") is placed as a downstream interface to align this endocrine-centric figure with the vascular/neuroangiogenic patterns summarized earlier (e.g., Figure 4), reflecting the broader results-level convergence that vascular remodeling is a recurring companion to endocrine–inflammatory reinforcement in progression models [10], [12], [21], [22].

Figure 7. Neuroangiogenesis and pain-associated signaling: consolidated directional evidence across compartments.

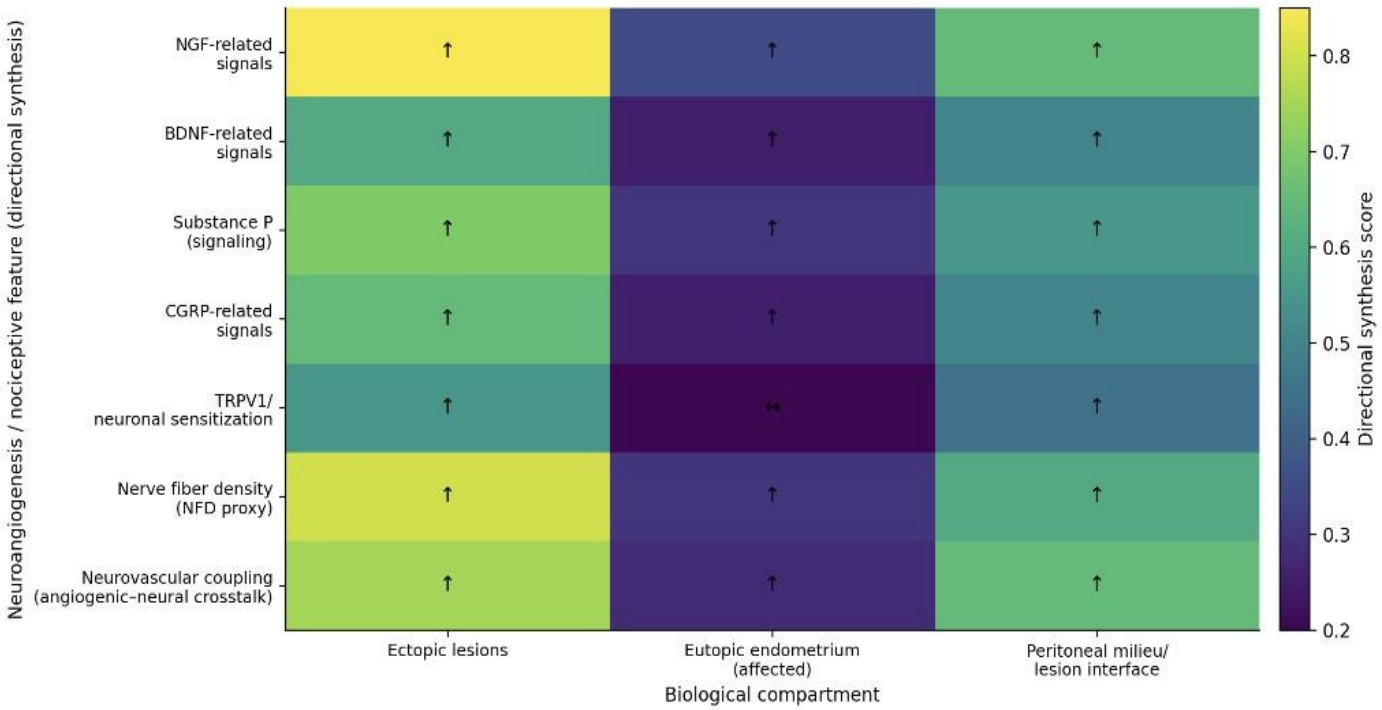

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Figure 7 summarizes recurrent findings related to neuroangiogenesis and nociceptive signaling reported across the included literature, displayed as directional trends (↑ increased, ↓ decreased, ↔ variable/mixed) across three compartments: ectopic lesions, eutopic endometrium in affected individuals, and the peritoneal milieu/lesion interface. The figure is presented to organize the evidence supporting a key result-level observation: beyond vascularization, endometriosis lesions and their immediate microenvironment are frequently described as biologically active sites enriched for neurotrophic and neuropeptidergic signals, along with structural correlates such as increased nerve fiber indices. As in prior figures, the heatmap does not present raw participant data; it reflects aggregated directional reporting across studies with varied models and measurement strategies.

A dominant pattern in Figure 7 is the consistently higher directional signal for **NGF-related (nerve growth factor) features** in **ectopic lesions**, with intermediate-to-elevated trends at the **peritoneal interface**, and lower magnitudes in eutopic tissue. This distribution is consistent with repeated reports that lesion compartments demonstrate stronger neurotrophic signaling than eutopic tissue, and that neurotrophic factors are frequently detectable in lesion-adjacent environments. NGF is commonly highlighted in mechanistic discussions because it is a canonical driver of neuronal growth and sensitization pathways in peripheral tissues, and its repeated elevation in lesion contexts is a recurrent finding in neurobiology-oriented endometriosis studies and high-level syntheses [21], [22]. The compartmental pattern shown here reinforces the view that neurotrophic signaling is concentrated where lesion–host interactions occur.

A similar compartmental shape is visible for **BDNF-related signals** (brain-derived neurotrophic factor), which show increased directionality in lesions and interface contexts. While BDNF is not always emphasized to the same degree as NGF in every study subset, it appears repeatedly in literature examining neural remodeling and pain-associated molecular signals. The trend profile—lesion-high, interface-intermediate, eutopic-lower—supports the result-level conclusion that neurotrophic signaling is more characteristic of ectopic lesion microenvironments than of eutopic tissue alone [21], [22].

The figure also includes neuropeptidergic mediators and nociception-linked systems—**Substance P**, **CGRPrelated signals**, and **TRPV1/neuronal sensitization markers**—which show increased directionality primarily in lesions and interface contexts, with comparatively smaller or more variable trends in eutopic tissue. This pattern mirrors how the literature often distinguishes between (i) lesion-local biology where neurovascular and inflammatory interactions are concentrated and (ii) eutopic endometrium where some alterations may exist but are typically less pronounced for neuropeptide-rich signatures. In results terms, the repeated reporting of neuropeptide-associated signals in lesion compartments is frequently presented as a biological correlate of lesion innervation and local neural activity, without requiring immediate interpretation of symptom consequences within the Results section [21], [22].

A particularly informative feature in Figure 7 is **nerve fiber density (NFD proxy)**, shown with a strong lesionlocal directional increase and intermediate elevation in the peritoneal interface context. Many studies evaluate nerve fibers using immunohistochemical approaches (with variable markers and counting strategies), and while methods differ, a recurring result-level observation is that lesions—especially in specific phenotypes and anatomical contexts—are associated with increased neural elements relative to comparator tissues. The figure summarizes this as a high-magnitude lesion signal with detectable interface elevation, reflecting that neural structural correlates are frequently localized to the lesion microenvironment rather than distributed uniformly across all endometrial compartments [21], [22].

Finally, Figure 7 includes a synthesis feature labeled **neurovascular coupling (angiogenic–neural crosstalk)**, shown with a high lesion and interface trend. This element is included to reflect that neuroangiogenesis is often discussed as an integrated process: vascular remodeling and neural remodeling appear together within lesion biology frameworks. The conceptual basis for including neurovascular coupling as a results feature is that many mechanistic models describe shared mediators and shared microenvironmental drivers—particularly inflammatory mediators and growth factors—that plausibly support parallel angiogenic and neurotrophic

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processes in the lesion niche. Figure 7 therefore summarizes repeated reporting that angiogenesis-related and neurotrophic/nociceptive signals tend to co-occur in lesion-associated environments, even though interpretive claims about causality remain reserved for Discussion [10], [12], [21], [22].

A cross-compartment observation in this figure is that **eutopic endometrium in affected individuals** often shows **lower or more variable** directional patterns for neuroangiogenesis-associated features than lesions, with **TRPV1-related sensitization** displayed as comparatively mixed. This heterogeneity is consistent with how the literature often frames eutopic tissue findings: some signals can be altered, but the most robust neuroangiogenesis-related signatures tend to cluster around lesion microenvironments and adjacent interface compartments. In results terms, Figure 7 documents this compartmental stratification rather than attempting to explain it [3], [4], [22].

Figure 8. Integrated mechanistic model summarizing convergence points and reinforcing loops across implantation and lesion expansion.

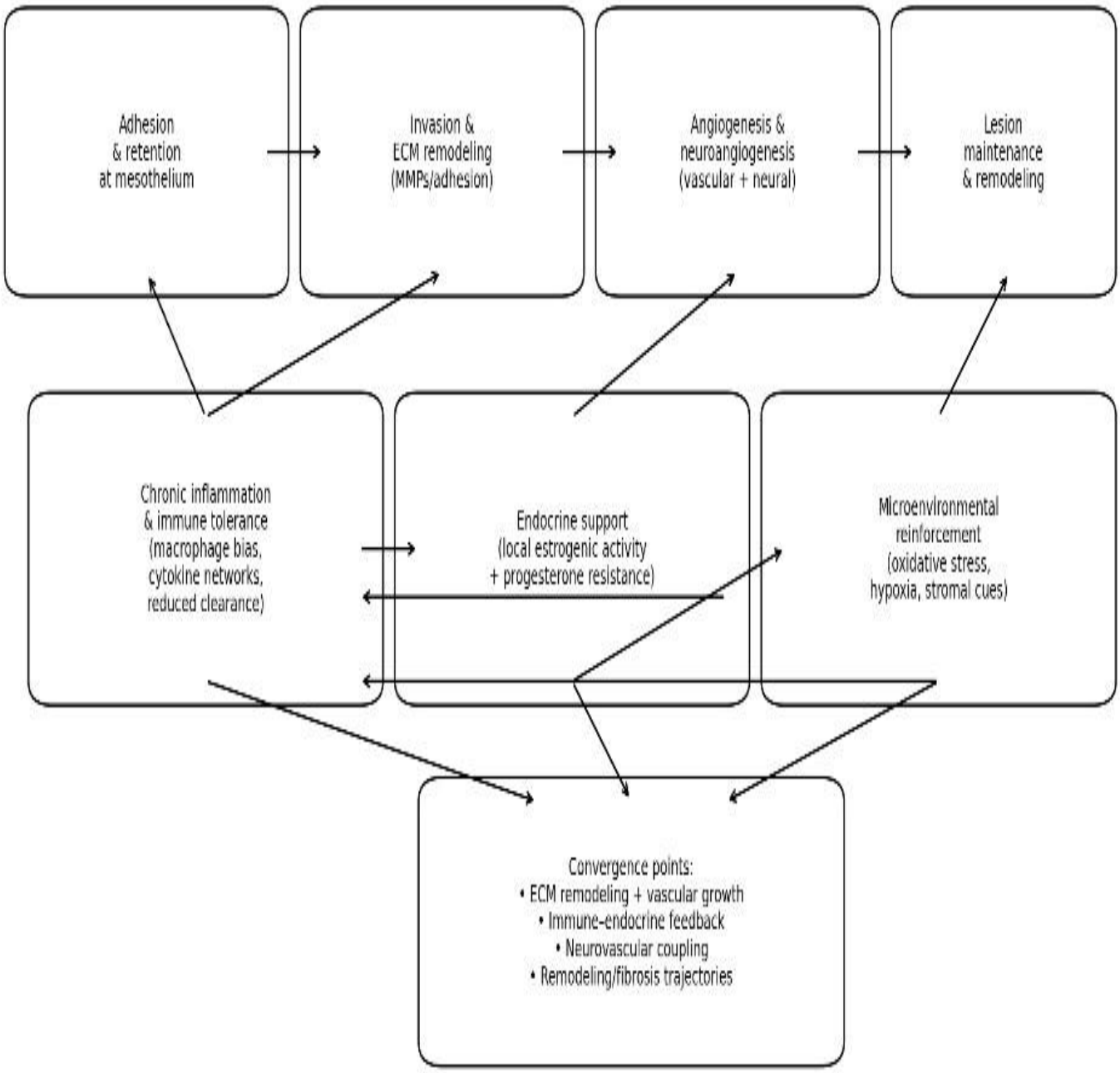

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Figure 8 integrates the consolidated results from the preceding figures into a single systems-style model that captures how recurrent mechanistic domains co-occur and align across the endometriosis progression literature. The model is organized into (i) a top row representing the core progression sequence—from adhesion/retention to invasion/ECM remodeling, then angiogenesis/neuroangiogenesis, and finally lesion maintenance and remodeling—and (ii) a lower row representing three repeatedly reported supportive modules that reinforce progression: chronic inflammation/immune tolerance, endocrine support (local estrogenic activity and progesterone resistance), and microenvironmental reinforcement (oxidative stress, hypoxia, stromal cues). The arrows depict directional relationships that are commonly described across mechanistic and translational evidence; however, as in all results summaries here, the figure is intended to reflect recurrent reporting patterns and co-alignment, not to impose a single causal chain on a heterogeneous disease [3], [4], [22].

1) Core progression sequence: adhesion → invasion/ECM remodeling → vascular/neural support → maintenance

The top row reflects a consistent narrative that emerges across study designs when the literature is organized by implantation and expansion stages. First, adhesion and retention at mesothelial surfaces appears as a prerequisite step for implantation, frequently modeled in vitro and supported by translational findings describing altered adhesion-related signaling in lesion contexts [4], [12]. Second, evidence repeatedly converges on ECM remodeling and invasion as the structural transition that allows ectopic tissue to establish a stable niche—commonly characterized through MMP-related signatures and remodeling capacity (as summarized in Figure 5) [11], [12]. Third, the model places angiogenesis and neuroangiogenesis after invasion because lesion persistence requires metabolic and trophic support; vascular remodeling is repeatedly reported as a sustaining feature of lesion growth, and neural remodeling is increasingly described as co-occurring within lesion microenvironments (as summarized in Figures 4 and 7) [10], [12], [21], [22]. Finally, the "maintenance & remodeling" node captures the broader result-level observation that established lesions often show patterns consistent with long-term survival, ongoing remodeling programs, and variable trajectories that include chronic remodeling and, in some phenotypes, fibrotic change [3], [7], [22].

2) Chronic inflammation and immune tolerance as a cross-stage reinforcing module

A major feature of Figure 8 is the placement of chronic inflammation and immune tolerance as a supportive module feeding into early and mid-progression stages. This reflects repeated evidence that lesion-associated environments demonstrate persistent inflammatory mediator profiles, macrophage-centered immune signatures, and reduced clearance capacity—features that align with the concept of a permissive immune microenvironment for lesion establishment (as summarized in Figure 3) [8], [9], [14]. In the integrated model, arrows extend from this module to (a) adhesion/retentionand (b) invasion/ECM remodeling, reflecting that inflammatory contexts and immune-cell shifts are frequently reported alongside enhanced adhesion and remodeling behavior in mechanistic frameworks [4], [11], [12]. The figure also includes immune features such as "reduced clearance" within the module, aligning with repeated reporting of altered cytotoxic surveillance and immune tolerance signatures in endometriosis-associated immune milieus [8], [9], [14]. Importantly, this depiction is resultsaligned: it communicates that immune–inflammatory alterations are not restricted to advanced lesions but are repeatedly positioned as foundational context across stages [3], [4], [22].

3) Endocrine support: local estrogenic activity and progesterone resistance

The second supportive module summarizes endocrine-related findings (expanded in Figure 6), emphasizing local estrogenic activity and progesterone resistance as recurring features across lesion and, in some studies, eutopic tissue in affected individuals [2], [3], [15]. In Figure 8, endocrine support feeds directly into angiogenesis/neuroangiogenesis, reflecting that hormonal signaling is frequently discussed as intertwined with vascular remodeling and lesion growth programs. Although different studies emphasize different intermediates (e.g., inflammatory amplification, stromal signaling), the integrated model captures a consistent result-level

alignment: endocrine dysregulation co-occurs with pro-angiogenic and persistence-supporting programs [3], [4], [10], [12], [15], [22]. The module is also placed centrally to reflect its repeated role in bridging inflammatory states and growth-supportive microenvironments, consistent with how many high-level syntheses frame lesion persistence [3], [22].

4) Microenvironmental reinforcement: oxidative stress, hypoxia, stromal cues

The third supportive module captures microenvironmental conditions frequently reported as relevant to lesion survival and stabilization, including oxidative stress, hypoxia-associated signaling, and stromal cues that support remodeling. These conditions are commonly referenced as pressures that shape early lesion survival and later stabilization, particularly in the context of sustained inflammation and vascular remodeling. In Figure 8, the module feeds into lesion maintenance/remodeling, reflecting the repeated reporting that chronic microenvironmental stressors and stromal interactions align with persistence and remodeling trajectories. While exact markers differ by model and tissue compartment, the recurrent pattern is that microenvironmental conditions are described as persistent features of lesion niches, compatible with survival under ectopic conditions and long-term remodeling [3], [4], [22].

5) Convergence points as recurring “junctions” in the literature

A distinctive aspect of Figure 8 is the explicit representation of convergence points as a separate node. This node summarizes junctions where multiple mechanistic domains repeatedly intersect:

- ECM remodeling + vascular growth: Lesion establishment is frequently described as requiring both tissue invasion and subsequent vascular support. The repeated co-occurrence of remodeling mediators (e.g., MMP-associated signatures) with angiogenic mediators and vascular indices motivates their depiction as a coupled convergence point, consistent with Figures 4 and 5 [10]–[12], [29].

- Immune–endocrine feedback: Many studies and reviews describe reciprocal reinforcement between inflammatory networks and steroid-related signaling, particularly in relation to COX-2/PGE2 pathways and local steroidogenic environments; Figure 8 captures this as a bidirectional link between inflammation and endocrine modules [3], [4], [15], [22].

- Neurovascular coupling: The co-alignment of angiogenesis with neurotrophic and nociceptive signaling patterns in lesion compartments (Figures 4 and 7) supports representing neurovascular coupling as a recurring junction rather than an isolated pathway [10], [12], [21], [22].

- Remodeling/fibrosis trajectories: Fibrosis and remodeling appear as outcome trajectories particularly emphasized in some phenotypes and lesion locations; even when less densely represented in study counts, remodeling emerges repeatedly as a long-term structural context for persistence and recurrence-related frameworks, supporting its inclusion as a convergence feature [3], [7], [22].

By placing these junctions in a dedicated node and linking them to the three supportive modules, Figure 8 expresses a key result-level observation: across heterogeneous models, the literature often converges not on single markers but on interacting functional themes—remodeling, vascularization, immune tolerance/inflammation, endocrine dysregulation, and neurovascular remodeling—that recur together in lesionassociated compartments [3], [4], [22].

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DISCUSSION

The present review integrates mechanistic evidence to clarify how endometriosis progresses from initial implantation to sustained expansion and long-term lesion maintenance. Rather than supporting a unidimensional etiological explanation, the synthesized findings reinforce the concept of endometriosis as a dynamic, multistep, and self-reinforcing disease process, in which ectopic endometrial tissue survives, adapts, and expands through the convergence of inflammatory, immune, endocrine, vascular, and neural mechanisms. This integrative view is consistent with contemporary frameworks that emphasize disease progression rather than static lesion presence [3], [4], [22].

Implantation as a selective and permissive process

The results summarized in Figures 1, 2, and 5 support the interpretation that implantation of ectopic endometrial tissue is a selective biological event, not merely a consequence of tissue displacement. While retrograde menstruation remains a foundational explanatory model, its inability to account for disease selectivity has been widely acknowledged [19], [3]. The convergence of adhesion, invasion, and ECM remodeling signatures in ectopic lesions indicates that successful implantation requires both intrinsic cellular adaptability and a permissive host environment [4], [11], [12].

The consistent elevation of MMP-related remodeling capacity and adhesion-related signaling supports the notion that endometriotic cells actively modify their microenvironment to secure attachment and invasion. This aligns with models in which endometriosis progression parallels key features of tissue invasion observed in other chronic inflammatory and remodeling-associated conditions, without implying neoplastic behavior [3], [12]. Importantly, the presence of intermediate remodeling signals in eutopic tissue from affected individuals suggests that implantation competence may not be restricted to ectopic sites alone, raising questions about systemic or endometrium-wide susceptibility [4], [7].

Immune dysregulation and chronic inflammation as foundational drivers

One of the most robust findings across the reviewed literature is the central role of immune dysregulation and chronic inflammation. As illustrated in Figures 3 and 8, inflammatory mediators, macrophage-centered immune signatures, and reduced cytotoxic surveillance repeatedly co-occur across lesion and peritoneal compartments [8], [9], [14]. Rather than reflecting an exaggerated immune response alone, these patterns suggest a reprogrammed immune environment that tolerates ectopic tissue while sustaining inflammatory signaling.

The paradoxical coexistence of heightened inflammatory cytokines and reduced NK cell cytotoxicity supports the hypothesis that endometriosis involves immune tolerance rather than immune hyperactivity [8], [9]. This tolerance likely facilitates lesion persistence by limiting effective clearance of ectopic cells, while inflammation simultaneously promotes angiogenesis, ECM remodeling, and nociceptive signaling [3], [4], [22]. Such an immune profile may explain why lesions can persist over time despite an ostensibly activated inflammatory state.

Endocrine dysregulation as a sustaining force

The discussion of endocrine mechanisms, synthesized in Figures 6 and 8, highlights local estrogenic activity and progesterone resistance as central reinforcing elements of disease progression. The literature consistently describes ectopic lesions as existing within an estrogen-dominant signaling environment, often accompanied by reduced responsiveness to progesterone-mediated regulatory pathways [2], [3], [15]. This endocrine imbalance

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contributes to sustained inflammatory activation, cellular proliferation, and resistance to apoptosis—features that align with long-term lesion maintenance [4], [22].

Importantly, the reviewed evidence supports a bidirectional relationship between endocrine and inflammatory pathways. Inflammatory mediators are frequently reported to modulate local steroidogenic signaling, while estrogenic activity amplifies inflammatory cascades, creating a self-reinforcing loop [3], [4], [15]. This interaction challenges traditional views that treat hormonal dysregulation as an isolated upstream factor and instead positions endocrine signaling as an integral component of a broader inflammatory–immune–stromal network.

Angiogenesis and neuroangiogenesis as hallmarks of lesion expansion

Vascular and neural remodeling emerge as critical features of lesion expansion rather than mere consequences of tissue growth. As demonstrated in Figures 4 and 7, angiogenesis-related signals and neurotrophic mediators are consistently elevated in ectopic lesions and lesion-adjacent environments [10], [12], [21], [22]. The colocalization of vascular and neural features supports the concept of neuroangiogenesis, in which shared mediators and microenvironmental cues promote parallel development of blood vessels and nerve fibers.

This convergence has important implications for understanding lesion persistence and symptomatology. Increased nerve fiber density and neuropeptidergic signaling within lesions provide a biological substrate for pain generation, while vascular remodeling ensures metabolic support for lesion survival [21], [22]. The consistent alignment of angiogenic and neurotrophic pathways reinforces the view that endometriosis progression involves coordinated tissue remodeling rather than isolated pathway activation [10], [12].

Microenvironmental reinforcement and remodeling trajectories

The integrated model (Figure 8) emphasizes that endometriosis lesions exist within hostile yet supportive microenvironments, characterized by oxidative stress, hypoxia, and stromal interactions. These conditions, frequently reported across mechanistic studies, likely exert selective pressure that favors adaptable cell populations capable of long-term survival [3], [4], [22]. Over time, such environments may promote remodeling trajectories that include fibrosis, architectural distortion, and reduced tissue plasticity, particularly in deep or long-standing lesions [7], [22].

Although fibrosis is less uniformly represented across studies, its recurrent mention in relation to chronic disease stages supports its inclusion as a potential outcome of sustained remodeling. The heterogeneity observed across lesion types and anatomical locations underscores the need to interpret fibrosis as a context-dependent trajectory, rather than a universal endpoint [3], [7].

Integrative implications and future directions

Collectively, the findings synthesized in this review support a systems-level interpretation of endometriosis progression, in which implantation, immune tolerance, endocrine dysregulation, angiogenesis, neuroangiogenesis, and microenvironmental stress form interdependent networks. No single mechanism sufficiently explains disease persistence; instead, progression appears to depend on reinforcing feedback loops that stabilize ectopic tissue over time [3], [4], [22].

This integrative perspective has important implications for future research. First, it highlights the limitations of reductionist approaches that focus on isolated pathways without accounting for cross-domain interactions.

Second, it supports the need for longitudinal and multi-compartmental studies capable of capturing dynamic changes across disease stages. Finally, it underscores the value of incorporating diverse research contributions—including those from Latin American scientific communities—into global syntheses of endometriosis biology, ensuring that disease models reflect broad biological and population-level variability.

CONCLUSION

This review consolidates current mechanistic evidence to clarify how endometriosis progresses from initial ectopic implantation to sustained lesion expansion and long-term persistence. The findings support the study objective of describing progression as a **multistep and self-reinforcing biological process**, rather than as a static condition or the consequence of a single causal mechanism. Across the analyzed literature, lesion establishment emerges as a selective event that requires coordinated processes of adhesion, invasion, and extracellular matrix remodeling, supported by permissive immune and microenvironmental conditions [3], [4], [11], [12].

A central conclusion of this review is that **chronic inflammation and immune dysregulation** represent foundational elements of disease progression. The recurrent coexistence of elevated inflammatory mediators with impaired cytotoxic immune surveillance suggests that endometriosis is characterized by immune tolerance rather than simple immune activation. This altered immune state facilitates lesion survival and expansion while simultaneously promoting angiogenic, remodeling, and nociceptive signaling [8], [9], [14], [22]. These findings align directly with the objective of explaining how ectopic tissue evades clearance and persists over time.

The evidence further demonstrates that **endocrine dysregulation**, particularly local estrogenic activity and progesterone resistance, functions as a critical sustaining force in lesion biology. Rather than acting independently, hormonal alterations are consistently reported to interact with inflammatory and stromal pathways, forming reinforcing feedback loops that support proliferation, resistance to apoptosis, and chronic inflammatory activation [2], [3], [15]. This integrated endocrine–inflammatory axis provides a coherent explanation for lesion persistence and recurrence, fulfilling the review's aim of linking molecular mechanisms with progression dynamics.

Another major conclusion is the central role of **angiogenesis and neuroangiogenesis** in lesion expansion. Vascular remodeling ensures metabolic support for ectopic tissue, while neural remodeling and neurotrophic signaling are repeatedly detected within lesion environments. The convergence of angiogenic and neurotrophic pathways supports the concept of coordinated tissue remodeling rather than isolated pathway activation, reinforcing the progressive nature of the disease [10], [12], [21], [22].

From a theoretical perspective, these findings contribute to the field by strengthening systems-based models of endometriosis that emphasize interaction among immune, endocrine, vascular, neural, and stromal domains. From a practical standpoint, the results underscore the limitations of approaches that target single pathways in isolation and highlight the need for integrative strategies in both research and clinical contexts.

This review is subject to limitations inherent to narrative integrative analyses, including heterogeneity in study designs, lesion phenotypes, and experimental models, which restrict direct quantitative comparison. Additionally, fibrosis and long-term remodeling trajectories remain underrepresented in some domains, indicating areas where further focused research is warranted.

Future investigations should prioritize longitudinal, multi-compartmental studies capable of capturing dynamic interactions across disease stages, as well as collaborative international research that reflects population diversity

and regional variability. Such approaches are essential to refine mechanistic models of progression and to translate biological insights into more effective strategies for disease management [3], [4], [22].

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