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La endometriosis como modelo de inflamación sistémica: implicaciones clínicas, moleculares y traslacionales

Endometriosis as a Model of Systemic Inflammation: Clinical, Molecular, and Translational Implications

Augusto Cam Rojas
Clínica San Felipe
augusto@upch.pe
https://orcid.org/0000-0003-1602-8457

Maria Fernanda Venero Acurio
Universidad Peruana de Ciencias Aplicadas
mariafernandaveneroacurio@gmail.com
https://orcid.org/0009-0009-5427-0878

Daniel Alberto Madrid González
Universidad del Valle de Cuernavaca
drmadridgonzalez@gmail.com
https://orcid.org/0000-0002-4453-8625

Jorge Angel Velasco Espinal
Universidad del Valle de Cuernavaca
jorgeangelvelascoespinal@gmail.com
https://orcid.org/0009-0000-3567-0774

Abdiel Arias Estrada
Universidad del Valle de Cuernavaca
ariasabdiel69@gmail.com
https://orcid.org/0009-0000-0050-4274

Delia Mercedes Balarezco Páez
PUCE
delybalarezo.paez@gmail.com
https://orcid.org/0009-0007-5715-3840

Perla Gabriela Hershberger Arrechea
Facultad de Medicina La Salle
perlahersh.04@gmail.com
https://orcid.org/0009-0004-2101-6367

Berenice Lira Hernández
ISSSTE
berenice.lira.h@gmail.com
https://orcid.org/0009-0004-2474-3367

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***Autor de correspondencia:** augusto@upch.pe

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RESUMEN

La endometriosis se reconoce cada vez más como una **enfermedad inflamatoria sistémica** y no únicamente ginecológica. Esta revisión integra evidencia molecular y clínica reciente que demuestra cómo la inflamación crónica, el estrés oxidativo y las vesículas extracelulares (EVs) interactúan para generar manifestaciones locales y sistémicas. Citocinas elevadas como IL-1β, IL-6, TNF-α, IL-8, MCP-1 y VEGF promueven angiogénesis, activación inmune y persistencia

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de las lesiones, mientras que la disminución de IL-10 deteriora la inmunorregulación. El estrés oxidativo, derivado de la sobrecarga férrica peritoneal y de la disfunción mitocondrial, amplifica las vías inflamatorias NF-κB y TGF-β/SMAD, favoreciendo fibrosis, resistencia a la apoptosis y sensibilización del dolor. Las EVs actúan como mediadores de comunicación sistémica, transportando microARN y proteínas que modifican células inmunes, endoteliales y neuronales, vinculando la inflamación pélvica con comorbilidades cardiovasculares, metabólicas y autoinmunes. La evidencia muestra un mayor riesgo de hipertensión, dislipidemia, enfermedades autoinmunes y alteraciones neuroendocrinas, junto con daño oxidativo y genómico que explican su relación con carcinomas ováricos. Reconocer a la endometriosis como trastorno multisistémico impulsa el desarrollo de estrategias diagnósticas y terapéuticas integrales basadas en biomarcadores de citocinas y EVs, junto con terapias antiinflamatorias, antioxidantes y antiangiogénicas. Las contribuciones de México, Colombia y Ecuador subrayan la necesidad de investigación inclusiva y medicina de precisión. Así, la endometriosis se consolida como un **modelo de inflamación sistémica**, donde los ejes inmune, oxidativo y endocrino convergen en un mismo proceso patológico.

PALABRAS CLAVE

Endometriosis; inflamación sistémica; citocinas; estrés oxidativo; vesículas extracelulares; fibrosis; enfermedad cardiovascular; comorbilidades autoinmunes; regulación neuroinmune; medicina de precisión.

ABSTRACT

Endometriosis is increasingly recognized as a **systemic inflammatory disease** rather than a localized gynecological disorder. This review integrates recent molecular and clinical evidence demonstrating how chronic inflammation, oxidative stress, and extracellular vesicle (EV) signaling interact to shape both local and systemic pathophysiology. Elevated cytokines such as IL-1β, IL-6, TNF-α, IL-8, MCP-1, and VEGF sustain angiogenesis, immune activation, and lesion persistence, while diminished IL-10 impairs immunoregulation. Concurrently, oxidative stress arising from peritoneal iron overload and mitochondrial dysfunction amplifies inflammatory signaling through NF-κB and TGF-β/SMAD pathways, promoting fibrosis, apoptosis resistance, and nociceptor sensitization. Recent discoveries highlight EVs as mediators of systemic communication, transferring microRNAs and proteins that modulate immune, endothelial, and neural targets, thereby linking pelvic inflammation to cardiovascular, metabolic, and autoimmune comorbidities. Evidence from multiple studies indicates that endometriosis confers elevated risks of hypertension, dyslipidemia, autoimmune disorders, and mood disturbances—hallmarks of systemic immune and vascular dysregulation. Furthermore, chronic oxidative and inflammatory exposure fosters genomic instability, explaining the observed association with ovarian clear-cell and endometrioid carcinomas. Recognizing endometriosis as a multisystemic disorder supports the development of integrative diagnostic and therapeutic strategies, including cytokine and exosomal biomarker panels and targeted anti-inflammatory, antioxidant, and anti-angiogenic treatments. Contributions from Mexico, Colombia, and Ecuador emphasize the need for regionally inclusive research and precision-medicine approaches. Endometriosis thus emerges as a **model of systemic inflammation**, exemplifying how immune, oxidative, and endocrine networks converge to produce both reproductive and extra-pelvic disease manifestations.

KEYWORDS

Endometriosis; systemic inflammation; cytokines; oxidative stress; extracellular vesicles; fibrosis; cardiovascular disease; autoimmune comorbidities; neuroimmune regulation; precision medicine.

INTRODUCCIÓN

Endometriosis is a chronic, estrogen-dependent, and highly debilitating condition characterized by the presence of endometrial-like tissue outside the uterine cavity, primarily affecting the pelvic peritoneum, ovaries, and rectovaginal septum (Zondervan et al., 2020). Affecting an estimated 190 million women and individuals assigned female at birth worldwide, it has profound implications not only for reproductive health but also for quality of life, mental well-being, and systemic physiological balance. Traditionally defined as a gynecological disorder confined to the reproductive system, endometriosis has recently emerged as a model of chronic systemic inflammation, reflecting complex

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interactions among endocrine, immune, and metabolic pathways that extend far beyond the pelvis (Bao et al., 2022; Cano-Herrera et al., 2024).

The pathophysiological basis of endometriosis involves an interplay between hormonal dysregulation and a chronic inflammatory microenvironment. The ectopic endometrial cells exhibit enhanced survival, proliferation, and resistance to apoptosis, sustained by elevated concentrations of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF) (Oală et al., 2024). These mediators promote angiogenesis, fibrosis, and neuroinflammation, resulting in chronic pelvic pain, infertility, and fatigue (García et al., 2022). Beyond the local environment, this persistent inflammatory state exerts systemic effects, influencing endothelial function, oxidative stress responses, and immune tolerance mechanisms (Didžiokaitė et al., 2023; Scutiero et al., 2017). Such systemic manifestations have prompted researchers to reconsider endometriosis as a multi-organ disease that mirrors the molecular hallmarks of other chronic inflammatory and autoimmune disorders.

Recent genomic and transcriptomic studies have reinforced this systemic concept. Bao et al. (2022) provided strong evidence that the gene expression profiles of patients with endometriosis overlap with those observed in systemic inflammatory and immune-mediated diseases. These findings align with observations from Mariadas et al. (2025) and Garmendia and Sánchez (2025), who emphasize the dysregulation of immune checkpoints, T-cell activation, and macrophage polarization as central elements of the disease's chronicity. Furthermore, extracellular vesicles (EVs) and exosomes have gained attention as molecular vehicles that mediate intercellular communication between endometriotic lesions and distant organs (Chu et al., 2024; Scheck et al., 2022). Their cargo—comprising microRNAs, cytokines, and metabolic enzymes—contributes to systemic inflammation and might explain the development of extra-pelvic symptoms and comorbidities.

Clinically, endometriosis has been increasingly associated with an elevated risk of cardiovascular disease, as confirmed by meta-analyses conducted by Okoli et al. (2023) and Parsa et al. (2025). The underlying mechanisms are believed to include chronic low-grade inflammation, endothelial dysfunction, and metabolic alterations. Similarly, Petraglia et al. (2025) reported correlations with autoimmune diseases and mood disorders, supporting the hypothesis that endometriosis is not an isolated gynecological condition but part of a broader inflammatory and metabolic spectrum. The oxidative stress generated by persistent inflammatory reactions not only perpetuates tissue injury and fibrosis but also contributes to systemic redox imbalance, further enhancing disease chronicity (Jackson et al., 2005; Didžiokaitė et al., 2023).

From a diagnostic perspective, the current challenge lies in translating these molecular insights into clinically applicable tools. Despite substantial advances in imaging and laparoscopy, diagnostic delays often exceed seven years, mainly due to symptom variability, lack of awareness, and the absence of reliable biomarkers (Griffiths et al., 2024). Promising approaches involving cytokine panels, exosomal microRNAs, and proteomic profiling are being explored to overcome this limitation (Krygere et al., 2024; Santos et al., 2025). Nevertheless, heterogeneity among study designs, ethnic backgrounds, and regional health systems—particularly in underrepresented regions such as Latin America—hampers the standardization of results and the implementation of early detection strategies.

Recognizing these gaps, this international collaboration among researchers from Mexico, Colombia, and Ecuador seeks to reframe endometriosis as a paradigm of systemic inflammation that integrates molecular, immunological, and clinical dimensions. By examining the interplay between inflammatory mediators, oxidative stress, and immune dysfunction, the present review aims to elucidate how localized pelvic lesions can exert systemic effects influencing cardiovascular, metabolic, and neuroimmune health. Moreover, this work underscores the importance of addressing endometriosis as a public health concern, demanding coordinated efforts in education, early diagnosis, and research integration across countries and disciplines.

The present review is guided by three main questions: (1) How does systemic inflammation drive the initiation and persistence of endometriotic lesions? (2) What molecular and immunological pathways link endometriosis to extra-pelvic comorbidities? and (3) Which emerging biomarkers and molecular signals hold promise for improving diagnosis and personalized therapy? By synthesizing current evidence, this article provides an updated framework that situates endometriosis at the intersection of inflammation, immunity, and systemic disease—an approach essential for transforming the clinical management and understanding of this complex condition.

DESARROLLO

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Endometriosis represents a multifaceted condition in which inflammation, immune dysregulation, and oxidative stress converge to generate a systemic inflammatory milieu. This section presents the current evidence that supports the systemic nature of endometriosis, exploring the molecular, immunological, and clinical mechanisms involved in its pathophysiology. The reviewed studies highlight that this disease transcends the boundaries of gynecology, positioning itself as a systemic disorder with implications in cardiovascular, metabolic, and immune health.

1. Chronic Inflammation and Immune Dysregulation

Inflammation plays a central role in the establishment and persistence of endometriosis. The peritoneal fluid of affected patients shows elevated levels of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, TNF-α, and monocyte chemoattractant protein-1 (MCP-1), which collectively enhance the survival and invasiveness of ectopic endometrial cells (Oală et al., 2024; Cano-Herrera et al., 2024). These cytokines also recruit activated macrophages and neutrophils, promoting angiogenesis and tissue remodeling. Bao et al. (2022) demonstrated that gene expression profiles in endometriotic lesions reflect chronic immune activation similar to that observed in autoimmune diseases, with upregulation of genes involved in antigen presentation and T-cell signaling.

Moreover, immune tolerance mechanisms are profoundly altered. Regulatory T cells (Tregs), which normally suppress excessive immune reactions, exhibit functional impairment in women with endometriosis (Garmendia & Sánchez, 2025). This contributes to persistent inflammation, lesion survival, and pain sensitization. Simultaneously, natural killer (NK) cell cytotoxicity is reduced, diminishing immune clearance of ectopic tissue. This immune imbalance—marked by simultaneous pro-inflammatory activation and insufficient immunoregulation—creates a self-perpetuating cycle of inflammation and tissue injury.

2. Oxidative Stress and Fibrotic Remodeling

Reactive oxygen species (ROS) and oxidative stress have been identified as pivotal contributors to the chronicity of endometriosis (Didžiokaitė et al., 2023; Scutiero et al., 2017). Iron overload derived from retrograde menstruation increases oxidative damage in the peritoneal cavity, activating nuclear factor-kappa B (NF-κB) and transforming growth factor-beta (TGF-β) pathways. These cascades lead to fibroblast activation and extracellular matrix deposition, culminating in the formation of fibrotic adhesions (García et al., 2022).

Jackson et al. (2005) established early evidence that elevated lipid peroxidation products and decreased antioxidant enzyme activity correlate with disease severity. More recent research supports that oxidative stress is not confined to local tissues but exerts systemic consequences, impairing endothelial function and promoting vascular inflammation (Didžiokaitė et al., 2023). These mechanisms may partly explain the epidemiological association between endometriosis and cardiovascular diseases reported in multiple meta-analyses (Okoli et al., 2023; Parsa et al., 2025).

3. Extracellular Vesicles and Molecular Communication

The discovery of extracellular vesicles (EVs), including exosomes and microvesicles, has reshaped the understanding of intercellular communication in endometriosis. These nanoscale structures transport proteins, lipids, and nucleic acids that modulate immune and vascular responses both locally and systemically (Chu et al., 2024; Scheck et al., 2022). EVs derived from endometriotic stromal cells have been shown to induce angiogenesis and alter macrophage polarization toward a pro-inflammatory M2 phenotype, perpetuating lesion growth.

Santos et al. (2025) emphasized the role of exosomal microRNAs—particularly miR-22, miR-214, and miR-451a—as potential epigenetic biomarkers capable of distinguishing between eutopic and ectopic endometrial tissues. Their regulatory influence extends beyond lesion sites, affecting immune cell gene expression and systemic inflammatory signaling. These findings highlight EVs as both biomarkers and active mediators in the systemic propagation of disease processes, potentially linking endometriosis to extra-pelvic comorbidities.

4. Systemic Manifestations and Comorbidities

Endometriosis exhibits numerous systemic manifestations that reinforce its inflammatory and metabolic nature. Cardiovascular risk, for instance, is significantly elevated among affected women, even after adjustment for age and hormonal exposure (Marchandot et al., 2022). The proposed mechanisms involve endothelial dysfunction, elevated C-

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reactive protein levels, and persistent oxidative imbalance (Petraglia et al., 2025). Similarly, associations with autoimmune diseases such as systemic lupus erythematosus and autoimmune thyroiditis have been described, suggesting a shared immunopathogenic background (Mariadas et al., 2025).

Additionally, chronic inflammation may affect neuroendocrine pathways, leading to fatigue, anxiety, and depression—symptoms commonly reported in clinical practice but often underestimated in research (Zondervan et al., 2020). The systemic hormonal and inflammatory disruptions can also influence metabolic homeostasis, contributing to insulin resistance and lipid abnormalities. Collectively, these findings demonstrate that endometriosis behaves as a systemic inflammatory syndrome rather than a localized disorder.

5. Diagnostic and Therapeutic Implications

Despite significant progress in molecular research, clinical diagnosis continues to rely largely on imaging and surgical visualization. The heterogeneity of symptoms and limited biomarker specificity contribute to diagnostic delays exceeding seven years on average (Griffiths et al., 2024). Krygere et al. (2024) proposed a diagnostic panel combining IL-6, TNF-α, and IL-10 serum levels as potential non-invasive indicators, while Santos et al. (2025) and Chu et al. (2024) suggested that exosomal microRNAs could revolutionize early detection.

Therapeutically, understanding endometriosis as a systemic inflammatory disorder opens opportunities for targeted treatments aimed at modulating immune pathways, oxidative stress, and cytokine signaling rather than focusing solely on hormonal suppression. Emerging interventions include anti-inflammatory agents, antioxidants, and biological therapies directed at cytokine or angiogenic pathways (Cano-Herrera et al., 2024). However, most of these remain in experimental phases, underscoring the need for large-scale, multiethnic clinical trials—especially in underrepresented regions such as Latin America.

6. Integrative Perspective and Future Directions

From an international standpoint, the collaborative analysis between researchers from Mexico, Colombia, and Ecuador highlights regional variations in disease presentation and diagnostic approaches. Differences in healthcare access, cultural perceptions of menstrual pain, and research infrastructure may affect epidemiological data and the translation of molecular findings into practice. This cooperation aims to contribute to a more comprehensive understanding of endometriosis as a global health issue that intersects with social and biological determinants.

Future research must prioritize longitudinal studies that explore systemic inflammatory biomarkers, molecular profiling across ethnic populations, and the integration of omics technologies. Furthermore, recognizing endometriosis as a chronic systemic condition reinforces the need for multidisciplinary care involving gynecologists, immunologists, cardiologists, and mental health specialists. By bridging clinical, molecular, and public health dimensions, the systemic model of endometriosis offers a promising framework for early detection, precision medicine, and holistic patient management.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To analyze endometriosis as a model of systemic inflammation through an integrative review of clinical, molecular, and immunological evidence, highlighting its pathophysiological mechanisms, systemic implications, and potential biomarkers that may contribute to improving diagnostic and therapeutic strategies at a global and regional (Mexico, Colombia, Ecuador) level.

Specific Objectives

1. To describe the molecular and immuno-inflammatory mechanisms that underpin the systemic nature of endometriosis, emphasizing the role of cytokines, oxidative stress, and immune dysregulation in the persistence of the disease.
2. To examine the association between endometriosis and extra-pelvic comorbidities—particularly cardiovascular, autoimmune, and metabolic disorders—based on current clinical and epidemiological evidence.

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3. To identify the role of extracellular vesicles, exosomal microRNAs, and cytokine biomarkers as potential diagnostic and prognostic tools for endometriosis within the context of systemic inflammation.
4. To compare the relevance and applicability of recent molecular findings to diverse populations, integrating perspectives from Mexico, Colombia, and Ecuador to highlight regional differences in pathophysiological understanding and clinical approaches.
5. To propose a conceptual framework that situates endometriosis within the broader spectrum of systemic inflammatory diseases, facilitating future interdisciplinary research and the development of precision medicine strategies.

OBJETO DE ESTUDIO

The object of this study is the **systemic inflammatory dimension of endometriosis**, examined through its molecular, immunological, and clinical components that position it as a paradigm of chronic inflammation extending beyond the reproductive system. Traditionally classified as a localized gynecological condition, endometriosis has revealed, through recent evidence, an intricate network of pathophysiological mechanisms involving sustained immune activation, oxidative stress, and abnormal cellular communication. These processes contribute to both the persistence of endometrial lesions and the emergence of extra-pelvic manifestations that affect cardiovascular, metabolic, and immune homeostasis.

In this context, the study focuses on the **biological foundations** of endometriosis as a systemic disorder. It explores the role of cytokines—such as IL-1β, IL-6, TNF-α, and VEGF—in promoting angiogenesis, fibrosis, and pain sensitization; the impact of oxidative stress on endothelial dysfunction and tissue remodeling; and the participation of exosomal signaling in mediating intercellular communication between endometrial and distant tissues. These molecular events are not isolated phenomena but rather interconnected elements of a global inflammatory response that links the local pathology of endometriosis to systemic physiological alterations.

Furthermore, the object of the study includes the **clinical and epidemiological implications** of this systemic framework. The growing association between endometriosis and comorbidities such as cardiovascular disease, autoimmune disorders, depression, and metabolic syndrome reinforces the concept that the disease behaves as a chronic inflammatory syndrome. Understanding these links is essential to redefine diagnostic and therapeutic strategies and to promote multidisciplinary approaches that integrate gynecology, immunology, and internal medicine.

The investigation also recognizes the **sociocultural and regional context** as a determinant factor in the manifestation and management of endometriosis. By incorporating the perspectives of researchers from Mexico, Colombia, and Ecuador, the study acknowledges the heterogeneity of genetic backgrounds, environmental exposures, and healthcare systems that shape disease presentation in Latin America. This regional inclusion allows for a more comprehensive understanding of endometriosis as both a biomedical and public health issue, demanding regional collaboration and contextualized health policies.

Therefore, the object of this study encompasses a **dual approach**: on one hand, the molecular and cellular mechanisms that underlie the chronic inflammatory processes characteristic of endometriosis, and on the other, the clinical and systemic repercussions that demonstrate its multisystemic behavior. Through this integrated lens, the study seeks to consolidate endometriosis as a model of systemic inflammation capable of explaining a broad range of physiological and pathological interactions within the female organism.

Ultimately, this focus aspires to transcend traditional diagnostic and therapeutic paradigms, contributing to a deeper understanding of the disease's complexity and to the development of innovative, personalized, and globally applicable approaches for its management.

METODOLOGÍA

This study was conducted as a **comprehensive narrative review** with an international and multidisciplinary scope, integrating current evidence from molecular biology, immunology, and clinical research related to endometriosis and

its systemic manifestations. The methodological framework was designed to ensure scientific rigor, transparency, and replicability, combining qualitative synthesis of findings with analytical interpretation of the mechanisms that define endometriosis as a model of systemic inflammation.

1. Study Design and Scope

The review followed a structured narrative design aimed at identifying, analyzing, and integrating relevant literature published in peer-reviewed scientific journals. The main purpose was to synthesize current knowledge regarding the inflammatory, immunological, and molecular aspects of endometriosis, as well as its clinical correlations and comorbidities. Unlike systematic reviews that emphasize quantitative meta-analysis, this approach prioritized **interpretative integration**, allowing the inclusion of studies with diverse designs (experimental, clinical, translational, and review-based) that contribute to a global and contextualized understanding of the topic.

The review incorporated perspectives from **Mexico, Colombia, and Ecuador**, emphasizing Latin America's contribution to global research and acknowledging regional epidemiological patterns, diagnostic challenges, and resource disparities. Collaborative discussion among researchers from these countries enriched the interpretation of results and ensured a balanced view that considered both universal mechanisms and local realities.

2. Search Strategy and Information Sources

The literature search was carried out across major biomedical databases, including **PubMed/MEDLINE**, **Scopus**, **Web of Science**, and **ScienceDirect**, complemented by targeted searches in **Google Scholar** to identify additional references not indexed in traditional repositories. The search covered the period from **January 2005 to October 2025**, ensuring inclusion of both foundational studies and recent advances.

The following keywords and Boolean operators were used:
"endometriosis" AND ("systemic inflammation" OR "oxidative stress" OR "cytokines" OR "immune dysregulation" OR "extracellular vesicles" OR "microRNA" OR "comorbidities" OR "cardiovascular disease" OR "autoimmune disorders" OR "metabolic alterations").
Additionally, filters were applied for English-language publications, open-access availability, and peer-reviewed sources. Reference lists of selected articles were manually examined to identify **secondary citations** that contributed conceptual or methodological value to the topic.

A total of **423 initial records** were retrieved. After eliminating duplicates and applying relevance criteria, **72 full-text articles** were evaluated, and **20 key references** were ultimately selected for in-depth analysis, representing high-impact journals such as *The New England Journal of Medicine*, *Trends in Molecular Medicine*, *Frontiers in Immunology*, *Biomedicines*, *International Journal of Molecular Sciences*, and *Reproductive Biology and Endocrinology*.

3. Inclusion and Exclusion Criteria

Inclusion criteria encompassed:

- Original research articles, clinical studies, systematic reviews, or meta-analyses published between 2005 and 2025.
- Studies addressing the molecular, inflammatory, immunological, or systemic aspects of endometriosis.
- Research describing comorbidities or systemic consequences associated with endometriosis (e.g., cardiovascular, autoimmune, or metabolic).
- Articles available in full text and published in English.

Exclusion criteria included:

- Case reports or studies with insufficient methodological description.
- Non-peer-reviewed sources, editorials, or commentaries.
- Studies limited exclusively to fertility outcomes without discussion of inflammatory or systemic mechanisms.

These criteria ensured the inclusion of literature that provided both biological and clinical insights relevant to the systemic conceptualization of endometriosis.

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4. Data Extraction and Analysis

A thematic and conceptual synthesis approach was used. Each selected article was reviewed independently by participating authors from Mexico, Colombia, and Ecuador. Data extraction included:

- **Author(s), year, and country of publication**
- **Study design and sample characteristics**
- **Molecular or immunological pathways discussed**
- **Reported systemic manifestations or comorbidities**
- **Main findings and conclusions**

The extracted information was classified into analytical categories:

1. Chronic inflammation and immune dysregulation
2. Oxidative stress and fibrosis
3. Extracellular vesicles and molecular communication
4. Systemic manifestations and comorbidities
5. Diagnostic and therapeutic implications

Cross-analysis of these categories allowed identification of recurring patterns, contradictions, and emerging hypotheses. Special emphasis was placed on connecting molecular findings with clinical outcomes, illustrating how localized lesions contribute to systemic effects.

5. Validation and Collaborative Interpretation

To reinforce analytical consistency, results and interpretations were discussed among multidisciplinary teams from the three participating countries. The collaboration included specialists in gynecology, immunology, internal medicine, and molecular biology. This **tri-national approach** allowed for a comparative interpretation of results, identifying regional gaps in research and practice.

The integration of Latin American perspectives also contributed to the validation of theoretical models through contrast with local epidemiological data and healthcare realities. Ethical research practices were observed at all times, adhering to principles of academic integrity and intellectual transparency.

6. Methodological Rationale

The narrative review format was selected for its capacity to **synthesize diverse types of evidence** and to explore theoretical and mechanistic questions that may not yet be addressed by quantitative meta-analyses. This approach is particularly suitable for complex biomedical topics—such as endometriosis—where systemic interrelations between molecular, clinical, and environmental factors demand interpretative flexibility.

The methodological coherence lies in linking micro-level evidence (molecular and cellular data) with macro-level implications (clinical and systemic effects). This analytical integration supports the central objective of establishing endometriosis as a **model of systemic inflammation**.

7. Limitations

While this study provides an updated and integrative synthesis, it acknowledges certain limitations. The narrative nature of the review does not allow for statistical meta-analysis or pooled effect estimation. Additionally, the heterogeneity of diagnostic criteria and study populations among the analyzed literature may introduce variability in findings. Nonetheless, the inclusion of high-quality, peer-reviewed sources and triangulation among international collaborators enhance the reliability and interpretative depth of the review.

FASES DEL DESARROLLO

The development of this study followed a structured and sequential process designed to ensure methodological rigor, interpretative coherence, and thematic depth. Each phase was strategically defined to integrate molecular, clinical, and

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epidemiological perspectives into a comprehensive understanding of endometriosis as a systemic inflammatory model. The phases outlined below describe the logical and analytical progression of the review, from the initial conceptual framework to the synthesis of conclusions.

Phase I. Conceptual Definition and Theoretical Framework Formation

The first phase involved defining the conceptual foundations of endometriosis from a **systemic and immunoinflammatory perspective**. This required reviewing historical definitions and contrasting them with recent findings that challenge the traditional gynecological view of the disease.
Through the analysis of classical and contemporary literature (Zondervan et al., 2020; Bao et al., 2022; Cano-Herrera et al., 2024), the research team established that endometriosis exhibits pathophysiological characteristics consistent with systemic inflammatory disorders—namely chronic cytokine activation, oxidative stress, and immune dysregulation.

This phase culminated in the **construction of a theoretical matrix**, identifying key biological pathways such as:

- Cytokine signaling (IL-1β, IL-6, TNF-α, VEGF)
- Oxidative stress mechanisms mediated by reactive oxygen species (ROS)
- Extracellular vesicle (EV)–mediated cellular communication
- Fibrotic and angiogenic remodeling processes

The outcome of this phase was a **conceptual redefinition** of endometriosis as a systemic entity, laying the groundwork for subsequent analytical phases.

Phase II. Literature Search, Selection, and Organization

In the second phase, a structured and exhaustive literature search was conducted to identify studies related to the **molecular, immunological, and systemic dimensions** of endometriosis. The inclusion of international and Latin American perspectives was essential to achieve representativeness and diversity in data interpretation.

Databases such as PubMed, Scopus, Web of Science, and ScienceDirect were systematically explored using Boolean search terms. A total of **423 records** were retrieved, from which **72 articles** were selected for full-text review. After applying eligibility criteria, **20 publications** of high methodological quality and relevance were included for the final synthesis.

This phase also involved **classification of evidence** according to study type (experimental, clinical, or review) and focus area (inflammation, oxidative stress, extracellular vesicles, systemic comorbidities). The organized database served as the empirical foundation for the next stages of analysis.

Phase III. Analytical Integration of Molecular and Clinical Evidence

The third phase constituted the core analytical stage of the review. Here, the team synthesized information across studies to explore how local inflammatory processes in endometriosis generate **systemic effects**.

Key molecular mediators such as IL-6, TNF-α, MCP-1, and VEGF were identified as consistent contributors to chronic inflammation and angiogenesis (Oală et al., 2024; Cano-Herrera et al., 2024). Simultaneously, studies on oxidative stress (Didžiokaitė et al., 2023; Scutiero et al., 2017) highlighted how peritoneal iron overload and ROS production promote fibrosis and endothelial dysfunction—mechanisms that extend to cardiovascular and metabolic alterations.

This phase also incorporated evidence on **extracellular vesicles and exosomal microRNAs** as mediators of intercellular communication, which propagate inflammatory signals beyond the pelvic environment (Chu et al., 2024; Santos et al., 2025). Integrating these molecular data with clinical findings allowed the formulation of a systemic model linking endometriosis with extra-pelvic comorbidities such as cardiovascular disease, autoimmune conditions, and metabolic syndrome.

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Phase IV. Regional and Comparative Analysis (Mexico, Colombia, Ecuador)

The fourth phase emphasized **interregional collaboration** to contextualize global findings within the Latin American healthcare landscape. Researchers from Mexico, Colombia, and Ecuador examined regional epidemiological trends, healthcare access, diagnostic barriers, and differences in clinical presentation.

This comparative approach sought to identify **sociocultural and environmental factors** that could modulate disease expression or delay diagnosis, such as limited awareness, disparities in medical resources, and underrepresentation of local populations in large-scale studies.
The integration of these insights allowed the team to propose a model adaptable to the realities of developing health systems, highlighting the importance of **regional research cooperation** for understanding and managing endometriosis from a systemic and equitable perspective.

Phase V. Thematic Synthesis and Conceptual Model Construction

In the fifth phase, results were organized into **five thematic categories** that structured the development of the article:

1. Chronic inflammation and immune dysregulation
2. Oxidative stress and fibrotic remodeling
3. Extracellular vesicles and molecular communication
4. Systemic manifestations and comorbidities
5. Diagnostic and therapeutic implications

Each category was synthesized to reveal cause-effect relationships and cross-mechanistic links. This process led to the **formulation of an integrative conceptual model** that illustrates endometriosis as a condition where immune, vascular, and metabolic processes converge in a systemic inflammatory continuum.

This phase also emphasized the **translational dimension** of research—how basic molecular findings can inform clinical interventions, biomarker development, and new diagnostic criteria.

Phase VI. Validation, Discussion, and Critical Reflection

The sixth phase consisted of **validation through multidisciplinary and international dialogue**. Experts in gynecology, immunology, and molecular medicine from the three participating countries reviewed the synthesized data, ensuring consistency and interpretative accuracy.

During this stage, the authors compared existing theoretical models with new evidence, identifying both convergences and gaps in knowledge. Emphasis was placed on unresolved questions regarding the bidirectional relationship between systemic inflammation and reproductive health, as well as the need for longitudinal studies to confirm molecular hypotheses in diverse populations.

The phase concluded with the consolidation of an interpretative framework capable of explaining endometriosis as a **systemic inflammatory disorder with clinical, molecular, and psychosocial implications**.

Phase VII. Final Integration and Formulation of Proposals

In the final phase, the findings were synthesized into a cohesive narrative that connects molecular biology, clinical practice, and public health. The review concludes with the identification of emerging biomarkers—such as exosomal microRNAs and cytokine panels—that could be implemented as diagnostic tools in early detection and personalized therapy.

Additionally, the study proposes **future research directions**, including:

- Large-scale, multicenter studies involving Latin American populations.

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- Integration of omics technologies (genomics, proteomics, metabolomics).
- Development of patient-centered diagnostic and therapeutic protocols.

This final synthesis not only consolidates the systemic vision of endometriosis but also reinforces the need for **international collaboration** and the inclusion of underrepresented regions in global research agendas.

RESULTADOS Y DISCUSIÓN

In this section, the most significant findings are presented and organized according to the analytical categories established in the methodological framework. The results integrate molecular, immunological, and clinical data reported in the reviewed literature, illustrating the systemic nature of endometriosis and its implications beyond the pelvic cavity. The information presented aims to provide a coherent and structured overview of the current scientific evidence that supports the conceptualization of endometriosis as a model of systemic inflammation.

The selected studies reveal consistent trends across multiple domains of investigation, including inflammatory biomarkers, oxidative stress parameters, extracellular vesicle profiles, and associated comorbidities. Rather than focusing on isolated molecular or clinical outcomes, the analysis emphasizes interconnections between these elements and their contribution to the chronicity and systemic dissemination of disease mechanisms.

Descriptive and comparative synthesis was used to summarize the findings, prioritizing studies that presented reproducible data, validated biomarkers, or translational relevance to clinical practice. Figures are employed to organize the information and visually represent the relationships between molecular markers, systemic pathways, and disease outcomes. Each figure provides a focused synthesis that contributes to understanding the systemic dimension of endometriosis.

A total of **five figures** were developed for this section:

- **Figure 1:** Cytokine expression patterns and inflammatory mediators associated with endometriosis.
- **Figure 2:** Oxidative stress pathways and molecular consequences in endometriotic tissue.
- **Figure 3:** Role of extracellular vesicles and exosomal microRNAs in systemic communication.
- **Figure 4:** Clinical comorbidities associated with endometriosis and systemic inflammation.
- **Figure 5:** Conceptual model integrating molecular, immune, and systemic mechanisms of the disease.

Each figure is described in detail below, providing a narrative synthesis of the findings reported in recent studies that collectively reinforce the systemic inflammatory paradigm of endometriosis.

Figure 1.

Cytokine expression patterns and inflammatory mediators associated with endometriosis

Cytokine / Mediator	Primary Source	Biological Function	Observed Alterations in Endometriosis
IL-1β (Interleukin-1 beta)	Activated macrophages and stromal cells	Pro-inflammatory mediator; stimulates prostaglandin synthesis	Increased concentration in peritoneal fluid and plasma; promotes lesion survival
IL-6 (Interleukin-6)	Endometrial epithelial and immune cells	Regulates acute-phase response and immune cell differentiation	Overexpressed in serum and lesion sites; correlates with pain severity
TNF-α (Tumor Necrosis Factor-alpha)	Macrophages, T lymphocytes, endometrial tissue	Promotes apoptosis, angiogenesis, and inflammation	Persistent elevation in serum and peritoneal fluid; promotes oxidative stress
IL-8 (Interleukin-8)	Endothelial and immune cells	Neutrophil chemotaxis and angiogenic factor	High peritoneal levels; linked to lesion vascularization
MCP-1 (Monocyte Chemoattractant Protein-1)	Macrophages and endometrial stromal cells	Recruitment of monocytes and macrophages	Elevated expression in peritoneal and serum samples
VEGF (Vascular Endothelial Growth Factor)	Endometrial epithelial cells and macrophages	Stimulates angiogenesis and vascular permeability	Overexpression in ectopic lesions and serum
IL-10 (Interleukin-10)	Regulatory T cells and macrophages	Anti-inflammatory and immunomodulatory cytokine	Decreased levels in advanced disease stages

Figure 1 illustrates the complex network of cytokine dysregulation that underpins the inflammatory pathophysiology of endometriosis, emphasizing its systemic character. Across multiple studies, the cytokine profile in affected

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individuals reveals a **persistent pro-inflammatory state** that not only maintains the ectopic lesions but also triggers systemic alterations involving endothelial, metabolic, and immune functions (Oală et al., 2024; Cano-Herrera et al., 2024).

The cytokine **IL-1β** serves as one of the earliest initiators of the inflammatory cascade in endometriosis. Derived primarily from activated macrophages within the peritoneal cavity, IL-1β stimulates the production of prostaglandins and cyclooxygenase-2 (COX-2), creating an environment conducive to pain, angiogenesis, and tissue adhesion (Oală et al., 2024). Cano-Herrera et al. (2024) confirmed that high IL-1β levels correlate with increased expression of adhesion molecules (ICAM-1 and VCAM-1), which facilitate the attachment of endometrial cells to peritoneal surfaces and the subsequent formation of lesions. The systemic implications of this cytokine include heightened inflammatory signaling through the NF-κB pathway, promoting a chronic activation of immune cells that extends beyond the pelvic environment.

Similarly, **IL-6** has been identified as one of the most consistently elevated cytokines in both the peritoneal fluid and systemic circulation of patients with endometriosis (Bao et al., 2022). This cytokine acts as a bridge between local and systemic inflammation, modulating the hepatic synthesis of acute-phase reactants such as C-reactive protein (CRP) and fibrinogen, both of which are elevated in women with advanced disease. Krygere et al. (2024) proposed IL-6 as a potential biomarker due to its dual role in lesion proliferation and systemic vascular inflammation. The sustained activation of IL-6/STAT3 signaling promotes endothelial dysfunction, oxidative stress, and vascular remodeling—mechanisms that directly link endometriosis to increased cardiovascular risk.

Tumor necrosis factor-alpha (TNF-α), another critical cytokine in this inflammatory axis, amplifies immune cell recruitment, promotes angiogenesis, and induces apoptosis-resistant phenotypes in ectopic endometrial cells. Oală et al. (2024) and Cano-Herrera et al. (2024) reported that TNF-α levels are markedly higher in both serum and peritoneal fluid, suggesting a **systemic spillover** of local inflammation. TNF-α stimulates the generation of reactive oxygen species (ROS), contributing to oxidative stress and the activation of fibroblasts, ultimately leading to fibrosis and adhesion formation (García et al., 2022). Moreover, chronic exposure to TNF-α has been associated with **endothelial dysfunction and microvascular injury**, which may partially explain the epidemiological association between endometriosis and cardiovascular disease (Marchandot et al., 2022).

Chemokines such as **IL-8** and **MCP-1** play essential roles in perpetuating immune cell infiltration. IL-8, produced by endothelial and epithelial cells, acts as both a chemotactic and angiogenic factor, facilitating the migration of neutrophils and promoting vascular proliferation within the lesions (Garmendia & Sánchez, 2025). Mariadas et al. (2025) demonstrated that IL-8 overexpression contributes to lesion vascularization and chronic pain by activating nociceptive nerve endings. MCP-1, on the other hand, sustains macrophage recruitment and activation, maintaining a persistent cycle of immune stimulation. Cano-Herrera et al. (2024) observed that MCP-1 levels remain elevated in both serum and peritoneal samples, supporting its role as a **driver of chronic inflammation and macrophage polarization** toward a pro-inflammatory M1 phenotype.

Vascular endothelial growth factor (VEGF) is another pivotal molecule that connects inflammation with systemic vascular pathology. According to Griffiths et al. (2024), VEGF overexpression in endometriotic lesions enhances vascular permeability and promotes the formation of fragile neovessels, which contribute to recurrent microbleeding and tissue hypoxia. Marchandot et al. (2022) expanded this concept, linking VEGF-mediated angiogenesis to endothelial dysfunction and systemic vascular remodeling, thus reinforcing the link between endometriosis and elevated cardiovascular risk. The sustained exposure to angiogenic and oxidative stimuli generated by VEGF leads to chronic vascular activation, representing one of the main systemic pathways of disease dissemination.

Conversely, **IL-10**, an anti-inflammatory cytokine secreted by regulatory T cells and macrophages, appears consistently **decreased in women with severe endometriosis** (Garmendia & Sánchez, 2025). Mariadas et al. (2025) demonstrated that low IL-10 concentrations impair immune tolerance and permit sustained activation of macrophages and Th17 lymphocytes. The imbalance between IL-10 and TNF-α or IL-6 highlights a **defective immunoregulation** that transforms endometriosis from a localized inflammatory condition into a chronic systemic disorder with autoimmune-like features.

Overall, the findings summarized in Figure 1 illustrate a **profound cytokine imbalance** in endometriosis, dominated by elevated pro-inflammatory mediators (IL-1β, IL-6, TNF-α, IL-8, MCP-1, VEGF) and insufficient anti-inflammatory

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control (IL-10). This dysregulated cytokine network perpetuates chronic inflammation, promotes oxidative stress, and disrupts immune homeostasis. Such processes extend their impact to systemic vascular and metabolic systems, explaining the increasing recognition of endometriosis as a **systemic inflammatory disease** rather than a purely gynecological condition (Bao et al., 2022; Petraglia et al., 2025; Mariadas et al., 2025).

Furthermore, the cytokine patterns observed support the concept of **bidirectional interaction** between the endometrium and systemic circulation: while local inflammation contributes to systemic immune activation, systemic factors (such as oxidative stress and hormonal imbalance) reinforce lesion survival. This interconnected feedback loop provides the biological basis for understanding the chronicity, recurrence, and comorbidity profile of endometriosis as described in recent translational research (Griffiths et al., 2024; Petraglia et al., 2025).

In summary, Figure 1 demonstrates that cytokine dysregulation is not an isolated phenomenon but a **central pathogenic mechanism** linking the local microenvironment of endometriosis with systemic inflammatory pathways. The persistent elevation of IL-6, TNF-α, and VEGF, together with reduced IL-10 activity, represents the immunological hallmark of a disease that transcends its reproductive origins to influence the entire organism—bridging molecular inflammation, vascular dysfunction, and immune disturbance into a unified systemic process (Oală et al., 2024; Cano-Herrera et al., 2024; Bao et al., 2022; Mariadas et al., 2025; Petraglia et al., 2025).

Figure 2.
Oxidative stress pathways and molecular consequences in endometriotic tissue

ROS/Redox Source	Upstream Triggers	Key Molecular Pathways	Primary Tissue-Level Consequences
Iron overload in peritoneal cavity	Retrograde menstruation; erythrocyte hemolysis	Fenton reaction → •OH; NF-κB activation; TGF-β/SMAD signaling	Lipid peroxidation; fibroblast activation; collagen I/III deposition; adhesion formation
Mitochondrial ROS (mtROS)	Hypoxia in ectopic implants; inflammatory cytokines (IL-1β, TNF-α)	HIF-1α stabilization; mtDNA damage; impaired OXPHOS	Neoangiogenesis; apoptosis resistance of stromal cells
NADPH oxidase (NOX) activity	Macrophage/M1 polarization; estrogen signaling	NOX-derived superoxide; MAPK/ERK and PI3K/AKT activation	Proliferation of eutopic/ectopic endometrium; inflammatory amplification
Unbalanced antioxidant defenses	Depletion of SOD, GPx, catalase; low GSH	Reduced detox of H2O2/•O2−; redox-sensitive transcription (AP-1, NF-κB)	Heightened oxidative injury; extracellular matrix (ECM) remodeling
Lipid peroxidation by-products	ROS attack on PUFAs (arachidonic acid)	4-HNE, MDA adducts; COX-2/PGE2 upregulation	Nociceptor sensitization; neuroangiogenesis
ROS–TGF-β–EMT axis	Persistent cytokine milieu (IL-6, TNF-α); hypoxia	TGF-β/SMAD; Snail/Slug; β-catenin; ROS feedback loop	**EMT** of epithelial cells; enhanced invasion/ motility
Redox-driven endothelial dysfunction	Circulating IL-6, TNF-α; VEGF excess; ox-LDL	eNOS uncoupling; reduced NO bioavailability; oxidative vasculopathy	Microvascular rarefaction; pro-thromboinflammatory state

Figure 2 synthesizes convergent evidence that **oxidative stress is a central, self-reinforcing driver** of endometriosis biology, connecting local lesion dynamics with **systemic inflammatory and vascular sequelae**. Early observations by Jackson et al. (2005) showed elevated lipid peroxidation products (e.g., malondialdehyde) and decreased antioxidant enzyme activity in affected patients, correlating with disease severity—findings later consolidated by the systematic review of Scutiero et al. (2017), which positioned redox imbalance as a hallmark across phenotypes.

A principal upstream source of ROS is **peritoneal iron overload** due to retrograde menstruation and erythrocyte breakdown. Labile iron catalyzes hydroxyl radical generation via the **Fenton reaction**, activating NF-κB and **TGF-β/SMAD** signaling. Downstream, fibroblasts acquire an activated, ECM-producing phenotype, driving **adhesion formation and collagen deposition** (García et al., 2022; Scutiero et al., 2017). This pro-fibrotic loop provides a mechanistic bridge between cyclical bleeding, oxidative damage, and the **adhesive/fibrotic substrate** typical of deep infiltrating disease (Jackson et al., 2005; García et al., 2022).

Within ectopic implants, **hypoxia** and inflammatory cytokines (IL-1β, TNF-α) stimulate **mitochondrial ROS (mtROS)**. These signals stabilize **HIF-1α**, impair oxidative phosphorylation, and promote neoangiogenesis and **apoptosis resistance** in stromal cells—features that favor **lesion persistence and recurrence** (Didžiokaitė et al., 2023; Oală et al., 2024; Cano-Herrera et al., 2024). In parallel, **NADPH oxidase (NOX)** isoforms in immune and endometrial

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cells generate superoxide that feeds **MAPK/ERK** and **PI3K/AKT** cascades, amplifying proliferation and inflammatory gene expression (Didžiokaitė et al., 2023; Oală et al., 2024).

Critically, the redox burden is exacerbated by **depleted antioxidant defenses**—lower activities of SOD, GPx, and catalase, and reduced glutathione pools—weakening peroxide detoxification and enhancing **redox-sensitive transcription** (NF-κB, AP-1). This imbalance creates a biochemical environment where inflammatory cues are **easier to initiate and harder to extinguish**, aligning with the flare-like clinical course described in observational cohorts (Jackson et al., 2005; Scutiero et al., 2017).

Downstream of ROS, **lipid peroxidation by-products** such as 4-HNE and MDA form protein adducts that sustain COX-2 expression and **PGE2** synthesis, sensitizing nociceptors and supporting **neuroangiogenesis**—a plausible substrate for **chronic pelvic pain and dysmenorrhea** (Jackson et al., 2005; Scutiero et al., 2017; Oală et al., 2024). In the stromal and epithelial compartments, a **ROS–TGF-β–EMT axis** emerges: oxidative cues and TGF-β signaling activate EMT transcription factors (Snail/Slug), weaken epithelial adhesion, and enhance cell motility and invasion, linking oxidative stress directly to **lesion aggressiveness and fibrosis** (García et al., 2022; Hosseinirad et al., 2025).

Importantly, these redox phenomena are **not confined to the pelvis**. Circulating IL-6 and TNF-α, together with VEGF-driven angiogenic stress, promote **endothelial dysfunction** by uncoupling eNOS and reducing nitric oxide bioavailability, fostering a **pro-thromboinflammatory vascular phenotype** (Marchandot et al., 2022). This mechanism coheres with epidemiologic signals of **heightened cardiovascular risk** reported by Okoli et al. (2023) and the meta-analysis by Parsa et al. (2025), situating oxidative stress at the crossroads of gynecologic pathology and systemic vasculopathy.

Collectively, the pathways in Figure 2 support a unifying model where **iron-driven ROS, mitochondrial dysfunction, NOX activation, and antioxidant depletion** converge to: (i) maintain inflammatory signaling (NF-κB/AP-1), (ii) **remodel tissue** via TGF-β-mediated fibrosis and EMT, (iii) **sensitize pain** circuits through peroxidation products and prostaglandins, and (iv) extend to **systemic endothelial injury**. This model complements cytokine data (Figure 1) and explains how a local disease state evolves into a **systemic inflammatory–oxidative syndrome** with clinically relevant extra-pelvic consequences (Didžiokaitė et al., 2023; Scutiero et al., 2017; Jackson et al., 2005; García et al., 2022; Marchandot et al., 2022; Okoli et al., 2023; Parsa et al., 2025; Oală et al., 2024; Cano-Herrera et al., 2024; Hosseinirad et al., 2025).

Figure 3.
Role of extracellular vesicles (EVs) and exosomal microRNAs in systemic communication

EV Source	Representative Cargo (miRNAs / proteins / lipids)	Primary Targets / Pathways	Functional Effects (Local → Systemic)
Ectopic endometrial stromal cells	miR-21, miR-22, miR-214, miR-451a; MMPs; TGF-β–related proteins	Macrophage polarization (TLR/NF-κB); fibroblast TGF-β/SMAD; endothelial VEGF axis	M2-skewing of macrophages; fibroblast activation and ECM deposition; angiogenesis
Eutopic endometrium (in affected patients)	miR-146a, miR-155; cytokine-rich cargo	Dendritic cell maturation; T-cell activation (Th17/Treg balance)	Heightened antigen presentation; loss of tolerance → systemic immune priming
Peritoneal macrophage–derived EVs	Pro-inflammatory lipids; TNF-α–inducible proteins; miR-223	Endometrial cells (NF-κB), nociceptors (PGE2), endothelium (eNOS)	Feed-forward inflammation; nociceptor sensitization; endothelial dysfunction
Platelet/endothelium-derived EVs	Tissue factor; adhesion molecules (ICAM-1/ VCAM-1); miR-126	Coagulation cascade; leukocyte adhesion; angiogenesis	Microthrombo-inflammation; vascular remodeling → CVD linkage
Neurovascular niche EVs (lesion microenvironment)	NGF-linked cargo; miR-132/212 axis	Neuroangiogenesis; pain circuitry plasticity	Sprouting of sensory fibers; chronic pelvic pain maintenance
Adipose/metabolic tissue EVs (comorbidity context)	miR-122, miR-34a; ceramides	Hepatic/vascular insulin signaling; endothelial NO bioavailability	Metaflammation; dyslipidemia; endothelial injury

Figure 3 integrates evidence that **extracellular vesicles (EVs)**—including exosomes and microvesicles—operate as mobile inflammatory "paracrine packages" that connect pelvic lesions with distant tissues, thereby **operationalizing the systemic phenotype** of endometriosis. Comprehensive reviews demonstrate that EVs shuttle **microRNAs, proteins, and lipids** capable of reprogramming immune cells, fibroblasts, endothelial cells, and nociceptive networks (Scheck et al., 2022; Chu et al., 2024).

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Lesion-derived EVs are particularly enriched in **pro-angiogenic and pro-fibrotic cargo** (e.g., miR-21/miR-214, MMPs, TGF-β–related proteins), which induces **M2 macrophage polarization**, enhances **fibroblast SMAD signaling**, and augments **VEGF-driven angiogenesis**. This triad supports lesion survival locally while exporting an inflammatory–angiogenic signature into circulation, aligning molecular communication with systemic endothelial activation (Chu et al., 2024; García et al., 2022). In parallel, **eutopic endometrium** from affected patients releases EVs carrying **immune-modulatory miRNAs** (e.g., miR-146a/miR-155) that tilt **Th17/Treg balance** and amplify antigen presentation, offering a mechanistic bridge between **local immune dysregulation** and **systemic immune priming** (Scheck et al., 2022; Garmendia & Sánchez, 2025).

Macrophage-derived EVs sustain a **feed-forward loop**: TNF-α–induced cargo activates **NF-κB** in endometrial cells, promotes **PGE2** synthesis (nociceptor sensitization), and perturbs endothelial **eNOS/NO** signaling—effects that dovetail with clinical reports of pain chronicity and vascular dysfunction (Scheck et al., 2022; Chu et al., 2024; Marchandot et al., 2022). Concomitantly, **platelet/endothelium-derived EVs** enriched with **tissue factor and adhesion molecules** escalate **microthrombo-inflammation** and leukocyte rolling, mechanistically reinforcing the **epidemiologic association with cardiovascular disease** observed in cohort studies and meta-analyses (Marchandot et al., 2022; Okoli et al., 2023; Parsa et al., 2025).

Within the **neurovascular niche** of lesions, EVs carrying **NGF-linked cargo and miR-132/212** stimulate **neuroangiogenesis** and synaptic plasticity, providing a plausible molecular substrate for **chronic pelvic pain** independent of lesion size—an observation repeatedly noted clinically (Scheck et al., 2022; Chu et al., 2024). Beyond the pelvis, EVs released by **metabolic tissues** (adipose, liver) contribute **metaflammatory signals** (e.g., miR-122, ceramides) that impair insulin pathways and NO bioavailability, integrating endometriosis with **metabolic and endothelial dysfunction** (Garmendia & Sánchez, 2025; Marchandot et al., 2022).

From a translational angle, **exosomal miRNA panels**—notably **miR-21, miR-22, miR-214, miR-451a**—consistently emerge as **non-invasive biomarkers** capable of differentiating eutopic from ectopic endometrium and grading fibrotic risk (Santos et al., 2025). Systematic surveys underscore that **circulating EV counts and cargo composition** can function as readouts of **systemic disease activity** and **CVD risk**, potentially complementing cytokine assays to build multi-analyte diagnostic signatures (Scheck et al., 2022; Marchandot et al., 2022; Okoli et al., 2023; Parsa et al., 2025).

In sum, the EV landscape in endometriosis provides a **mechanistic conveyor belt** that exports local inflammatory, fibrotic, and neurovascular programming to the systemic compartment. This model coheres with Figures 1–2: cytokine and redox imbalances are not confined to lesions but are **packaged into EVs** that disseminate pathologic instructions, thereby **linking pelvic disease to immune, metabolic, and vascular comorbidities** (Chu et al., 2024; Scheck et al., 2022; Santos et al., 2025; García et al., 2022; Marchandot et al., 2022; Okoli et al., 2023; Parsa et al., 2025; Garmendia & Sánchez, 2025).

Figure 4.
Clinical comorbidities associated with endometriosis and systemic inflammation

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Comorbidity / Systemic Association	Underlying Mechanisms	Principal Biomolecular Pathways Involved	Clinical Evidence / Manifestations
Cardiovascular disease (CVD)	Chronic low-grade inflammation; endothelial dysfunction; oxidative stress	IL-6 / TNF-α–mediated endothelial activation; VEGF overexpression; eNOS uncoupling	Elevated C-reactive protein (CRP); increased carotid intima-media thickness; higher risk of hypertension and coronary disease
Autoimmune diseases	Immune dysregulation; molecular mimicry; impaired Treg function	Overactivation of Th17 cells; autoantibody formation; IL-10 downregulation	Increased prevalence of systemic lupus erythematosus, autoimmune thyroiditis, and rheumatoid arthritis
Metabolic syndrome and insulin resistance	Chronic inflammation and oxidative stress; adipose tissue dysfunction	TNF-α–induced insulin receptor inhibition; ROS-mediated lipid peroxidation	Hyperinsulinemia, dyslipidemia, increased BMI, elevated fasting glucose
Psychological and neuroendocrine alterations	Neuroinflammation and hypothalamic-pituitary-adrenal (HPA) axis dysregulation	Elevated IL-6, IL-8, and cortisol; altered serotonin signaling	Anxiety, depression, chronic fatigue, sleep disturbances
Chronic pain syndromes	Neuroangiogenesis and peripheral sensitization mediated by ROS and cytokines	NGF / TRPV1 upregulation; PGE2 production; miR-132/212 signaling	Pelvic pain, dyspareunia, dysmenorrhea, pain centralization
Fibrosis and tissue remodeling disorders	Oxidative stress, TGF-β/SMAD activation, epithelial–mesenchymal transition (EMT)	ROS–TGF-β–SMAD axis; collagen I/III overproduction	Pelvic adhesions, organ distortion, infertility
Cancer predisposition (ovarian clear cell / endometrioid)	Chronic oxidative stress and DNA damage; hormonal and immune alterations	Mutations in ARID1A, PTEN, PIK3CA; persistent inflammation and angiogenesis	Increased risk in women with long-standing or deep infiltrating disease

Figure 4 summarizes the growing body of evidence demonstrating that **endometriosis is not confined to the reproductive system** but behaves as a **systemic inflammatory condition** with far-reaching consequences across multiple physiological systems. The persistence of cytokine-driven inflammation, oxidative stress, and immune imbalance contributes to the development of comorbidities that extend well beyond gynecologic symptoms, confirming the disease's **multisystemic profile** (Marchandot et al., 2022; Petraglia et al., 2025).

1. Cardiovascular implications

Among systemic associations, **cardiovascular disease (CVD)** has emerged as one of the most robustly supported. Large-scale meta-analyses (Okoli et al., 2023; Parsa et al., 2025) demonstrate that women with endometriosis exhibit significantly higher risks of hypertension, ischemic heart disease, and myocardial infarction, independent of age and hormonal exposure. Mechanistically, this association is mediated by **chronic endothelial activation** driven by IL-6 and TNF-α, increased VEGF expression, and **eNOS uncoupling** resulting from oxidative stress (Marchandot et al., 2022). The elevated CRP levels and altered vascular reactivity documented in affected individuals support the hypothesis that systemic inflammation and oxidative injury act synergistically to impair endothelial homeostasis. This aligns with the redox-endothelial model previously detailed in Figure 2, reinforcing the systemic cardiovascular impact of endometriosis.

2. Autoimmune comorbidities

A growing number of studies support a **bidirectional relationship between endometriosis and autoimmune disorders**, including systemic lupus erythematosus, autoimmune thyroiditis, and rheumatoid arthritis (Mariadas et al., 2025; Garmendia & Sánchez, 2025). This connection is attributed to a combination of **impaired immune tolerance** (decreased IL-10 and Treg function) and **molecular mimicry**, where autoantibodies generated against endometrial antigens cross-react with systemic targets. The overactivation of Th17 cells and the chronic production of IL-17 and IL-23 promote autoimmune reactivity, suggesting that endometriosis may share **immunopathogenic pathways** with classical autoimmune diseases. Petraglia et al. (2025) emphasize that this chronic immune stimulation contributes not only to local inflammation but also to systemic immune dysregulation and heightened susceptibility to autoimmune pathology.

3. Metabolic and endocrine dysfunction

Metabolic complications are increasingly recognized as part of the **systemic spectrum of endometriosis**. Chronic exposure to TNF-α and IL-6 leads to **insulin receptor inhibition**, altered lipid metabolism, and adipokine imbalance, fostering **insulin resistance and dyslipidemia** (Garmendia & Sánchez, 2025). Oxidative stress contributes to lipid peroxidation, which disrupts mitochondrial energy metabolism and promotes a pro-inflammatory state known as **metaflammation** (Marchandot et al., 2022). This metabolic-immune cross-talk may help explain the increased

prevalence of weight gain and metabolic syndrome among women with endometriosis, further connecting reproductive, metabolic, and cardiovascular health.

4. Neuroendocrine and psychological outcomes

Neuroinflammation and **hypothalamic–pituitary–adrenal (HPA) axis dysregulation** are also implicated in the systemic manifestations of endometriosis. Elevated IL-6 and IL-8 levels, alongside chronic pain–related stress, trigger **cortisol overproduction** and serotonin imbalance, which contribute to **anxiety, depression, and fatigue** (Zondervan et al., 2020; Mariadas et al., 2025). Neuroinflammatory mediators such as PGE2 and neurotrophins sensitize pain pathways, reinforcing the connection between immune activation and emotional dysregulation. The psychosomatic dimension of endometriosis thus reflects its systemic inflammatory load, underlining the need for integrative clinical management approaches.

5. Chronic pain syndromes

Pain represents one of the most debilitating aspects of endometriosis and is sustained by **neuroangiogenesis, oxidative stress, and cytokine-mediated sensitization**. IL-6, IL-8, TNF-α, and ROS increase nociceptor excitability through the upregulation of **NGF and TRPV1**, perpetuating hyperalgesia and pain centralization (Scheck et al., 2022; Chu et al., 2024). The miR-132/212 axis, carried via extracellular vesicles (as shown in Figure 3), further modulates synaptic plasticity and long-term potentiation in pain pathways. This neuroinflammatory amplification explains why pain intensity often fails to correlate with lesion size, supporting the concept of endometriosis as a **neuroimmune disorder** rather than merely a mechanical one.

6. Fibrotic and structural complications

The **fibrosis characteristic of advanced endometriosis** stems from persistent oxidative stress and **TGF-β–driven epithelial–mesenchymal transition (EMT)** (García et al., 2022; Hosseinirad et al., 2025). Didžiokaitė et al. (2023) demonstrated that reactive oxygen species (ROS) trigger fibroblast differentiation and excessive collagen synthesis through SMAD activation. These events result in **dense adhesions and tissue remodeling**, leading to infertility and chronic pelvic pain. The fibrotic process mirrors systemic fibro-inflammatory syndromes, again illustrating the convergence between local and systemic pathogenesis.

7. Oncogenic potential

Although endometriosis is a benign condition, chronic inflammation and oxidative DNA damage elevate the risk of **malignant transformation**, particularly to **ovarian clear cell and endometrioid carcinomas** (Bao et al., 2022; Petraglia et al., 2025). Mutations in **ARID1A, PTEN, and PIK3CA**, observed in long-standing lesions, are thought to arise in a microenvironment of persistent oxidative stress and angiogenesis. Bao et al. (2022) provided genomic evidence supporting this transition, emphasizing that endometriosis constitutes a **pro-carcinogenic field** in which chronic systemic inflammation and local redox imbalance intersect with genetic susceptibility.

Figure 5.
Integrative conceptual model of endometriosis as a systemic inflammatory disease

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Layer	Core Components	Mechanistic Links	Outputs / Readouts
A. Triggers & Susceptibility	Retrograde menstruation, iron load; estrogen dominance; genetic/epigenetic background (ARID1A/PTEN/PIK3CA pathways); environmental factors	Heme/iron → Fenton chemistry; estrogen–immune crosstalk; permissive chromatin states	Pro-oxidant peritoneal milieu; primed immune set-point
B. Local Microenvironment	Ectopic endometrial epithelial/stromal cells; macrophages, neutrophils, mast cells; hypoxia	Cytokine surge (IL-1β, IL-6, TNF-α, IL-8, MCP-1); HIF-1α stabilization	Persistent inflammation, lesion survival, neovascularization
C. Molecular Pathways	NF-κB, STAT3, MAPK/ERK, PI3K/AKT; TGF-β/SMAD; COX-2/PGE2	Oxidative stress ↔ cytokine amplification; EMT and fibrosis; nociceptor sensitization	Adhesions; apoptosis resistance; pain signaling
D. Angiogenesis & Vascular Tone	VEGF axis; endothelial activation; eNOS uncoupling	Hypoxia/ROS → VEGF; IL-6/TNF-α → endothelial dysfunction	Fragile neovessels; microbleeding; altered reactivity
E. Intercellular Communication (EVs)	Exosomes/microvesicles from lesions, immune cells, endothelium	EV cargo (miR-21/22/214/451a; MMPs; TF) reprograms macrophages, fibroblasts, endothelium, neurons	Systemic propagation of inflammatory, fibrotic, and neurovascular programs
F. Systemic Dissemination	Circulating cytokines, EVs, ox-lipids	Endothelial dysfunction; metaflammation; immune priming	↑ CRP; vascular stiffness; insulin resistance
G. Clinical Phenotypes	Pelvic pain, dysmenorrhea, dyspareunia; infertility; fatigue, anxiety/depression	Neuroangiogenesis; HPA axis stress; Th17/Treg imbalance	Pain centralization; mood symptoms; reduced QoL
H. Comorbidities	Cardiovascular, autoimmune, metabolic	Shared inflammatory/oxidative pathways; endothelial injury; autoimmunity	↑ Hypertension/CAD risk; thyroiditis/SLE; dyslipidemia/IR
I. Biomarkers	Cytokine panels (IL-6/TNF-α/IL-10); exosomal miRNAs; EV counts	Diagnostic/prognostic signatures; activity monitoring	Non-invasive blood/menstrual fluid tests

This model integrates the multiscale evidence from Figures 1–4 into a single cascade. **Layer A** sets the stage: retrograde menstruation and iron deposition generate a redox-active peritoneal niche, while genetic/epigenetic traits and estrogen signaling create permissive conditions for ectopic implantation (Jackson et al., 2005; Bao et al., 2022; Scutiero et al., 2017). Within **Layer B**, ectopic lesions co-opt innate immune cells; hypoxia stabilizes **HIF-1α**, and a cytokine ensemble (IL-1β, IL-6, TNF-α, IL-8, MCP-1) entrenches inflammation and lesion persistence (Oală et al., 2024; Cano-Herrera et al., 2024).

In **Layer C**, oxidative stress couples to **NF-κB/STAT3/MAPK/PI3K-AKT** and **TGF-β/SMAD** signaling, driving **EMT**, fibrosis, and COX-2/PGE2-mediated nociceptor sensitization—molecular engines for adhesions and chronic pain (Didžiokaitė et al., 2023; García et al., 2022; Hosseinirad et al., 2025). **Layer D** highlights **VEGF-dependent angiogenesis** and endothelial dysfunction (eNOS uncoupling), linking local hypoxia/ROS with fragile neovessels and microvascular instability (Griffiths et al., 2024; Marchandot et al., 2022).

Crucially, **Layer E** operationalizes systemic spread: extracellular vesicles export miRNAs (miR-21/22/214/451a) and proteolytic/TF cargo to reprogram macrophages (M2 skew), fibroblasts (SMAD activation), endothelium (adhesion, coagulability), and neural circuits (neuroangiogenesis) (Scheck et al., 2022; Chu et al., 2024; Santos et al., 2025). **Layer F** captures the spillover—circulating cytokines, EVs, and ox-lipids sustain **endothelial injury, metaflammation, and immune priming**, aligning with epidemiologic signals for cardiovascular and metabolic risk (Okoli et al., 2023; Parsa et al., 2025).

These mechanisms manifest clinically in **Layer G** as pain, infertility, and neuroendocrine symptoms (fatigue, mood disorders), shaped by neuroimmune plasticity and HPA axis dysregulation (Zondervan et al., 2020; Mariadas et al., 2025). Over time, **Layer H** emerges: comorbid **CVD**, **autoimmunity**, and **metabolic dysfunction**—a multisystemic footprint of the same cytokine–redox–EV triad (Okoli et al., 2023; Petraglia et al., 2025; Marchandot et al., 2022).

Translationally, **Layer I** points to **non-invasive biomarkers**: cytokine panels (IL-6/TNF-α/IL-10 balance), **exosomal miRNA signatures**, and EV counts from blood or menstrual fluid (Krygere et al., 2024; Santos et al., 2025; Scheck et al., 2022). **Layer J** identifies **therapeutic nodes**—anti-inflammatory/anti-oxidant combinations, anti-angiogenics, immune modulators, and emerging EV/miRNA-targeted approaches—complementing hormonal management within **precision, multidisciplinary care pathways** (Cano-Herrera et al., 2024; Griffiths et al., 2024; Petraglia et al., 2025).

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In essence, the model shows how local pelvic pathology is amplified and exported via cytokines, oxidative circuits, and EV trafficking into a **body-wide inflammatory network**—explaining the coherence between molecular readouts, systemic biomarkers, and real-world comorbidity patterns.

Discussion

The findings synthesized in this review reinforce the concept of **endometriosis as a systemic inflammatory disease**, characterized by a dynamic interaction between local pelvic pathology, immune dysregulation, oxidative stress, and molecular communication through extracellular vesicles (EVs). This systemic model transcends traditional gynecologic boundaries and integrates biochemical, vascular, and neuroendocrine mechanisms, providing a holistic framework that aligns with recent molecular and clinical research.

At the **molecular level**, persistent activation of pro-inflammatory cytokines—particularly IL-1β, IL-6, TNF-α, IL-8, and MCP-1—creates a self-sustaining inflammatory loop that supports lesion survival and immune cell recruitment (Oală et al., 2024; Cano-Herrera et al., 2024). This cytokine network triggers downstream signaling pathways, including **NF-κB**, **STAT3**, and **MAPK/ERK**, which modulate gene expression and promote angiogenesis, apoptosis resistance, and fibrosis (García et al., 2022; Hosseinirad et al., 2025). The imbalance between pro- and anti-inflammatory mediators—marked by elevated IL-6 and TNF-α and diminished IL-10—represents one of the defining immunological hallmarks of endometriosis, consistent with the findings of Garmendia and Sánchez (2025) and Mariadas et al. (2025).

Cytokine-driven inflammation is intricately linked to **oxidative stress**, which serves as both a consequence and amplifier of inflammation. Iron overload resulting from retrograde menstruation generates hydroxyl radicals through the **Fenton reaction**, thereby enhancing lipid peroxidation, DNA damage, and fibrotic remodeling (Jackson et al., 2005; Scutiero et al., 2017). Didžiokaitė et al. (2023) demonstrated that mitochondrial ROS and hypoxia stabilize **HIF-1α**, promoting neoangiogenesis and resistance to apoptosis—mechanisms that explain the chronicity and recurrence of lesions. This redox imbalance perpetuates a **feed-forward cycle**, whereby ROS amplify cytokine signaling and activate **TGF-β/SMAD** and **COX-2/PGE2** pathways, producing a biochemical landscape of chronic inflammation, nociceptor sensitization, and tissue fibrosis (Cano-Herrera et al., 2024; García et al., 2022; Hosseinirad et al., 2025).

Parallel to these processes, the discovery of **extracellular vesicles (EVs)** has unveiled a critical dimension in the systemic propagation of inflammatory and fibrotic signals. EVs derived from endometrial, immune, and endothelial cells carry bioactive cargo—microRNAs (miR-21, miR-22, miR-214, miR-451a), enzymes (MMPs), cytokines, and lipids—that regulate target cell function locally and systemically (Chu et al., 2024; Santos et al., 2025). Scheck et al. (2022) demonstrated that these vesicles modulate macrophage polarization and endothelial activation, establishing communication pathways that extend beyond the pelvic cavity. Similarly, Garmendia and Sánchez (2025) reported that exosomal miRNAs influence Th17/Treg balance and immune tolerance, further supporting the hypothesis of **systemic immune priming**.

This molecular communication explains the growing list of **systemic comorbidities** associated with endometriosis. Cardiovascular manifestations—including endothelial dysfunction, hypertension, and coronary artery disease—arise from chronic low-grade inflammation and oxidative vascular injury (Marchandot et al., 2022; Okoli et al., 2023; Parsa et al., 2025). Elevated IL-6 and TNF-α levels impair endothelial nitric oxide synthase (eNOS) function and reduce nitric oxide bioavailability, promoting microvascular remodeling and increased vascular stiffness. Parsa et al. (2025) confirmed these findings through meta-analysis, reporting a significant association between endometriosis and cardiovascular risk, while Marchandot et al. (2022) highlighted the central role of VEGF and oxidative stress in endothelial dysfunction.

Similarly, **autoimmune comorbidities**—including systemic lupus erythematosus and autoimmune thyroiditis—reflect overlapping immunopathogenic mechanisms. Decreased IL-10 and impaired Treg activity facilitate chronic activation of Th17 lymphocytes, producing sustained autoantibody generation and cross-reactivity with self-antigens (Mariadas et al., 2025; Garmendia & Sánchez, 2025). Petraglia et al. (2025) extended this interpretation, linking endometriosis-related immune dysregulation with broader systemic disorders, including metabolic and neuroendocrine dysfunctions. These observations position endometriosis within a **continuum of systemic inflammatory syndromes**, sharing immune and molecular substrates with classical autoimmune diseases.

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Metabolic dysregulation also emerges as a direct outcome of chronic inflammation. TNF-α and IL-6 inhibit insulin receptor signaling and promote adipose tissue inflammation, while oxidative stress disrupts mitochondrial energy metabolism and lipid homeostasis (Garmendia & Sánchez, 2025; Marchandot et al., 2022). This leads to insulin resistance, dyslipidemia, and a state of chronic "metaflammation," linking endometriosis to the metabolic syndrome. In this context, endometriosis functions as both a local inflammatory disorder and a systemic metabolic disruptor, as corroborated by Bao et al. (2022) and Cano-Herrera et al. (2024), who emphasized the integration of immunometabolic and hormonal signaling in disease perpetuation.

The **neuroendocrine and psychological dimensions** of endometriosis also align with systemic inflammatory patterns. Elevated cytokine levels and oxidative stress markers affect the hypothalamic-pituitary-adrenal (HPA) axis, leading to hypercortisolemia and serotonin dysregulation, mechanisms associated with fatigue, anxiety, and depression (Zondervan et al., 2020; Mariadas et al., 2025). Moreover, EV-mediated neuroangiogenic signaling, especially via miR-132/212 and NGF-related proteins, contributes to pain sensitization and chronic pelvic pain syndromes (Scheck et al., 2022; Chu et al., 2024). This neuroimmune interface underscores that the burden of endometriosis extends beyond physical lesions, encompassing **central sensitization and affective disturbances** that significantly impair quality of life.

At a **pathological continuum**, persistent oxidative stress and TGF-β/SMAD signaling induce epithelial-mesenchymal transition (EMT), fibroblast activation, and excessive collagen synthesis, leading to extensive **fibrosis and organ adhesion** (García et al., 2022; Hosseinirad et al., 2025). Didžiokaitė et al. (2023) and Scutiero et al. (2017) demonstrated that redox imbalance drives fibrotic remodeling similar to that observed in systemic sclerosis and chronic hepatic fibrosis, further highlighting endometriosis as a prototype of fibro-inflammatory disease. In long-standing cases, the same pro-oxidant and angiogenic environment fosters **DNA damage and oncogenic transformation**, with frequent mutations in ARID1A, PTEN, and PIK3CA, linking endometriosis to ovarian clear-cell and endometrioid carcinomas (Bao et al., 2022; Petraglia et al., 2025).

The conceptual model summarized in **Figure 5** encapsulates these interrelated mechanisms. It positions endometriosis as a **multilayered pathophysiological network**: an initiating phase driven by hormonal and genetic susceptibility; a local inflammatory microenvironment sustained by cytokines and ROS; a molecular signaling cascade that promotes angiogenesis, fibrosis, and pain; and a systemic dissemination phase mediated by cytokines and EVs. The outcome is a **multisystemic clinical expression**, encompassing cardiovascular, metabolic, autoimmune, and neuroendocrine domains (Okoli et al., 2023; Marchandot et al., 2022; Petraglia et al., 2025).

This integrative framework aligns with the observations of Griffiths et al. (2024) and Cano-Herrera et al. (2024), who emphasize that endometriosis research must evolve from a purely gynecological perspective toward a **systemic and multidisciplinary paradigm**. Recognizing endometriosis as a chronic systemic inflammatory disorder mandates collaboration among gynecologists, immunologists, cardiologists, and neurologists. Furthermore, molecular insights into cytokine and EV signatures (Santos et al., 2025; Krygere et al., 2024) offer promising **biomarker platforms** for early detection and patient stratification.

Translationally, these findings advocate for therapeutic strategies that extend beyond hormonal suppression. Anti-inflammatory agents targeting IL-6 or TNF-α pathways, antioxidants modulating redox imbalance, anti-angiogenic compounds acting on VEGF signaling, and novel **EV- or microRNA-based interventions** represent innovative therapeutic frontiers (Cano-Herrera et al., 2024; Griffiths et al., 2024; Petraglia et al., 2025). Such integrative approaches align with current trends in precision medicine and may significantly improve long-term outcomes by addressing the systemic components of the disease.

Finally, the inclusion of **Latin American research perspectives**—from Mexico, Colombia, and Ecuador—broadens the understanding of epidemiological variability and contextual determinants. Limited access to specialized diagnostic resources and sociocultural normalization of menstrual pain often delay recognition of the disease. Collaborative regional studies are essential to develop **context-adapted clinical protocols** and to ensure that Latin American populations contribute to the global genomic and translational research agenda on endometriosis.

In conclusion, the discussion highlights that endometriosis represents a **paradigmatic model of chronic systemic inflammation**. Its study provides valuable insights into the intersection of immunology, oxidative biology, vascular pathology, and neuroendocrine regulation. Integrating molecular biomarkers, systemic comorbidity management, and

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regionally inclusive research is crucial to redefine both diagnostic and therapeutic standards. By acknowledging its systemic nature, endometriosis ceases to be viewed merely as a pelvic disorder and emerges as a **complex, multisystemic inflammatory condition**, demanding a unified and globally coordinated scientific response (Zondervan et al., 2020; Bao et al., 2022; Cano-Herrera et al., 2024; Griffiths et al., 2024; Petraglia et al., 2025; Oală et al., 2024; Didžiokaitė et al., 2023; Scheck et al., 2022; Chu et al., 2024; Garmendia & Sánchez, 2025; García et al., 2022; Hosseinirad et al., 2025; Marchandot et al., 2022; Okoli et al., 2023; Parsa et al., 2025; Scutiero et al., 2017; Jackson et al., 2005; Mariadas et al., 2025; Krygere et al., 2024; Santos et al., 2025).

CONCLUSIÓN

The present review establishes a comprehensive conceptualization of **endometriosis as a systemic inflammatory disease**, integrating molecular, immunological, and clinical evidence that positions this condition beyond its traditional definition as a localized gynecologic disorder. The convergence of cytokine dysregulation, oxidative stress, extracellular vesicle signaling, and immune–endocrine imbalance demonstrates that endometriosis represents a **multisystemic inflammatory and fibro-proliferative syndrome**, with both local and systemic consequences that affect the vascular, metabolic, and neuroimmune networks of the body.

At the core of its pathophysiology lies a **persistent inflammatory loop** sustained by cytokines such as IL-1β, IL-6, TNF-α, IL-8, MCP-1, and VEGF, which drive angiogenesis, immune activation, and lesion survival (Oală et al., 2024; Cano-Herrera et al., 2024; Griffiths et al., 2024). This inflammatory state is compounded by **oxidative stress**, triggered by peritoneal iron overload and mitochondrial dysfunction, generating ROS that damage lipids, proteins, and DNA, while activating profibrotic signaling through **TGF-β/SMAD** and **NF-κB** pathways (Jackson et al., 2005; Scutiero et al., 2017; Didžiokaitė et al., 2023; García et al., 2022; Hosseinirad et al., 2025). In parallel, **extracellular vesicles (EVs)** serve as molecular vectors that transport miRNAs, cytokines, and enzymes across distant tissues, establishing a systemic communication network that perpetuates inflammation, immune dysregulation, and endothelial dysfunction (Scheck et al., 2022; Chu et al., 2024; Santos et al., 2025).

Clinically, this molecular interplay translates into an expanded spectrum of **systemic comorbidities**: cardiovascular disease through endothelial injury and oxidative vasculopathy (Marchandot et al., 2022; Okoli et al., 2023; Parsa et al., 2025); autoimmune disorders via impaired immune tolerance and chronic Th17 activation (Mariadas et al., 2025; Garmendia & Sánchez, 2025; Petraglia et al., 2025); metabolic syndrome resulting from TNF-α–driven insulin resistance and adipose inflammation (Garmendia & Sánchez, 2025; Marchandot et al., 2022); and neuroendocrine disturbances through HPA axis dysregulation, cytokine neurotoxicity, and chronic pain sensitization (Zondervan et al., 2020; Mariadas et al., 2025; Chu et al., 2024). These systemic manifestations highlight that endometriosis not only impairs reproductive health but also compromises cardiovascular, immune, and mental well-being—thereby constituting a **public health issue of global scope**.

Moreover, the cumulative evidence indicates that **oxidative and inflammatory pathways intersect with genetic and epigenetic susceptibility**, explaining the heterogeneity in clinical expression and treatment response. Mutations in **ARID1A, PTEN, and PIK3CA**, coupled with estrogen-driven transcriptional activation, generate a permissive background for lesion persistence and, in rare cases, malignant transformation to ovarian clear-cell or endometrioid carcinoma (Bao et al., 2022; Petraglia et al., 2025). These insights reveal that chronic inflammation and redox imbalance not only sustain lesion growth but also induce genomic instability, emphasizing the importance of long-term surveillance in patients with severe or recurrent disease.

From a translational standpoint, recognizing endometriosis as a systemic inflammatory disorder opens new therapeutic and diagnostic possibilities. Emerging **biomarker panels**—comprising cytokine ratios (IL-6/TNF-α/IL-10) and exosomal microRNAs (miR-21, miR-22, miR-214, miR-451a)—offer promise for **non-invasive diagnosis and disease monitoring** (Krygere et al., 2024; Santos et al., 2025; Scheck et al., 2022). Likewise, molecular therapies targeting specific pathways—such as IL-6 or TNF-α inhibitors, antioxidants, anti-angiogenic agents, and EV-modulating drugs—represent the next generation of **precision interventions**, capable of complementing or replacing traditional hormonal suppression strategies (Cano-Herrera et al., 2024; Griffiths et al., 2024; Petraglia et al., 2025).

The integration of research efforts from **Mexico, Colombia, and Ecuador** within this review underscores the need to expand global understanding of endometriosis beyond industrialized settings. Regional variability in healthcare access,

diagnostic timing, and sociocultural perception of menstrual pain remains a determinant of underdiagnosis and inequity. Strengthening Latin American participation in clinical and translational studies is essential to build inclusive data frameworks that account for genetic diversity, environmental exposure, and resource limitations, ensuring that **precision medicine in endometriosis is globally representative**.

Ultimately, this study highlights that endometriosis embodies a **biological intersection of inflammation, immunity, oxidative stress, and systemic health**. Its management requires not only pharmacologic innovation but also a multidisciplinary clinical approach integrating gynecology, cardiology, endocrinology, immunology, and mental health. Future research should prioritize:

1. **Longitudinal multicenter studies** exploring systemic biomarkers and comorbidities in diverse populations.
2. **Omics-based investigations** (genomics, proteomics, metabolomics) to delineate patient subtypes and therapeutic targets.
3. **EV- and miRNA-centered diagnostics**, standardizing molecular assays for early detection.
4. **Interdisciplinary treatment protocols**, addressing both reproductive and systemic consequences.

In summary, the accumulated evidence consolidates endometriosis as a **systemic inflammatory and oxidative disorder**, in which molecular signals originating from ectopic lesions influence distant tissues through complex immune and metabolic pathways. By redefining this disease as a systemic condition, the medical and scientific community can transcend conventional paradigms, moving toward early diagnosis, personalized therapy, and comprehensive care that recognizes the full scope of its biological and societal impact (Zondervan et al., 2020; Bao et al., 2022; Cano-Herrera et al., 2024; Griffiths et al., 2024; Petraglia et al., 2025; Oală et al., 2024; Didžiokaitė et al., 2023; Scheck et al., 2022; Chu et al., 2024; Garmendia & Sánchez, 2025; García et al., 2022; Hosseinirad et al., 2025; Marchandot et al., 2022; Okoli et al., 2023; Parsa et al., 2025; Scutiero et al., 2017; Jackson et al., 2005; Mariadas et al., 2025; Krygere et al., 2024; Santos et al., 2025).

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