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PATHOGENESIS OF ENDOMETRIOSIS: AN UMBRELLA REVIEW OF RECENT SYSTEMATIC REVIEWS AND META-ANALYSES

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ABSTRACT

Endometriosis is a chronic, estrogen-dependent inflammatory disease affecting approximately 10% of women of reproductive age and remains a major cause of pelvic pain and infertility. Despite its high prevalence and substantial clinical burden, the biological mechanisms underlying endometriosis are still incompletely understood. Although numerous systematic reviews and meta-analyses have addressed individual pathogenic domains, their findings are often fragmented, methodologically heterogeneous, and partially overlapping. This umbrella review aimed to provide a comprehensive synthesis of recent evidence on the pathogenesis of endometriosis while critically appraising methodological quality and overlap of primary studies.

An umbrella review was conducted in accordance with the PRISMA 2020 guidelines. PubMed was searched for systematic reviews and meta-analyses published between January 2019 and January 2026. Methodological quality was assessed using the AMSTAR 2 tool, and overlap of primary studies was evaluated using the corrected covered area (CCA). Evidence was synthesized narratively using a predefined domain-based framework.

Eighteen systematic reviews and meta-analyses were included, covering seven major pathogenic domains, including genetic and epigenetic susceptibility, immunological dysregulation, oxidative stress, tissue remodeling, microbiota dysbiosis, and systems-level molecular networks. Most reviews demonstrated moderate methodological quality, with limited overlap across most domains, except for microbiota-related evidence (CCA = 20%). Overall, the findings support a multifactorial, network-based model of endometriosis pathogenesis involving interactions between genetic susceptibility, immune dysfunction, hormonal signaling, and environmental modifiers. This umbrella review highlights key pathogenic domains, identifies areas of evidentiary fragility, and underscores the need for integrative, systems-level research to inform future mechanistic studies and targeted clinical interventions.

KEYWORDS

Endometriosis, Adenomyosis, Dysbiosis, Autoimmunity, Inflammatory

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1. Introduction

1.1 Clinical and Biological Relevance

Endometriosis is a chronic, estrogen-dependent inflammatory disease characterized by the presence of endometrial-like tissue outside the uterine cavity. It affects approximately 10% of women of reproductive age and represents a leading cause of chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility [1,2]. Beyond its gynecological manifestations, endometriosis is increasingly recognized as a systemic disorder with broad implications for immune function, metabolic regulation, and overall quality of life. Despite its high prevalence and substantial disease burden, the biological mechanisms underlying endometriosis remain incompletely understood. The implantation theory proposed by Sampson, which attributes lesion formation to retrograde menstruation and ectopic implantation of viable endometrial cells, has historically dominated explanations of disease pathogenesis [3]. However, retrograde menstruation occurs in the majority of menstruating women, whereas only a subset develop endometriosis, indicating that additional biological susceptibility factors are required [4]. Alternative and complementary hypotheses—including coelomic metaplasia, embryonic cell rests, immune dysfunction, stem cell involvement, and genetic and epigenetic predisposition—have been proposed to explain this discrepancy [5]. Accumulating evidence suggests that endometriosis arises from the convergence of multiple interacting pathogenic mechanisms rather than a single causal pathway. Advances in molecular biology, immunology, and systems medicine have substantially expanded understanding of the biological complexity of endometriosis. Genetic association studies have identified susceptibility loci related to hormone signaling, inflammation, and tissue remodeling [6]. Epigenetic investigations have demonstrated widespread alterations in DNA methylation and chromatin regulation affecting genes essential for endometrial receptivity and immune tolerance [7]. In parallel, immunological studies have revealed profound local immune dysregulation, characterized by impaired cytotoxic responses, altered immune checkpoint signaling, and chronic inflammation within the peritoneal environment [8]. Additional lines of evidence implicate oxidative stress, iron overload, fibrosis, aberrant angiogenesis, microbiota dysbiosis, environmental endocrine-disrupting chemicals, and dysregulated molecular networks as central contributors to lesion persistence and disease progression [9,10,11].

1.2 Rationale for Umbrella Review

The rapid expansion of research into endometriosis pathogenesis has been accompanied by a growing number of systematic reviews and meta-analyses, each focusing on specific biological or environmental domains. While these reviews provide valuable insights within their respective scopes, their findings are frequently fragmented across disciplines and occasionally overlapping. Methodological heterogeneity, differences in inclusion criteria, and variable quality further complicate integration of evidence across reviews.

The coexistence of multiple systematic reviews addressing related pathogenic mechanisms raises the risk of redundant interpretation of primary studies and inconsistent weighting of evidence. Moreover, individual reviews rarely assess the extent of overlap between primary studies or formally evaluate how such overlap may influence the apparent strength of evidence within a given domain. As a result, clinicians and researchers may face difficulties in forming a coherent, high-level understanding of endometriosis pathogenesis.

Umbrella reviews offer a structured methodological framework to address these challenges by synthesizing evidence from multiple systematic reviews and meta-analyses. This approach enables simultaneous evaluation of the breadth of evidence, methodological quality, consistency of findings, and overlap of primary studies. By integrating evidence across domains, umbrella reviews facilitate identification of robust pathogenic mechanisms, areas of uncertainty, and critical gaps in current knowledge.

1.3 Objective

The objective of this umbrella review was to provide a comprehensive and methodologically rigorous synthesis of recent systematic reviews and meta-analyses addressing the pathogenesis of endometriosis. Specifically, we aimed to:

1. Map the major biological and environmental domains implicated in the development and progression of endometriosis.
2. Assess the methodological quality of existing systematic reviews using the AMSTAR 2 tool.
3. Evaluate overlap of primary studies across reviews to minimize redundancy and overinterpretation of evidence.
4. Integrate findings into a coherent, domain-based pathogenic framework to inform future research directions and translational strategies.

2. Methods

2.1 Protocol and Reporting

This umbrella review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12]. The methodological approach followed established recommendations for umbrella reviews synthesizing evidence from systematic reviews and meta-analyses. A review protocol was developed a priori to define objectives, eligibility criteria, search strategy, and analytical framework; however, the protocol was not registered in a public database. The absence of protocol registration is acknowledged as a limitation and is discussed accordingly.

2.2 Eligibility Criteria

Systematic reviews and meta-analyses were considered eligible if they met the following criteria:

- Study design: Systematic reviews with or without meta-analysis.
- Population: Human studies investigating endometriosis; experimental animal and in vitro studies were included only when synthesized within eligible systematic reviews.
- Focus: Reviews primarily addressing mechanisms involved in the pathogenesis of endometriosis, including genetic, epigenetic, immunological, hormonal, fibrotic, angiogenic, environmental, and molecular network–related pathways.
- Publication characteristics: Articles published in English within the predefined time frame and available as full-text publications.

Exclusion criteria were:

- Narrative reviews, scoping reviews, editorials, commentaries, and conference abstracts.
- Reviews primarily focused on clinical outcomes (e.g., infertility, IVF outcomes, pain, surgical results), diagnostics, therapeutic interventions, or malignant transformation, without a primary emphasis on disease pathogenesis.
- Reviews addressing multiple gynecological or systemic diseases without providing endometriosis-specific mechanistic synthesis.

2.3 Information Sources and Search Strategy

A comprehensive literature search was conducted in PubMed to identify relevant systematic reviews and meta-analyses. The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords related to endometriosis, pathogenesis, and systematic review methodology.

The initial search was performed without filters. Subsequently, predefined filters were applied, including publication date, language (English), and article type (systematic reviews and meta-analyses). The complete search strategy is provided in the Supplementary Material (Supplement 1).

2.4 Study Selection

All records identified through database searching were imported into a reference management system. After removal of duplicate records, titles and abstracts were screened to exclude studies that did not address endometriosis pathogenesis or did not meet criteria for systematic reviews or meta-analyses.

Full-text articles were retrieved for records deemed potentially eligible. Full-text screening was performed to confirm eligibility based on predefined inclusion and exclusion criteria. Reviews were excluded at this stage if they were not primarily focused on endometriosis pathogenesis, addressed mixed populations without endometriosis-specific synthesis, or fell outside the conceptual scope of this umbrella review. Reasons for full-text exclusion are summarized in the PRISMA flow diagram and detailed in a supplementary table (Supplement 2).

2.5 Data Extraction

Data were extracted independently from each included systematic review using a standardized data extraction form. Extracted information included:

- bibliographic details (authors, year of publication),
- objectives and scope of the review,
- number and type of primary studies included,
- main methodological characteristics,
- key findings relevant to endometriosis pathogenesis,
- reported limitations.

When applicable, information on meta-analytic methods, effect measures, and heterogeneity was also recorded. Discrepancies in data extraction were resolved through discussion.

2.6 Methodological Quality Assessment

The methodological quality of included systematic reviews was assessed using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2) instrument [13]. This tool evaluates critical and non-critical domains related to review design, conduct, and reporting, and classifies overall confidence in the results of each review as high, moderate, low, or critically low.

AMSTAR 2 assessments were used to inform interpretation of findings across domains rather than to exclude reviews from the synthesis. Detailed results of the quality assessment are provided in the Supplementary Material (Supplement 3).

2.7 Assessment of Overlap of Primary Studies

Overlap of primary studies across included systematic reviews was assessed to minimize redundancy and potential overestimation of evidence. Where multiple systematic reviews addressed similar research questions and included comparable types of primary studies, quantitative overlap was evaluated using the corrected covered area (CCA) method [14].

CCA values were interpreted according to established thresholds, with higher values indicating greater overlap. In domains characterized by heterogeneous evidence types or fundamentally different study designs (e.g., experimental versus epidemiological studies), overlap was assessed narratively, CCA was calculated only when ≥2 reviews addressed the same biological question and synthesized comparable primary study designs.. Results of overlap assessment are reported by domain, and detailed calculations are provided in the Supplementary Material (Supplement 4).

2.8 Data Synthesis

A narrative synthesis approach was employed due to heterogeneity in study designs, outcomes, and analytical methods across included systematic reviews. Evidence was synthesized by predefined pathogenic domains, allowing integration of findings across molecular, cellular, tissue-level, and environmental mechanisms.

No additional meta-analyses were performed at the umbrella review level. Emphasis was placed on identifying convergent and divergent patterns of evidence, methodological strengths and limitations, and areas requiring further investigation.

3. Results

3.1 Study Selection

The study selection process is summarized in the PRISMA 2020 flow diagram (Figure 1). The initial database search identified 801 records. After applying predefined filters (publication date, language, and article type), 455 records remained. Following removal of 2 duplicate records, 453 records were screened based on titles and abstracts.

During title and abstract screening, 420 records were excluded because they did not primarily address endometriosis pathogenesis or did not meet criteria for systematic reviews or meta-analyses. Consequently, 33 full-text articles were retrieved and assessed for eligibility.

Full-text assessment led to the exclusion of 15 reviews that, despite being related to endometriosis, did not align with the predefined objectives of this umbrella review (e.g., focus on infertility outcomes, diagnostic or therapeutic applications, or insufficient endometriosis-specific mechanistic synthesis). The reasons for full-text exclusion are detailed in the PRISMA flow diagram and Supplement 2.

Ultimately, 18 systematic reviews and meta-analyses were included in the final synthesis.

3.2 Characteristics of Included Reviews

The main characteristics of the included systematic reviews are summarized in Table 1. The reviews were published between 1 January 2019 and 6 January 2026, collectively covered a broad range of pathogenic domains relevant to endometriosis.

Included reviews addressed genetic and epigenetic susceptibility, implantation-related mechanisms, immune dysregulation, oxidative stress and ferroptosis, tissue remodeling and fibrosis, angiogenesis, microbiota dysbiosis, environmental exposures, and systems-level molecular networks. The number of primary studies included per review varied substantially, reflecting differences in domain maturity and scope.

Most reviews synthesized observational human studies, while several also incorporated experimental animal and in vitro evidence. Meta-analyses were conducted in selected domains, including implantation-related mechanisms, environmental exposures, and microbiota-related studies, whereas other reviews employed narrative or qualitative synthesis due to methodological heterogeneity.

Table 1. Characteristics of included systematic reviews

First author (Ref)	Year	Domain	Type	Primary studies (n)	Study designs included	Population / model
Systematic review on the DNA methylation role in endometriosis [15]	2022	Genetics / Epigenetics	Systematic review	29	Human observational, experimental	Women with endometriosis (eutopic and ectopic tissue)
Expression of HOXA10 Gene in Women with Endometriosis [16]	2021	Genetics / Epigenetics	Systematic review	14	Human observational	Women with surgically confirmed endometriosis
An integrated multi-tissue approach for endometriosis candidate biomarkers [17]	2023	Genetics / Epigenetics / Multi-tissue	Systematic review	45	Human observational	Endometrium, ectopic lesions, blood, peritoneal fluid
Systematic review of genome-wide association studies on susceptibility to endometriosis [18]	2020	Genetics	Systematic review	17	GWAS	Women of reproductive age
Functional determinants of uterine contractility in endometriosis and adenomyosis [19]	2022	Implantation / Uterine dynamics	Systematic review and meta-analysis	9	Human observational	Women with endometriosis and adenomyosis
Müllerian anomalies and endometriosis: pathogenic theories [20]	2021	Implantation / Developmental	Systematic review and meta-analysis	16	Human observational	Women with Müllerian anomalies
The association between endometriosis and autoimmune diseases [21]	2019	Immunology	Systematic review	27	Human observational	Population-based cohorts and case–control studies
CTLA4-Linked Autoimmunity in the Pathogenesis of Endometriosis [22]	2022	Immunology	Systematic review	5 (human) + 1 experimental	Human observational, animal, in vitro	Women with endometriosis; experimental models
The role of CD8+ T cells in endometriosis [23]	2023	Immunology	Systematic review	18	Human observational, experimental	Peripheral blood, peritoneal fluid, lesions

Oxidative stress and ferroptosis in endometriosis [24]	2024	Oxidative stress / Ferroptosis	Systematic review	38	Human, animal, in vitro	Endometriosis tissues and experimental models
The role of fibrosis in endometriosis [25]	2023	Fibrosis / Tissue remodeling	Systematic review	42	Human, animal, in vitro	All endometriosis phenotypes
The role of TGF-β superfamily in endometriosis [26]	2024	Fibrosis / Signaling	Systematic review	51	Human, animal, in vitro	Endometriotic lesions and stromal cells
Vascularisation in Deep Endometriosis [27]	2022	Angiogenesis	Systematic review (narrative)	21	Human observational	Deep infiltrating endometriosis
Gut and Vaginal Microbiota in Endometriosis [28]	2023	Microbiota	Systematic review and meta-analysis	18	Human observational	Gut, vaginal, cervical, peritoneal samples
Correlation between dysbiosis of vaginal microecology and endometriosis [29]	2022	Microbiota	Systematic review	8	Human observational	Vaginal microbiota
Associations between Exposure to Organochlorine Chemicals and Endometriosis [30]	2020	Environmental exposure	Systematic review	30+	Animal, in vitro, human	Experimental and epidemiological models
Unravelling the link between phthalate exposure and endometriosis [31]	2021	Environmental exposure	Systematic review and meta-analysis	16	Human observational	Blood and urine biomonitoring
Proteomics approach to discovering non-invasive diagnostic biomarkers [32]	2024	Omics / Systems biology	Systematic review and meta-analysis	26	Human observational	Serum, plasma, urine, menstrual blood

3.3 Methodological quality (AMSTAR 2)

The methodological quality of the included systematic reviews was assessed using the AMSTAR 2 tool. Overall confidence in the results varied across reviews and domains.

Based on AMSTAR 2 classification, 17% of reviews were rated as high confidence, 72% as moderate confidence, 0% as low confidence, and 11% as critically low confidence (Figure 1). Reviews addressing genetic, epigenetic, and immunological mechanisms generally demonstrated higher methodological quality, whereas reviews in emerging domains, such as microbiota dysbiosis and environmental exposures, more frequently exhibited methodological limitations.

Common methodological weaknesses included lack of protocol registration, incomplete assessment of publication bias, and limited consideration of confounding at the primary study level. AMSTAR 2 ratings were used to contextualize, but not exclude, evidence in subsequent analyses. No review was excluded on the basis of AMSTAR 2 rating alone.

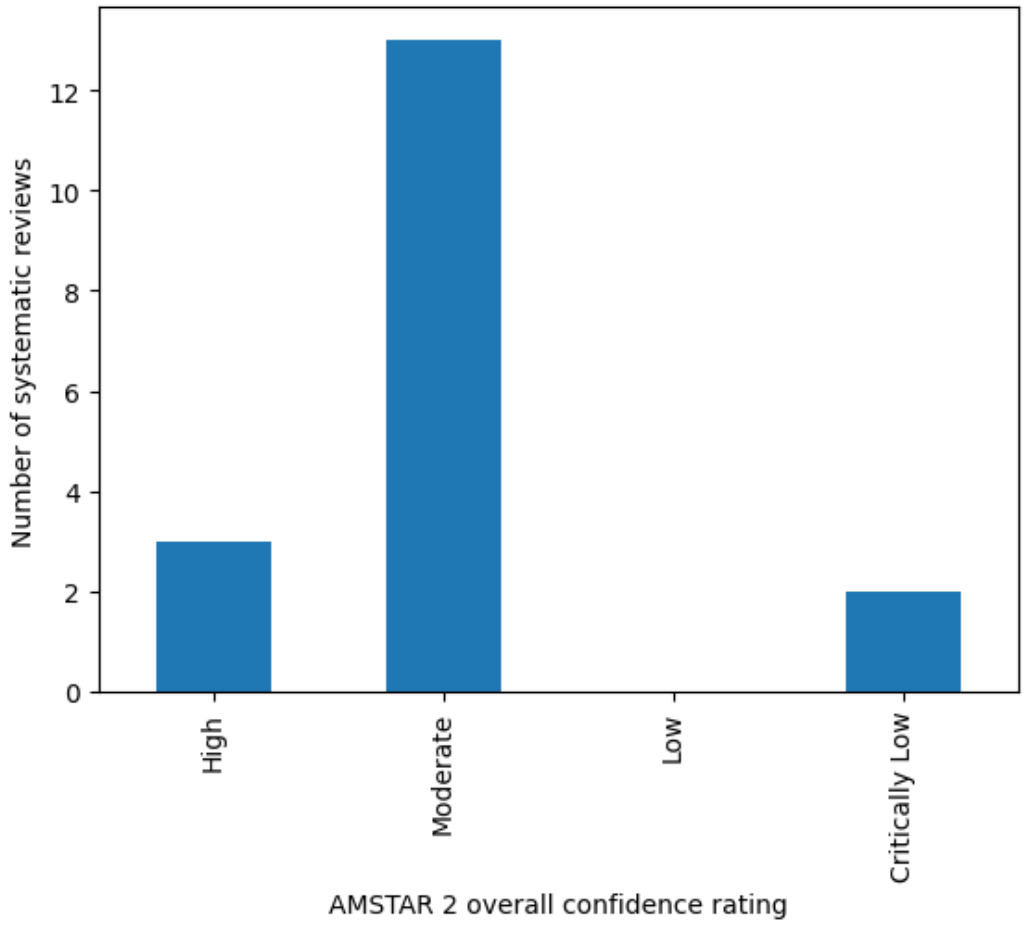

Fig. 1. *Methodological quality of included studies*

3.4 Overlap of Primary Studies Across Reviews

Overlap of primary studies across included systematic reviews was assessed to evaluate the independence of the evidence base. Quantitative overlap assessment using the corrected covered area (CCA) was performed where reviews addressed similar research questions and synthesized comparable types of primary studies.

Overlap was minimal or absent in most pathogenic domains, including genetic and epigenetic susceptibility, immunological mechanisms, oxidative stress and ferroptosis, and tissue remodeling. In these domains, included reviews drew on largely independent sets of primary studies, supporting the robustness of the synthesized findings.

In contrast, substantial overlap was observed in microbiota-related reviews. Quantitative assessment revealed a high CCA value (20%), reflecting shared observational cohorts and the limited number of available primary microbiome studies in endometriosis. This overlap indicates partial redundancy of evidence and necessitates cautious interpretation of conclusions in this domain.

For domains characterized by fundamentally different evidence types, such as experimental toxicological studies versus human observational studies in environmental exposure research, quantitative overlap assessment was not applicable. In these cases, overlap was assessed narratively.

Overall, overlap assessment informed domain-specific interpretation of evidence strength and highlighted areas where future independent studies are most urgently needed.

3.5. Synthesis of Evidence by Domain

3.5.1 Genetic and Epigenetic Susceptibility in Endometriosis

Genetic and epigenetic susceptibility constitutes a fundamental domain in the pathogenesis of endometriosis, reflecting both inherited risk and environmentally modulated molecular alterations. Evidence synthesized in recent systematic reviews indicates that endometriosis arises from the interplay between genomic variants, epigenetic modifications, and downstream transcriptional dysregulation affecting endometrial function and immune tolerance. A systematic review focusing on DNA methylation patterns in endometriosis demonstrated widespread epigenetic remodeling in both eutopic and ectopic endometrial tissues [15]. Aberrant methylation was consistently reported in genes involved in steroid hormone signaling, immune regulation, inflammation, cell adhesion, and tissue remodeling. Importantly, these epigenetic alterations were observed across different lesion types and disease stages, supporting the concept that epigenetic dysregulation may precede and facilitate lesion establishment rather than representing a mere consequence of ectopic implantation. Complementary evidence was provided by a systematic review addressing HOXA10 gene expression in women with endometriosis [16]. This review identified consistent downregulation of HOXA10 in the eutopic endometrium, frequently associated with promoter hypermethylation. Given the central role of HOXA10 in endometrial receptivity, decidualization, and implantation, these findings establish a mechanistic link between epigenetic gene silencing and endometriosis-associated infertility.

An integrated multi-tissue systematic review further expanded this framework by examining candidate biomarkers across eutopic endometrium, ectopic lesions, peritoneal fluid, and peripheral blood [17]. This review emphasized that genetic and epigenetic alterations manifest systemically rather than being confined to ectopic lesions alone. The identification of overlapping molecular signatures across tissues supports the concept of endometriosis as a systemic disorder characterized by shared pathogenic pathways, including dysregulated immune signaling, angiogenesis, and extracellular matrix remodeling.

Additional support for inherited susceptibility was provided by a systematic review of genome-wide association studies investigating genetic risk loci for endometriosis [18]. This review identified multiple susceptibility loci associated with genes involved in hormone signaling, inflammation, cell adhesion, and developmental pathways. Importantly, GWAS findings were largely independent of epigenetic and transcriptomic studies, reflecting distinct methodological approaches and minimal overlap of primary studies.

Collectively, evidence from genetic, epigenetic, and multi-omic systematic reviews supports a model in which inherited susceptibility loci interact with epigenetic modifications to shape aberrant gene expression profiles in endometrial and immune cells. These molecular alterations compromise endometrial receptivity, promote immune tolerance toward ectopic tissue, and facilitate lesion persistence. Due to methodological heterogeneity and the distinct molecular layers examined, the risk of overlap between primary studies within this domain was considered minimal and was therefore assessed narratively rather than through quantitative overlap analysis.

3.5.2 Implantation-Related Mechanisms and Uterine Dynamics

Abnormalities of uterine anatomy and function have long been implicated in the pathogenesis of endometriosis, particularly in relation to implantation-related mechanisms and retrograde menstruation. In this domain, two systematic reviews were included, addressing complementary aspects of uterine physiology and development: altered uterine contractility [19] and congenital Müllerian anomalies as natural models to test pathogenic theories of endometriosis [20].

A systematic review and meta-analysis evaluating functional determinants of uterine contractility demonstrated a markedly increased risk of retrograde uterine contraction patterns during menstruation in women with endometriosis compared with controls, with low heterogeneity and moderate certainty of evidence for this outcome [19]. Additional findings included increased frequency and amplitude of uterine contractions, particularly during the menstrual and luteal phases, supporting the hypothesis that dysperistalsis and hyperperistalsis facilitate transtubal reflux of endometrial tissue.

Complementary evidence was provided by a systematic review and meta-analysis examining the prevalence of endometriosis in women with obstructive and non-obstructive Müllerian anomalies [20]. A substantially higher prevalence of endometriosis was observed in women with obstructive anomalies, whereas no significant difference was found in women with non-obstructive anomalies compared with controls. These findings support retrograde menstruation as an initiating factor in endometriosis pathogenesis, while not excluding the contribution of genetic and tissue-specific susceptibility.

Given the distinct mechanistic levels, study designs, and outcomes addressed by these reviews, overlap of primary studies was considered minimal. Consequently, overlap was assessed narratively, and quantitative overlap analysis using the corrected covered area (CCA) was not performed for this domain.

3.5.3 Immunological Dysregulation in Endometriosis

Immune dysregulation represents a central mechanism in the pathogenesis of endometriosis, contributing to impaired clearance of ectopic endometrial tissue, chronic inflammation, and lesion persistence. A systematic review examining associations between endometriosis and autoimmune diseases demonstrated increased prevalence of several autoimmune conditions among affected women, supporting shared immunopathogenic mechanisms [21].

More direct mechanistic insight was provided by a systematic review focusing on CTLA4-linked immune dysregulation [22], which identified altered immune checkpoint signaling associated with increased regulatory T cell activity and suppression of cytotoxic immune responses. These findings suggest that immune checkpoint imbalance contributes to immune tolerance toward ectopic endometrial tissue.

Further refinement of this model was provided by a systematic review addressing the role of CD8+ T cells in endometriosis [23]. This review demonstrated enrichment of phenotypically altered CD8+ T cells within ectopic lesions, characterized by features of tissue residency, functional exhaustion, and reduced cytotoxicity, indicating localized immune suppression rather than systemic immune deficiency.

Overlap assessment indicated no shared primary studies between the immune-related systematic reviews (CCA = 0). The CTLA4-focused review synthesized mechanistic and immunophenotyping studies, whereas the autoimmune diseases review relied exclusively on epidemiological data, confirming independence of the evidence base and complementarity of immune-related findings.

3.5.4 Oxidative Stress, Iron Overload, and Ferroptosis

A systematic review addressing iron overload–induced oxidative stress and ferroptosis highlighted iron accumulation as a consistent feature of the endometriotic microenvironment [24]. Excess iron promotes reactive oxygen species generation and lipid peroxidation, facilitating inflammation, angiogenesis, and lesion progression.

Despite iron overload, ectopic endometrial tissue exhibits resistance to ferroptotic cell death through dysregulation of glutathione metabolism, overexpression of GPX4, and activation of ferroptosis-suppressing pathways. Conversely, excessive ferroptosis in ovarian and embryonic cells contributes to infertility, underscoring the dual and context-dependent role of ferroptosis in endometriosis.

As only one systematic review addressed this domain, overlap was assessed narratively, and quantitative overlap analysis was not performed.

3.5.5 Tissue Remodeling, Fibrosis, and Vascularisation

Progressive tissue remodeling represents a defining pathological feature of endometriosis and underlies lesion persistence, invasiveness, pain generation, and resistance to hormonal therapy. Fibrosis, aberrant extracellular matrix (ECM) deposition, and pathological vascularisation are increasingly recognized as tightly interconnected processes that collectively shape the endometriotic microenvironment. In this domain, three complementary systematic reviews were included, addressing fibrosis as a core pathological hallmark [25], upstream profibrotic signaling mediated by the TGF-β superfamily [26], and angiogenesis and vascularisation with a specific focus on deep endometriosis [27].

A comprehensive systematic review synthesizing experimental, clinical, and animal studies identified fibrosis as a ubiquitous feature of endometriotic lesions across anatomical locations and disease phenotypes [25]. Fibrotic remodeling was particularly pronounced in deep infiltrating endometriosis, where excessive ECM accumulation, increased tissue stiffness, and contractile activity contribute to lesion fixation and distortion of surrounding organs. Myofibroblasts emerged as the principal effector cells driving fibrosis, characterized by α-smooth muscle actin expression and enhanced production of collagen I and III.

Multiple cellular sources of myofibroblasts were identified, including fibroblast-to-myofibroblast transdifferentiation, epithelial-to-mesenchymal transition, endothelial-to-mesenchymal transition, and mesothelial–mesenchymal transition. Importantly, fibrotic progression was associated with reduced progesterone responsiveness, altered prostaglandin signaling, increased nerve fiber density, and enhanced mechanotransduction, providing mechanistic links between fibrosis, chronic pelvic pain, and treatment resistance [25].

Mechanistic insight into fibrotic remodeling was further provided by a systematic review focusing on the role of the TGF-β superfamily in endometriosis pathogenesis [26]. This review demonstrated that TGF-β signaling acts as a central upstream regulator of fibrosis by promoting myofibroblast differentiation, ECM

synthesis, and tissue contractility. Dysregulation of canonical Smad2/3 signaling and non-canonical pathways, including PI3K–AKT, MAPK, and NF-κB, was consistently reported. Beyond fibrosis, TGF-β signaling was shown to orchestrate immune modulation, angiogenesis, neuroinflammation, and epithelial–mesenchymal plasticity, reinforcing the concept of endometriosis as a disease of aberrant tissue repair rather than passive ectopic implantation.

Angiogenesis and vascularisation were specifically addressed in a systematic review focusing on deep endometriosis [27]. Deep lesions consistently exhibited increased microvessel density and elevated expression of angiogenic markers such as vascular endothelial growth factor (VEGF), VEGF receptors, and hypoxia-inducible factor-1α (HIF-1α), compared with eutopic endometrium and superficial lesions. Angiogenesis was closely linked to hypoxia, fibrotic remodeling, and hormonal modulation, with evidence suggesting partial responsiveness to progestin treatment despite advanced fibrosis. These findings support a model in which pathological vascularisation cooperates with fibrosis to sustain lesion growth, facilitate tissue infiltration, and maintain chronic inflammation.

Although fibrosis and angiogenesis are biologically interconnected, the included systematic reviews addressed distinct mechanistic layers and disease phenotypes. The fibrosis-focused review synthesized broad lesion-level remodeling mechanisms [25], the TGF-β review examined upstream molecular signaling pathways [26], and the vascularisation review concentrated on angiogenic features specific to deep endometriosis [27]. Consequently, the risk of overlap between primary studies was considered low and was assessed narratively rather than through quantitative calculation of the corrected covered area (CCA).

3.5.6 Microbiota Dysbiosis and Environmental Exposures

Growing evidence indicates that alterations in host–environment interactions contribute significantly to the pathogenesis of endometriosis. In particular, dysbiosis of the reproductive and gastrointestinal microbiota and exposure to environmental endocrine-disrupting chemicals (EDCs) have emerged as important modifiers of immune function, estrogen signaling, and inflammatory responses. In this domain, two distinct but interacting pathogenic axes were identified: microbiota-related mechanisms and environmentally mediated endocrine disruption.

Systematic reviews addressing gut and vaginal microbiota demonstrated that women with endometriosis exhibit qualitative alterations in microbial composition rather than consistent changes in alpha diversity [28]. Reported features of dysbiosis included reduced dominance of Lactobacillus species in the vaginal niche and enrichment of anaerobic and pro-inflammatory taxa across reproductive and intestinal compartments. Proposed mechanisms linking dysbiosis to endometriosis pathogenesis included impaired epithelial barrier integrity, altered estrogen metabolism via the estrobolome, endotoxin-driven immune activation, and amplification of chronic pelvic inflammation.

Complementary evidence was provided by a systematic review focusing on vaginal microecology [29], which identified increased prevalence of bacterial vaginosis–associated microbial communities and reduced Lactobacillus dominance in women with endometriosis. Such alterations may facilitate ascending inflammatory signaling and disrupt local immune homeostasis, thereby contributing to lesion persistence and symptom severity.

Quantitative overlap assessment using the corrected covered area (CCA) revealed a very high overlap between microbiota-related systematic reviews (CCA = 20%), reflecting shared observational cohorts and the limited number of available microbiome studies in endometriosis. This substantial overlap underscores the need for cautious interpretation of pooled conclusions and highlights the necessity for larger, independent cohorts and standardized sampling methodologies.

Environmental exposure to endocrine-disrupting chemicals represents a parallel and interacting pathogenic axis. A systematic review integrating experimental evidence demonstrated that organochlorine compounds, including dioxins and polychlorinated biphenyls, promote lesion establishment and growth through aryl hydrocarbon receptor activation, immune modulation, progesterone resistance, angiogenesis, and enhanced invasive capacity of endometrial cells [30]. These findings provide strong biological plausibility linking persistent organic pollutants to endometriosis pathogenesis.

Evidence from human observational studies was synthesized in a systematic review and meta-analysis focusing on phthalate exposure [31]. This review reported associations between selected phthalate metabolites and the presence or severity of endometriosis, although heterogeneity in exposure assessment and study design was substantial. Proposed mechanisms included endocrine disruption, oxidative stress, impaired steroidogenesis, and dysregulated inflammatory signaling.

Due to fundamental differences in the underlying evidence base—experimental in vivo and in vitro studies versus human observational data—quantitative overlap assessment between environmental exposure reviews was not applicable. Instead, overlap was assessed narratively, and the reviews were considered complementary in linking mechanistic toxicology with population-level associations.

3.5.7 Omics and Systems-Level Molecular Networks

Omics-based approaches have enabled a systems-level perspective on endometriosis pathogenesis, moving beyond reductionist models focused on individual genes or pathways. Among these approaches, proteomics provides a functional snapshot of disease-related molecular alterations and bridges genetic, epigenetic, and environmental influences. A recent systematic review and meta-analysis synthesized proteomic evidence to identify non-invasive biomarkers and molecular networks involved in endometriosis pathogenesis [32].

Across 26 observational studies, proteomic analyses of serum, plasma, urine, menstrual blood, and cervical mucus identified extensive dysregulation of protein expression in women with endometriosis. Functional enrichment analyses revealed coordinated perturbations in pathways related to inflammation, immune regulation, angiogenesis, extracellular matrix remodeling, cell adhesion, and metabolic regulation. These findings align with pathogenic mechanisms described in other domains of this umbrella review, reinforcing the systemic nature of endometriosis.

Protein–protein interaction network analyses identified multiple hub proteins with central regulatory roles, including ALB, FN1, CD44, S100A8/S100A9, CXCL1, and IL1RN [32]. The recurrent identification of these hubs across different biological matrices suggests convergence of diverse pathogenic stimuli onto shared molecular networks rather than isolated lesion-specific processes.

Importantly, the review emphasized the limited diagnostic utility of single-protein biomarkers and highlighted the superiority of integrative, network-based approaches. The authors advocated for multi-marker panels and integrative multi-omics strategies combining proteomics with transcriptomics, epigenetics, and metabolomics to improve disease stratification and mechanistic insight. Such systems-level approaches may facilitate the development of non-invasive diagnostics and support precision medicine strategies in endometriosis.

These domains do not act sequentially but form a dynamic, self-reinforcing pathogenic network.

4. Discussion

4.1 Principal Findings

This umbrella review synthesizes evidence from recent systematic reviews and meta-analyses to provide an integrated overview of the multifactorial pathogenesis of endometriosis. Several key findings emerge from this domain-based synthesis.

First, endometriosis appears to be driven by a convergence of inherited susceptibility and acquired molecular dysregulation, rather than by a single etiological mechanism. Genetic predisposition identified through genome-wide association studies provides a permissive background upon which epigenetic modifications, including aberrant DNA methylation and altered gene expression, shape disease-specific transcriptional profiles. These alterations affect endometrial receptivity, immune tolerance, and cellular plasticity, supporting a model in which early molecular programming contributes to disease onset and persistence.

Second, the evidence supports a central role of localized immune dysfunction, characterized by immune tolerance toward ectopic endometrial tissue rather than systemic immune deficiency. Dysregulation of immune checkpoint pathways, altered regulatory T-cell activity, and functional impairment of CD8+ T cells collectively contribute to immune escape within the peritoneal and lesion microenvironment. Epidemiological associations with autoimmune diseases further suggest shared immunopathogenic pathways, although causality remains unresolved.

Third, progressive tissue remodeling—encompassing fibrosis, extracellular matrix accumulation, and pathological vascularisation—emerges as a core driver of lesion persistence and invasiveness, particularly in deep endometriosis. Profibrotic signaling mediated by the TGF-β superfamily and sustained angiogenesis cooperate to create a mechanically stiff, hypoxic, and inflammation-prone microenvironment that promotes pain, organ dysfunction, and resistance to hormonal therapy.

Fourth, environmental modifiers, including microbiota dysbiosis and exposure to endocrine-disrupting chemicals, appear to interact with host susceptibility factors to amplify inflammatory and hormonal dysregulation. While microbiota-related evidence is currently limited by substantial overlap and small cohorts,

experimental and epidemiological data on endocrine-disrupting chemicals provide biologically plausible mechanisms linking environmental exposure to endometriosis risk and severity.

Finally, systems-level omics analyses highlight endometriosis as a network-driven disease, involving coordinated dysregulation across inflammatory, immune, angiogenic, and extracellular matrix–related pathways. Proteomics-based network analyses demonstrate that disease biology cannot be adequately captured by single biomarkers, underscoring the need for integrative multi-omics approaches to improve mechanistic understanding, phenotypic stratification, and the development of non-invasive diagnostics.

4.2 Integration of Pathogenic Mechanisms

The findings of this umbrella review support a unifying model in which endometriosis arises from the interaction of genetic susceptibility, immune dysregulation, aberrant tissue remodeling, and environmental modifiers, rather than from a single causative pathway. These mechanisms operate across different biological scales and reinforce one another within a permissive peritoneal and tissue microenvironment.

Genetic and epigenetic susceptibility represents an upstream layer of disease risk that shapes endometrial and immune cell behavior before lesion establishment. Genome-wide association studies identify loci involved in hormone signaling, inflammation, and cell adhesion, while epigenetic alterations modulate transcriptional programs governing endometrial receptivity, immune tolerance, and cellular plasticity. These early molecular perturbations may determine why only a subset of women exposed to retrograde menstruation develop endometriosis, providing a biological explanation for interindividual variability in disease susceptibility.

Implantation-related mechanisms, including altered uterine contractility and obstructive Müllerian anomalies, likely act as facilitators of ectopic tissue dissemination rather than sole etiological drivers. Increased retrograde flow enhances exposure of the peritoneal cavity to endometrial fragments; however, lesion establishment depends on the ability of these cells to evade immune clearance, adapt to ectopic environments, and engage tissue remodeling pathways. Thus, mechanical dissemination and molecular susceptibility appear to be necessary but individually insufficient components of disease pathogenesis.

Immune dysregulation constitutes a central integrative axis linking early susceptibility with lesion persistence. Evidence synthesized in this review supports a model of localized immune tolerance characterized by immune checkpoint imbalance, increased regulatory T-cell activity, and functional impairment of CD8+ T cells within lesions and the peritoneal environment. This immune landscape enables ectopic endometrial cells to escape cytotoxic surveillance, sustain chronic inflammation, and interact with stromal and vascular compartments. Epidemiological associations with autoimmune diseases further suggest shared immune pathways, although the directionality of these relationships remains unclear.

Progressive tissue remodeling emerges as a downstream but self-reinforcing process that consolidates disease chronicity. Profibrotic signaling, driven in part by the TGF-β superfamily, promotes myofibroblast differentiation, extracellular matrix accumulation, and increased tissue stiffness. In parallel, pathological angiogenesis ensures oxygen and nutrient supply to metabolically active lesions, particularly in deep infiltrating endometriosis. These processes generate a mechanically rigid, hypoxic, and inflammation-prone microenvironment that exacerbates pain, facilitates nerve ingrowth, and contributes to resistance to hormonal therapies.

Environmental modifiers further amplify these pathogenic interactions. Microbiota dysbiosis may influence immune activation, estrogen metabolism, and barrier function, thereby modulating systemic and local inflammatory responses. Exposure to endocrine-disrupting chemicals provides an additional layer of risk by perturbing hormonal signaling, promoting oxidative stress, and altering immune and stromal cell function. Although the strength of evidence varies across environmental domains, the convergence of experimental and epidemiological findings supports a role for environmental exposures as disease modifiers rather than primary initiators.

Finally, systems-level omics analyses integrate these diverse mechanisms into coordinated molecular networks. Proteomic and network-based studies demonstrate that inflammatory, immune, angiogenic, and extracellular matrix–related pathways are not independently dysregulated but form interconnected regulatory circuits. This network-driven perspective aligns with the clinical heterogeneity of endometriosis and underscores the limitations of reductionist models focused on single pathways or biomarkers.

Taken together, the integrated evidence supports a multi-layered pathogenic framework in which genetic and epigenetic susceptibility, mechanical dissemination, immune tolerance, tissue remodeling, and environmental exposures interact dynamically over time. This model emphasizes endometriosis as a systemic,

network-driven disease and provides a conceptual foundation for future research aimed at stratified diagnostics and targeted therapeutic interventions.

4.3 Methodological Considerations Quality of the included systematic reviews

Methodological quality assessment using the AMSTAR 2 tool revealed substantial variability across included systematic reviews. Reviews addressing genetic, epigenetic, and immunological mechanisms generally demonstrated moderate to high methodological confidence, reflecting comprehensive search strategies, transparent study selection, and appropriate risk-of-bias assessments. In contrast, reviews focusing on emerging domains such as microbiota and environmental exposures more frequently exhibited methodological limitations, including incomplete assessment of publication bias, lack of protocol registration, and limited consideration of study-level confounding.

In molecular and mechanistic domains, many systematic reviews synthesized heterogeneous experimental and clinical evidence without formal quantitative pooling, which limited the strength of causal inferences. Additionally, variability in risk-of-bias assessment tools and incomplete reporting of study-level quality further constrained interpretability. Collectively, these factors underscore the need for higher-quality primary studies and more rigorous systematic reviews with standardized methodological frameworks.

Overlap of primary studies across reviews

Overlap of primary studies represents a critical methodological concern in umbrella reviews, as it may lead to double counting of evidence and overestimation of effect consistency. In this review, overlap was systematically evaluated using the corrected covered area (CCA) where methodologically appropriate, and assessed narratively when quantitative analysis was not applicable.

Quantitative overlap assessment revealed substantial overlap in microbiota-related reviews, reflecting the limited number of available cohorts and repeated use of the same primary studies. In contrast, immune-related and mechanistic domains demonstrated minimal or no overlap, supporting the independence of the synthesized evidence. For environmental exposure domains, quantitative overlap assessment was not feasible due to fundamental differences in underlying evidence types, including experimental versus epidemiological studies.

This domain-specific approach to overlap assessment enhances transparency and methodological rigor, while acknowledging the uneven maturity of evidence bases across pathogenic domains.

Heterogeneity of evidence

Heterogeneity was a pervasive feature across included systematic reviews and arose from multiple sources, including differences in study populations, diagnostic criteria, disease phenotypes, biological sample types, analytical platforms, and outcome definitions. Such heterogeneity was particularly pronounced in molecular, microbiota, and environmental exposure studies, where methodological diversity limited the feasibility of meta-analysis and contributed to inconsistent findings.

Clinical heterogeneity further complicated interpretation, as many studies did not stratify results by endometriosis stage, lesion type, symptom profile, or treatment status. Temporal heterogeneity, related to menstrual cycle phase and hormonal fluctuations, was also infrequently addressed despite its biological relevance. Although meta-analytic approaches were applied in selected domains, substantial between-study heterogeneity often persisted, underscoring the need for cautious interpretation of pooled estimates.

Overall, the heterogeneity observed across domains reflects both the biological complexity of endometriosis and methodological limitations of existing research. Addressing these challenges will require standardized diagnostic criteria, harmonized outcome measures, and coordinated multi-center studies capable of integrating clinical, molecular, and environmental data.

4.4 Implications for Research

The synthesis of evidence across pathogenic domains highlights substantial gaps that should guide future research priorities in endometriosis. Although the volume of published studies has increased markedly in recent years, important limitations in study design, mechanistic depth, and causal inference persist across multiple domains.

Domains requiring mechanistic and experimental studies

Several domains are characterized by strong associative evidence but limited mechanistic validation. Microbiota-related research exemplifies this gap. Despite consistent reports of dysbiosis across reproductive and gastrointestinal compartments, the causal role of microbial alterations in endometriosis remains uncertain. Future studies should prioritize mechanistic investigations integrating host–microbiome interactions, immune

modulation, and estrogen metabolism, using longitudinal designs, gnotobiotic animal models, and interventional approaches targeting microbial composition or function.

Similarly, environmental exposure research—particularly studies addressing endocrine-disrupting chemicals—would benefit from mechanistic clarification. While experimental models provide biological plausibility, human studies remain predominantly observational and vulnerable to exposure misclassification and residual confounding. Integrative studies combining toxicokinetics, molecular readouts, and tissue-specific effects are needed to bridge experimental findings with clinical relevance.

Immune-related mechanisms also warrant deeper mechanistic exploration. Although immune checkpoint dysregulation and altered CD8+ T-cell function are consistently reported, the temporal sequence of immune alterations relative to lesion establishment remains unclear. Studies employing single-cell multi-omics, spatial transcriptomics, and functional immune assays may help delineate whether immune dysfunction is a primary driver or a secondary adaptation to ectopic lesions.

Domains where randomized controlled trials are needed

Randomized controlled trials (RCTs) are notably scarce in domains with clear translational potential. Therapeutic strategies targeting oxidative stress, ferroptosis, fibrosis, and angiogenesis have demonstrated promising effects in preclinical models and small clinical studies, yet robust RCTs evaluating efficacy, safety, and fertility outcomes are largely lacking. Well-designed trials with stratification by disease phenotype and lesion type are essential to determine whether modulation of these pathways can meaningfully alter disease progression or symptom burden.

Interventional studies assessing microbiota modulation, including probiotics, dietary interventions, or microbiota-targeted therapies, represent another area where RCTs are urgently needed. Existing evidence is insufficient to support clinical recommendations, and controlled trials with standardized endpoints are required to move beyond associative findings.

Domains with apparently strong but methodologically fragile evidence

Certain domains present evidence that appears robust due to consistency across multiple studies but remains methodologically fragile upon closer inspection. Genetic association studies, including GWAS, have identified reproducible susceptibility loci; however, the functional relevance of many variants remains unclear, and effect sizes are generally modest. Integrative functional genomics studies are needed to translate statistical associations into biological mechanisms.

Similarly, fibrosis and tissue remodeling represent areas where mechanistic evidence is strong, yet clinical translation remains limited. Much of the supporting evidence is derived from animal models or in vitro systems that may not fully recapitulate human disease heterogeneity. The apparent strength of these findings may therefore overestimate their immediate therapeutic applicability.

Finally, proteomics and other omics-based studies generate compelling systems-level insights but often rely on cross-sectional designs and heterogeneous analytical platforms. The reproducibility and clinical utility of identified molecular signatures remain uncertain without prospective validation and standardized methodologies.

Toward integrative and stratified research frameworks

Collectively, these findings underscore the need for integrative research strategies that move beyond isolated pathogenic domains. Future studies should prioritize longitudinal designs, standardized phenotyping, and multi-layered data integration to capture the dynamic and heterogeneous nature of endometriosis. Emphasis on causal inference, mechanistic validation, and rigorously designed interventional studies will be essential to translate emerging insights into clinically meaningful advances.

4.5 Strengths and Limitations Strengths

The primary strength of this umbrella review lies in its high-level synthesis of evidence derived exclusively from recent systematic reviews and meta-analyses, allowing integration of findings across multiple biological and clinical domains of endometriosis pathogenesis. By organizing evidence into predefined pathogenic domains, this review provides a structured and mechanistically informed framework that facilitates interpretation of a complex and heterogeneous literature.

A further strength is the rigorous methodological appraisal of included systematic reviews using the AMSTAR 2 tool. This quality assessment enabled transparent evaluation of confidence in the synthesized evidence and informed domain-specific interpretation of findings. Incorporation of methodological quality considerations into the discussion strengthens the validity of conclusions and reduces the risk of overinterpretation of low-quality evidence.

Additionally, this review systematically assessed overlap of primary studies across included systematic reviews. Use of the corrected covered area (CCA), where methodologically appropriate, and narrative overlap assessment in domains with heterogeneous evidence types enhanced transparency and minimized the risk of double counting. This domain-specific approach to overlap represents a methodological strength and aligns with best practices for umbrella reviews.

Limitations

Several limitations should be acknowledged. First, the findings of this umbrella review are inherently dependent on the methodological quality, scope, and completeness of the included systematic reviews. Although AMSTAR 2 assessment was performed, deficiencies in review conduct or reporting may have influenced the synthesis, particularly in emerging domains where primary evidence is sparse or heterogeneous.

Second, despite systematic efforts to assess overlap, residual redundancy of primary studies cannot be entirely excluded. This limitation was most evident in microbiota-related domains, where a small number of observational cohorts contributed disproportionately to multiple systematic reviews. Although quantitative overlap assessment was applied and explicitly reported, high overlap limits the independence of evidence and necessitates cautious interpretation of conclusions in these areas.

Third, heterogeneity in study populations, diagnostic criteria, disease phenotypes, and outcome measures across primary studies constrained the strength of inferences that could be drawn. This heterogeneity was propagated through the included systematic reviews and limited the feasibility of quantitative synthesis in several domains.

Finally, as an umbrella review, this study did not reanalyze primary data and therefore cannot address unresolved confounding or bias at the individual study level. Consequently, causal relationships cannot be definitively established, and conclusions should be interpreted within the context of predominantly observational evidence.

5. Conclusions

This umbrella review integrates evidence from recent systematic reviews and meta-analyses to provide a comprehensive, domain-based synthesis of endometriosis pathogenesis. The findings support a multifactorial, network-driven disease model in which genetic and epigenetic susceptibility, immune dysregulation, aberrant tissue remodeling, and environmental modifiers interact dynamically to drive disease initiation, persistence, and progression.

Rather than representing a disorder caused by ectopic implantation alone, endometriosis emerges as a systemic condition characterized by localized immune tolerance, progressive fibrosis and pathological vascularisation, and coordinated molecular dysregulation across multiple biological pathways. These processes help explain clinical heterogeneity, variable treatment response, and the chronic nature of the disease.

By applying rigorous methodological appraisal and systematic overlap assessment, this review highlights both robust and methodologically fragile areas of the current evidence base. The synthesis underscores the need to move beyond reductionist models and to adopt integrative, systems-level approaches that combine molecular, environmental, and clinical data.

Overall, this umbrella review provides a unifying conceptual framework for understanding endometriosis pathogenesis and identifies key priorities for future mechanistic, translational, and clinical research aimed at improving diagnosis, stratification, and targeted therapeutic strategies.

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