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FUSOBACTERIUM AS A POTENTIAL PATHOGENETIC FACTOR IN ENDOMETRIOSIS: CURRENT EVIDENCE, METHODOLOGICAL CHALLENGES, AND CLINICAL IMPLICATIONS

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ABSTRACT

Background: Endometriosis is a chronic inflammatory gynecological disorder with an incompletely understood etiology. While hormonal, immunological, and genetic factors have been extensively studied, increasing attention has recently been directed toward the potential role of microbial agents in disease pathogenesis. Among these, Fusobacterium, particularly Fusobacterium nucleatum, has emerged as a candidate pathogen based on translational and experimental findings.
Objective: This narrative review aims to critically evaluate current evidence regarding the association between Fusobacterium and endometriosis, assess the biological plausibility of a pathogenic role, and identify methodological limitations and clinical implications.
Methods: A structured literature search was conducted in PubMed for publications addressing Fusobacterium in the context of endometriosis, including human studies, experimental models, and relevant commentaries. Evidence was synthesized thematically, with emphasis on study design, detection methods, and consistency of findings.
Results: Available data suggest that Fusobacterium may be present in endometrial tissues of some women with endometriosis and may promote inflammatory signaling and lesion development in experimental models. However, recent human studies have reported conflicting results, including a lack of significant Fusobacterium enrichment in eutopic endometrium. These discrepancies appear to be influenced by differences in patient selection, sampling strategies, low-biomass contamination risk, and microbiological detection techniques.
Conclusion: Although Fusobacterium represents a biologically plausible contributor to endometriosis pathophysiology, current evidence remains inconclusive. Further standardized, well-controlled studies are required before diagnostic or therapeutic strategies targeting this bacterium can be considered in clinical practice.

KEYWORDS

Endometriosis, Fusobacterium Nucleatum, Microbiome, Inflammation, Pathogenesis, Bacterial Infection

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1. Introduction

Endometriosis is a chronic, estrogen-dependent inflammatory disease defined by the presence of endometrial-like tissue outside the uterine cavity. It affects approximately 10% of women of reproductive age and represents a major cause of chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. Beyond its substantial impact on quality of life, endometriosis is associated with significant socioeconomic burden and remains a leading cause of diagnostic delay in gynecology. Despite decades of research, the etiology and pathogenesis of endometriosis remain incompletely understood, contributing to limited availability of causal and disease-modifying therapeutic strategies.

The most widely accepted theory of endometriosis development is retrograde menstruation, which proposes that viable endometrial cells reflux through the fallopian tubes into the peritoneal cavity during menstruation. However, retrograde menstruation alone does not adequately explain several key clinical and epidemiological observations. These include the high prevalence of retrograde menstruation among women without endometriosis, the occurrence of disease in premenarchal girls and postmenopausal women, and the marked interindividual variability in lesion distribution, symptom severity, and disease progression. Consequently, contemporary concepts increasingly view endometriosis as a multifactorial disorder arising from the interaction of hormonal imbalance, immune dysregulation, genetic and epigenetic susceptibility, and environmental influences.

Chronic inflammation and altered immune responses are now recognized as central features of endometriosis pathophysiology. Numerous studies have demonstrated increased concentrations of pro-inflammatory cytokines, chemokines, and growth factors within the peritoneal and endometrial environments,

accompanied by impaired immune surveillance and defective clearance of ectopic endometrial cells. Dysregulated activity of innate immune cells, including macrophages and natural killer cells, as well as aberrant activation of pattern recognition receptors, has been implicated in the persistence and progression of endometriotic lesions. These immune alterations not only sustain local inflammation but may also create a permissive microenvironment that favors lesion implantation, angiogenesis, and fibrosis.

In recent years, growing interest has focused on identifying potential triggers that could initiate or perpetuate this chronic inflammatory state. Advances in microbiome research have challenged the long-standing paradigm that the upper female reproductive tract is sterile. Using culture-independent molecular techniques, evidence has emerged supporting the existence of a microbial continuum extending from the vagina through the cervix to the endometrium. This paradigm shift has provided a biological rationale for investigating microbial contributions to gynecological disorders previously considered non-infectious in nature (Chen et al., 2017).

Within this evolving framework, microbial dysbiosis has been implicated in a range of reproductive conditions, including infertility, adverse pregnancy outcomes, and gynecological malignancies. The presence of bacteria within the endometrial cavity, even at low abundance, raises important questions regarding their potential role in modulating local immune responses and influencing disease susceptibility. In the context of endometriosis, it has been hypothesized that microbial components could act as inflammatory stimuli, amplifying immune activation and contributing to lesion establishment or maintenance.

Among bacterial candidates, Fusobacterium, particularly Fusobacterium nucleatum, has emerged as a microorganism of interest. F. nucleatum is a gram-negative, obligate anaerobe with well-established pro-inflammatory and immunomodulatory properties. It is capable of activating innate immune signaling pathways, including Toll-like receptor–mediated responses, and has been implicated in chronic inflammatory conditions beyond the reproductive tract. Notably, F. nucleatum has been associated with periodontal disease, colorectal cancer, and adverse pregnancy outcomes, highlighting its capacity to persist in diverse tissue environments and influence host immunity (Ghosh et al., 2024).

The growing body of evidence linking F. nucleatum to inflammation-driven diseases has prompted interest in its potential relevance to endometriosis. Analogies have been drawn to colorectal carcinogenesis, where Fusobacterium species are thought to promote disease progression through immune modulation rather than acting as classical infectious agents. Such observations have fueled speculation that similar mechanisms could operate within the endometrial or peritoneal environment, particularly in the setting of chronic inflammation. However, these comparisons also underscore the importance of distinguishing between causative roles and opportunistic colonization in inflamed tissues (Venkatesan, 2023).

A pivotal translational study brought this hypothesis into the field of endometriosis by reporting the presence of Fusobacterium species in endometrial tissues obtained from women with the disease. In addition to molecular detection in human samples, the authors demonstrated that experimental infection with Fusobacterium could promote the development of endometriosis-like lesions in animal models through activation of inflammatory signaling pathways. These findings suggested a potential mechanistic link between bacterial presence and lesion formation, generating significant interest and stimulating further research and expert commentary (Muraoka et al., 2023).

Nevertheless, subsequent investigations have revealed substantial heterogeneity and conflicting results. More recent human studies employing rigorous contamination control and carefully defined cohorts have failed to demonstrate significant enrichment of Fusobacterium nucleatum in the eutopic endometrium of women with endometriosis compared with controls. These findings have raised important concerns regarding methodological variability, low-biomass sampling, and the risk of false-positive bacterial detection in endometrial microbiome studies (Graciano-España et al., 2025).

The emerging controversy highlights the complexity of interpreting microbiological data in the context of endometriosis. Differences in patient selection, disease phenotype, sampling strategies, menstrual cycle phase, and microbiological detection techniques may all contribute to divergent findings across studies. Importantly, the endometrium represents a low-biomass environment in which background contamination from reagents or laboratory procedures can disproportionately influence results if not rigorously controlled. These challenges necessitate cautious interpretation of existing evidence and underscore the need for standardized methodologies and critical appraisal.

2. Materials and Methods

This narrative review was conducted using a structured literature search strategy to identify publications addressing the potential role of Fusobacterium, particularly Fusobacterium nucleatum, in the pathogenesis of endometriosis.

2.1. Data sources and search strategy

A structured literature search was conducted to identify publications addressing the potential role of Fusobacterium, particularly Fusobacterium nucleatum, in the pathogenesis of endometriosis. The primary database used for this review was PubMed, selected due to its comprehensive coverage of biomedical and life sciences literature and its widespread use in gynecological and microbiome research.

The search strategy combined Medical Subject Headings (MeSH) terms with free-text keywords to maximize sensitivity while maintaining thematic relevance. Search terms included combinations of "endometriosis," "Fusobacterium," "Fusobacterium nucleatum," "microbiome," "microbiota," "bacterial infection," and "inflammation." Boolean operators ("AND," "OR") were applied to refine search results and capture studies addressing both clinical and mechanistic aspects of microbial involvement in endometriosis.

The search was limited to articles published between January 2010 and March 2025 to reflect contemporary developments in microbiome research and advances in molecular detection techniques. No restrictions were applied regarding study design at the initial search stage, allowing inclusion of human clinical studies, experimental models, and expert commentaries relevant to the research question. Only articles published in English were considered eligible for inclusion.

To ensure completeness, reference lists of selected articles were manually screened for additional relevant publications not captured by the initial database search. This approach was particularly important given the limited number of studies directly addressing Fusobacterium in the context of endometriosis and the interdisciplinary nature of the topic, which spans gynecology, microbiology, and immunology.

2.2. Eligibility criteria

Studies were considered eligible if they met at least one of the following criteria:

(1) original human studies evaluating the presence or role of Fusobacterium in endometrial tissue, endometrial fluid, or endometriosis-associated lesions;

(2) experimental studies, including animal models or in vitro investigations, exploring mechanistic links between Fusobacterium and endometriosis-related processes;

(3) review articles or expert commentaries providing critical insights into microbial involvement in endometriosis, particularly those discussing Fusobacterium.

Articles were excluded if they lacked relevance to endometriosis, focused exclusively on non-gynecological conditions without translational relevance, or did not provide sufficient methodological detail regarding bacterial detection.

Given the emerging and controversial nature of the topic, review articles and expert commentaries were intentionally included to capture critical perspectives, methodological debates, and conceptual frameworks that may not yet be supported by large-scale clinical datasets. This approach reflects the exploratory status of research on microbial involvement in endometriosis and allows integration of both supportive and contradictory viewpoints. Studies focusing exclusively on non-gynecological conditions were included only if they provided translational insights relevant to inflammatory or immunological mechanisms applicable to endometriosis.

2.3. Study selection and data synthesis

Titles and abstracts retrieved through the database search were screened for relevance to the research question. Articles meeting the eligibility criteria underwent full-text assessment. Given the heterogeneity of study designs, populations, sampling strategies, and microbiological detection methods, a quantitative synthesis or meta-analysis was not considered appropriate.

Instead, a qualitative narrative synthesis was performed. Included studies were grouped thematically into human clinical investigations, experimental and mechanistic studies, methodological critiques, and expert commentaries. Particular emphasis was placed on differences in study design, patient selection, sample type, and bacterial detection methodology, as these factors were identified as major contributors to heterogeneity across findings.

This narrative approach enabled critical comparison of supportive and contradictory evidence, facilitated identification of methodological limitations, and allowed integration of biological plausibility with

clinical relevance. The synthesis focused not only on reported associations but also on the strength and reproducibility of evidence, thereby supporting a balanced interpretation of the potential role of Fusobacterium in endometriosis pathophysiology.

2.4. Methodological considerations of a narrative review

This review was designed as a narrative rather than a systematic review. A narrative approach was considered appropriate due to the limited number of available studies, the heterogeneity of methodologies, and the evolving nature of microbiome research in endometriosis. Unlike systematic reviews, which aim to provide exhaustive coverage and quantitative synthesis, narrative reviews allow integration of diverse forms of evidence, including experimental models and expert opinion, and facilitate critical discussion of emerging hypotheses.

The primary limitation of a narrative review lies in the potential for selection bias and lack of formal reproducibility. To mitigate these limitations, a structured search strategy and explicit eligibility criteria were applied, and both supportive and contradictory findings were intentionally included. Emphasis was placed on methodological rigor, contamination risk, and biological plausibility rather than on the frequency of reported associations alone.

This methodological framework aligns with the objective of the present review, which is to critically evaluate the current state of evidence, identify unresolved questions, and outline challenges that must be addressed before microbial hypotheses can be translated into clinical practice.

3. Results (Review of Evidence)

3.1. Evidence from Human Studies

The hypothesis implicating Fusobacterium as a potential pathogenetic factor in endometriosis is primarily based on observations derived from human endometrial samples combined with translational approaches. To date, only a limited number of studies have directly examined the presence of Fusobacterium in the eutopic endometrium or endometriosis-associated tissues of affected women (Hou et al., 2023).

A pivotal translational study reported the detection of Fusobacterium species in endometrial tissues obtained from women diagnosed with endometriosis. Using molecular detection techniques, the authors demonstrated a higher prevalence of Fusobacterium, particularly Fusobacterium nucleatum, in samples from patients with endometriosis compared with controls. Importantly, the presence of the bacterium was associated with increased inflammatory signaling, suggesting a potential link between bacterial colonization and disease-related immune activation (Muraoka et al., 2023).

These findings provided the first direct evidence supporting a possible association between Fusobacterium and endometriosis in humans and served as the basis for subsequent mechanistic and experimental investigations.

However, more recent human data have challenged this association. A study specifically evaluating the presence of Fusobacterium nucleatum in eutopic endometrial tissue across different stages of endometriosis failed to demonstrate a significant enrichment of this bacterium compared with control subjects. Notably, the authors emphasized rigorous contamination control and highlighted the low-biomass nature of endometrial samples as a critical methodological consideration (Graciano-España et al., 2025).

The discrepancy between these studies underscores the complexity of interpreting microbiological findings in the endometrium. Differences in patient selection, disease phenotype, sampling techniques, timing of tissue collection within the menstrual cycle, and bacterial detection methods may all contribute to divergent results. In particular, the distinction between eutopic endometrium and ectopic endometriotic lesions, as well as the use of endometrial biopsy versus alternative sampling approaches, may significantly influence bacterial detection rates.

Collectively, available human studies suggest that while Fusobacterium may be detectable in endometrial tissues of some women with endometriosis, its prevalence and clinical significance remain uncertain. Current evidence does not yet allow definitive conclusions regarding causality, and further well-controlled studies are required to clarify whether Fusobacterium represents a true pathogenic factor, an epiphenomenon of inflammation, or a consequence of methodological variability.

3.2. Experimental and Mechanistic Evidence

In addition to observations derived from human endometrial samples, experimental studies have sought to explore potential mechanistic links between Fusobacterium infection and endometriosis development. These studies are particularly important, as they provide insight into causality and biological plausibility beyond associative findings.

The translational study that first reported an association between Fusobacterium and endometriosis in humans also employed experimental models to investigate underlying mechanisms. Using a murine model of endometriosis, the authors demonstrated that infection with Fusobacterium promoted the establishment and growth of endometriosis-like lesions. This effect was accompanied by activation of innate immune signaling pathways, including Toll-like receptor 4 (TLR4), and increased local inflammatory responses (Muraoka et al., 2023).

Importantly, the study further showed that antibiotic treatment targeting Fusobacterium resulted in a reduction of lesion growth in the experimental model. These findings were interpreted as supporting a causal role for bacterial infection in lesion development and maintenance. However, while such results are intriguing, their interpretation requires caution.

Several authors have emphasized that the observed effects of antibiotic treatment in animal models may not necessarily reflect selective eradication of Fusobacterium alone. Antibiotics can exert broad immunomodulatory and anti-inflammatory effects, as well as alter the overall microbial ecosystem, which may independently influence disease progression. Consequently, the reduction in lesion size observed in experimental settings cannot be unequivocally attributed to the elimination of a single bacterial species (Venkatesan, 2023).

Additional expert commentaries have further highlighted the need to distinguish between bacterial causation and bacterial opportunism in endometriosis. It remains unclear whether Fusobacterium actively initiates pathological processes or preferentially colonizes an already inflamed or altered endometrial environment. This distinction is critical for interpreting mechanistic data and for designing future interventional studies (Khan et al., 2024).

Overall, experimental and mechanistic evidence supports the biological plausibility of a role for Fusobacterium in endometriosis-related inflammation. Nevertheless, current data are insufficient to establish a definitive causal relationship. Limitations inherent to animal models, differences between experimental infection and natural colonization, and the complexity of host–microbiome interactions necessitate further investigation before translating these findings into clinical applications.

3.3. Conflicting Findings and Sources of Heterogeneity

The conflicting results observed across human and experimental studies highlight several important sources of heterogeneity that complicate interpretation of the available evidence linking Fusobacterium to endometriosis. These discrepancies do not necessarily indicate irreconcilable findings, but rather reflect methodological and biological complexities inherent to microbiome research in the female reproductive tract.

One major source of heterogeneity relates to differences in patient selection and disease phenotype. Endometriosis represents a highly heterogeneous condition encompassing distinct clinical forms, including superficial peritoneal disease, ovarian endometriomas, and deep infiltrating endometriosis. Studies that do not stratify patients according to disease subtype, severity, or symptom profile may overlook important biological differences that influence microbial colonization or detection.

Sampling strategy constitutes another critical factor. The distinction between eutopic endometrium and ectopic endometriotic lesions is particularly relevant, as microbial presence and inflammatory milieu may differ substantially between these compartments. In addition, the use of endometrial biopsy, endometrial fluid aspiration, or surgical specimens introduces variability in sample composition and contamination risk. Timing of sampling within the menstrual cycle and prior exposure to hormonal or antimicrobial treatments may further affect microbial profiles (Hicks et al., 2025).

Methodological differences in bacterial detection also contribute significantly to inconsistent findings. Studies have employed a range of techniques, including targeted polymerase chain reaction (qPCR), 16S rRNA gene sequencing, and, less frequently, culture-based or histological approaches. Variations in DNA extraction protocols, sequencing regions, bioinformatic pipelines, and thresholds for bacterial abundance may lead to divergent results even when analyzing similar sample types.

Importantly, the low-biomass nature of endometrial samples poses a substantial challenge. In such settings, background contamination from reagents or the laboratory environment can disproportionately

influence results if not rigorously controlled. Studies incorporating comprehensive negative controls and contamination-aware analytical strategies may therefore yield findings that differ from earlier reports lacking such safeguards.

Taken together, these sources of heterogeneity underscore the need for cautious interpretation of current evidence. Rather than viewing conflicting findings as mutually exclusive, they should be considered within the context of methodological diversity and biological complexity. Addressing these issues through standardized protocols, transparent reporting, and well-defined patient cohorts will be essential for clarifying the potential role of Fusobacterium in endometriosis.

3.4. Low-Biomass Microbiome Research and Contamination-Related Bias

One of the most critical methodological challenges in investigating the role of Fusobacterium in endometriosis arises from the low-biomass nature of endometrial samples. Unlike the vaginal microbiome, which is typically dominated by abundant bacterial populations, the endometrium contains very low quantities of microbial DNA under physiological conditions. As a result, studies attempting to characterize the endometrial microbiome are particularly vulnerable to technical artifacts, contamination, and analytical bias. These issues are central to understanding the discrepancies observed across studies assessing Fusobacterium in endometriosis.

Low-biomass environments pose unique challenges for microbiome research, as exogenous DNA introduced during sample collection, DNA extraction, library preparation, or sequencing can represent a substantial proportion of the total detected microbial signal. Reagent contamination, often referred to as the "kitome," has been shown to introduce bacterial DNA originating from extraction kits, PCR reagents, and laboratory environments. In settings where endogenous bacterial load is minimal, such background contamination can lead to false-positive detection of bacterial taxa that are not truly present in the tissue of interest. This problem is particularly relevant for anaerobic bacteria such as Fusobacterium, which may be detected at low relative abundance and are therefore difficult to distinguish from contaminant signals without rigorous controls.

Recent studies emphasizing strict contamination-aware analytical strategies have highlighted the importance of including multiple negative controls at each stage of sample processing. These include blank extraction controls, PCR-negative controls, and sequencing controls, as well as transparent reporting of contaminant filtering procedures. Importantly, a recent human study specifically investigating Fusobacterium nucleatum in eutopic endometrial tissue employed comprehensive contamination control measures and failed to demonstrate significant enrichment of this bacterium in women with endometriosis compared with controls. The authors explicitly noted that earlier positive findings may, at least in part, reflect methodological limitations inherent to low-biomass microbiome studies rather than true biological differences (Graciano-España et al., 2025).

Beyond contamination, heterogeneity in sampling strategies further complicates interpretation. Endometrial microbiome studies have utilized a range of sample types, including endometrial biopsies, endometrial fluid aspirates, and surgical specimens obtained during laparoscopy. Each approach carries distinct risks of contamination from the lower genital tract and differs in cellular composition and microbial exposure. Moreover, subtle variations in sampling technique, such as transcervical access versus intraoperative collection, may significantly influence microbial profiles detected in sequencing-based analyses. These methodological differences limit comparability across studies and may contribute to inconsistent detection of Fusobacterium.

Analytical variability also plays a substantial role. Studies differ in the choice of bacterial detection methods, including targeted quantitative PCR, 16S rRNA gene sequencing with variable hypervariable regions, and distinct bioinformatic pipelines for taxonomic assignment. Thresholds for defining bacterial presence, relative abundance cutoffs, and statistical handling of low-abundance taxa vary widely. In the context of low-biomass samples, such analytical decisions can determine whether a bacterial signal is interpreted as biologically meaningful or dismissed as noise. These factors underscore the need for standardized protocols and transparent reporting in future investigations.

From a conceptual perspective, the low-biomass issue also raises important questions regarding biological interpretation. Detection of bacterial DNA does not necessarily imply the presence of viable organisms, active colonization, or pathogenic relevance. Inflammatory tissues may passively accumulate bacterial fragments or DNA through translocation or immune cell trafficking, particularly in chronic inflammatory conditions such as endometriosis. Consequently, the mere presence of Fusobacterium DNA

within endometrial samples should not be equated with infection or causation without corroborating functional or histological evidence (Venkatesan, 2023).

These methodological considerations are particularly relevant when interpreting early translational findings that reported enrichment of Fusobacterium in endometriosis. While such studies provided important hypothesis-generating insights, they were conducted at a time when awareness of low-biomass contamination issues was still evolving. Subsequent critical appraisals have emphasized that microbiome research in gynecology must adopt more stringent standards to avoid overinterpretation of preliminary or technically vulnerable data (Hou et al., 2023).

The implications of these challenges extend beyond academic interpretation to potential clinical translation. Without robust evidence demonstrating consistent, reproducible, and biologically meaningful enrichment of Fusobacterium in endometriosis, diagnostic testing or therapeutic targeting of this bacterium would be premature. Expert consensus has cautioned against extrapolating microbiome associations into clinical interventions in the absence of high-quality, reproducible human data, particularly given the risks associated with unnecessary antimicrobial exposure and disruption of the broader reproductive tract microbiome (Khan et al., 2024).

Taken together, the low-biomass nature of endometrial microbiome research represents a major source of bias and uncertainty in studies examining Fusobacterium in endometriosis. While advances in sequencing technology have expanded the ability to detect microbial DNA in previously inaccessible niches, they have also heightened the need for methodological rigor and critical interpretation. Addressing these challenges through standardized sampling, comprehensive contamination control, and integration of functional data will be essential for determining whether Fusobacterium represents a true contributor to endometriosis pathophysiology or an artifact of technical and analytical variability.

3.5. Interpreting Association Versus Causation in Human Microbiome Studies

One of the central challenges in evaluating evidence linking Fusobacterium to endometriosis lies in distinguishing associative findings from causal relationships. This issue is particularly pronounced in microbiome research, where detection of bacterial DNA within human tissues does not inherently imply pathogenic activity or etiological relevance. In the context of endometriosis, this distinction is further complicated by the chronic inflammatory nature of the disease and by the low-biomass environment of the endometrium.

Human studies reporting the presence of Fusobacterium in endometrial or lesion-associated samples are inherently observational. As such, they cannot determine whether bacterial presence precedes disease onset, contributes to lesion establishment, or represents secondary colonization of inflamed or structurally altered tissue. Chronic inflammation, impaired immune clearance, and tissue remodeling characteristic of endometriosis may create conditions that facilitate bacterial persistence or transient microbial DNA detection without implying a primary pathogenic role. This interpretative limitation applies even when molecular detection methods demonstrate statistically significant differences between patient groups (Hou et al., 2023; Khan et al., 2024).

Temporal ambiguity represents a key unresolved issue. Cross-sectional sampling provides a snapshot of microbial composition at a single time point, typically after disease establishment. Consequently, it remains unclear whether microbial signals observed in such studies reflect initiating events or downstream consequences of disease-related inflammation. This limitation has been emphasized in recent expert commentaries, which caution against inferring causality from microbiome associations in the absence of longitudinal or interventional data. Without evidence demonstrating that microbial exposure precedes lesion formation or that targeted modulation alters disease trajectory in humans, conclusions regarding causation remain speculative (Hou et al., 2023).

The issue of causality is further complicated by the heterogeneity of endometriosis itself. Variability in lesion type, anatomical distribution, symptom burden, hormonal milieu, and immune phenotype may influence both susceptibility to microbial signals and the likelihood of bacterial detection. Studies that aggregate diverse patient populations without stratification may therefore obscure subtype-specific associations or inflate apparent inconsistencies across cohorts. In this context, the absence of consistent Fusobacterium enrichment across studies does not necessarily refute biological plausibility but highlights the need for more refined analytical frameworks.

Another important consideration is the biological meaning of low-abundance microbial signals. Detection of Fusobacterium DNA at very low relative abundance raises questions regarding viability,

metabolic activity, and functional relevance. In low-biomass samples, bacterial DNA may originate from transient exposure, immune cell trafficking, or extracellular fragments rather than from actively replicating organisms. Without complementary evidence—such as RNA-based analyses, histological localization, or functional immune activation directly attributable to bacterial components—interpretation of such findings remains inherently limited (Graciano-España et al., 2025; Venkatesan, 2023).

Taken together, current human evidence supports at most an association between Fusobacterium and endometriosis in selected contexts, rather than a definitive causal role. Recognition of this distinction is essential to avoid overinterpretation of preliminary findings and to guide future research toward study designs capable of addressing temporality, functional relevance, and disease heterogeneity. Clarifying whether Fusobacterium acts as a trigger, amplifier, or bystander within the inflammatory milieu of endometriosis remains a central unresolved question in the field.

Taken together, these interpretative challenges indicate that the available evidence is best understood within explicit conceptual frameworks that distinguish between potential initiating, amplifying, and secondary roles of microbial signals in endometriosis.

3.6. Conceptual Models Linking Microbiota and Endometriosis

Given the heterogeneity of findings and the methodological challenges inherent to microbiome research in endometriosis, several conceptual models have been proposed to frame the potential relationship between microbial signals and disease pathophysiology. These models do not represent mutually exclusive hypotheses, but rather alternative interpretations of how bacterial presence—particularly that of Fusobacterium—could relate to chronic inflammation, lesion development, and disease persistence. Importantly, each model implies distinct expectations regarding temporality, consistency, and mechanistic evidence, thereby providing a useful framework for evaluating the strength and limitations of current data (Hou et al., 2023; Khan et al., 2024).

Fusobacterium as a potential disease trigger

In the first conceptual model, Fusobacterium is hypothesized to act as an initiating trigger that contributes to the early development of endometriosis. Under this scenario, bacterial exposure or colonization would precede lesion establishment and initiate inflammatory cascades that promote ectopic implantation, angiogenesis, and tissue remodeling. This model draws conceptual support from experimental findings demonstrating that Fusobacterium can activate innate immune pathways, including TLR4-mediated signaling, and enhance inflammatory responses in endometrial-derived cells.

However, translation of this trigger-based model to human disease remains limited by the absence of longitudinal data. Most available human studies assess microbial presence after disease diagnosis, precluding determination of whether bacterial signals precede or follow lesion formation. Furthermore, inconsistent detection of Fusobacterium across well-controlled cohorts challenges the expectation that a primary trigger would be reproducibly identifiable in affected individuals. As such, while experimental models support biological plausibility, current human evidence is insufficient to substantiate Fusobacterium as a universal initiating factor in endometriosis (Hou et al., 2023; Muraoka et al., 2023).

Fusobacterium as an amplifier of inflammation and disease progression

A second, and arguably more compatible, model conceptualizes Fusobacterium as an amplifier rather than an initiator of disease. In this framework, endometriosis arises through established hormonal, immunological, and genetic mechanisms, while bacterial components subsequently reinforce or perpetuate inflammatory signaling within an already permissive microenvironment. Chronic inflammation, impaired immune clearance, and altered tissue barriers characteristic of endometriosis may facilitate bacterial persistence or repeated exposure to microbial products, thereby sustaining pro-inflammatory and profibrotic pathways.

This amplification model aligns with observations that Fusobacterium is more plausibly linked to immune modulation than to classical infection. It also accommodates variability across patients, as bacterial signals may be detectable only in specific disease subtypes, stages, or inflammatory phenotypes. Importantly, this interpretation is consistent with the finding that antibiotic interventions in experimental models reduce lesion growth, while acknowledging that such effects may reflect broader immunomodulatory consequences rather than selective eradication of a single organism. From a translational perspective, this model underscores the need to evaluate microbial contributions in conjunction with host immune status rather than as isolated causal agents.

Fusobacterium as a bystander or secondary colonizer

A third conceptual model interprets Fusobacterium as a bystander or secondary colonizer of inflamed or structurally altered tissue. In this scenario, bacterial DNA detected in endometrial or lesion-associated samples reflects opportunistic presence rather than pathogenic involvement. Chronic inflammation, tissue injury, and immune cell trafficking may facilitate transient bacterial translocation or accumulation of microbial fragments without implying active colonization or functional relevance.

This bystander model is strongly supported by methodological considerations, particularly in low-biomass environments such as the endometrium. Detection of low-abundance bacterial DNA may result from contamination, passive transport, or non-viable bacterial remnants, especially when rigorous contamination control is not applied. The absence of consistent Fusobacterium enrichment in studies employing contamination-aware analytical pipelines reinforces the plausibility of this interpretation. Under this model, microbial signals are epiphenomena of disease-related inflammation rather than contributors to its pathogenesis (Graciano-España et al., 2025; Venkatesan, 2023).

Integrating conceptual models with current evidence

Rather than selecting a single explanatory framework, current evidence suggests that these conceptual models may coexist across different clinical contexts. Fusobacterium could plausibly act as an inflammatory amplifier in selected patients while representing a bystander signal in others, depending on disease phenotype, immune environment, and methodological factors. Importantly, none of the models can be conclusively validated or refuted based on existing cross-sectional human data alone.

Framing the evidence within these conceptual models highlights critical gaps that must be addressed to advance the field. Discriminating between trigger, amplifier, and bystander roles requires longitudinal sampling, functional validation of microbial activity, and integration of microbiome data with immunological and clinical phenotyping. Until such evidence becomes available, interpretations of Fusobacterium involvement in endometriosis should remain cautious and explicitly model-based rather than causal (Hou et al., 2023; Khan et al., 2024).

4. Clinical and Translational Implications

The growing interest in the potential role of Fusobacterium in endometriosis has naturally raised questions regarding possible diagnostic and therapeutic applications. However, translation of microbiome-related findings into clinical practice requires a level of evidentiary rigor that has not yet been achieved in this field. At present, available data do not support routine clinical testing for Fusobacterium or microbiome-targeted interventions in women with suspected or confirmed endometriosis.

From a diagnostic perspective, the inconsistent detection of Fusobacterium, particularly Fusobacterium nucleatum, across human studies limits its utility as a reliable biomarker. Differences in sampling strategies, detection methods, and contamination control substantially affect reported prevalence, undermining reproducibility. Moreover, the low-biomass nature of endometrial samples further complicates interpretation, as the presence of bacterial DNA does not necessarily indicate active colonization or pathogenic relevance. Consequently, incorporation of Fusobacterium-based assays into diagnostic algorithms would risk false-positive results and clinical misinterpretation (Graciano-España et al., 2025; Khan et al., 2024).

Therapeutically, early experimental findings demonstrating reduced lesion growth following antibiotic treatment in animal models have prompted speculation regarding antimicrobial strategies for endometriosis. However, such approaches remain highly speculative and are not supported by human clinical evidence. Antibiotics exert broad effects on the host microbiome and immune system, and their impact in experimental models cannot be attributed exclusively to eradication of a single bacterial species. Importantly, indiscriminate antimicrobial use carries well-recognized risks, including disruption of protective microbial communities, promotion of antimicrobial resistance, and potential exacerbation of dysbiosis (Muraoka et al., 2023; Venkatesan, 2023).

Expert commentaries have emphasized that premature adoption of microbiome-targeted therapies may reflect overinterpretation of associative data rather than evidence of causality. In the context of endometriosis, where chronic inflammation and immune dysregulation are already established features, bacterial presence may represent a secondary phenomenon rather than a primary driver of disease. Distinguishing between these possibilities is essential before considering interventional strategies aimed at microbial modulation (Hou et al., 2023; Khan et al., 2024).

Nevertheless, microbiome research may still hold translational value if approached within a broader, integrative framework. Rather than focusing on individual bacterial taxa, future studies may benefit from

examining host–microbe interactions, immune activation patterns, and functional pathways associated with inflammation. Integration of microbiome profiling with immunological, transcriptomic, and clinical data could provide insight into disease subtypes or inflammatory phenotypes, potentially informing personalized management strategies. Such approaches align with emerging concepts of endometriosis as a heterogeneous disorder rather than a single disease entity (Hou et al., 2023).

From a clinical research standpoint, future translational efforts should prioritize well-designed prospective studies with standardized sampling protocols, rigorous contamination control, and clearly defined clinical phenotypes. Randomized controlled trials would be required to evaluate the safety and efficacy of any microbiome-targeted interventions, whether antimicrobial, probiotic, or immunomodulatory in nature. Until such data are available, clinical management of endometriosis should remain grounded in established evidence-based approaches, with microbiome-related findings interpreted as hypothesis-generating rather than practice-changing (Khan et al., 2024; Venkatesan, 2023).

In summary, while Fusobacterium represents a biologically intriguing candidate within the evolving landscape of endometriosis research, current evidence does not justify diagnostic or therapeutic strategies targeting this bacterium in clinical practice. Continued investigation within a rigorous methodological and translational framework is necessary to determine whether microbiome-focused approaches will ultimately contribute to improved outcomes for women with endometriosis.

5. Discussion

This narrative review synthesizes current human and experimental evidence regarding the potential role of Fusobacterium, particularly Fusobacterium nucleatum, in the pathogenesis of endometriosis. Collectively, the available data support biological plausibility for bacterial involvement in endometriosis-related inflammation, while simultaneously highlighting substantial limitations that preclude definitive conclusions regarding causality.

Human studies investigating Fusobacterium in endometrial tissues have yielded inconsistent findings. While initial translational research reported an increased prevalence of Fusobacterium in women with endometriosis and suggested a link to inflammatory signaling, subsequent well-controlled studies failed to confirm significant enrichment of this bacterium in eutopic endometrium. These discrepancies underscore the challenges inherent to microbiome research in low-biomass environments and emphasize the importance of rigorous contamination control, standardized sampling, and careful patient stratification.

Experimental models provide additional insight into potential mechanisms by which Fusobacterium could influence endometriosis development. Activation of innate immune pathways, including TLR4-mediated signaling, and modulation of inflammatory responses observed in animal models support the concept that bacterial factors may contribute to lesion establishment or progression. However, extrapolation of these findings to human disease remains limited by differences between experimental infection models and naturally occurring microbial exposure, as well as by the non-specific effects of antibiotic interventions.

An important unresolved question concerns whether Fusobacterium acts as a primary pathogenic driver or as an opportunistic colonizer of an already altered or inflamed endometrial environment (Hou et al., 2023; Khan et al., 2024; Ul Ain, 2024). Chronic inflammation, tissue remodeling, and immune dysregulation characteristic of endometriosis may create conditions that favor bacterial persistence without implying causation. Distinguishing between these possibilities is critical, as it directly influences the interpretation of microbiological findings and the rationale for potential therapeutic strategies.

From a clinical perspective, current evidence does not support routine diagnostic testing for Fusobacterium in women with suspected or confirmed endometriosis, nor does it justify antimicrobial treatment targeting this bacterium outside of research settings (Khan et al., 2024; Venkatesan, 2023). Premature translation of preliminary findings into clinical practice may carry risks, including unnecessary antibiotic exposure and disruption of the broader reproductive tract microbiome.

Future research should prioritize well-designed prospective studies incorporating standardized sampling protocols, comprehensive contamination controls, and clearly defined clinical phenotypes. Integration of microbiome profiling with immunological, molecular, and clinical data may help clarify whether Fusobacterium represents a meaningful contributor to disease pathophysiology or a secondary feature of the endometriotic microenvironment. Ultimately, randomized controlled trials would be required to assess the safety and efficacy of any microbiome-targeted interventions.

In summary, Fusobacterium represents a biologically plausible but as yet unproven factor in endometriosis pathogenesis. Continued investigation within a rigorous methodological framework is essential to determine its true relevance and to avoid overinterpretation of preliminary or heterogeneous findings.

6. Conclusions

Current evidence suggests that Fusobacterium, particularly Fusobacterium nucleatum, represents a biologically plausible but not yet proven contributor to the pathogenesis of endometriosis. Human and experimental studies provide initial support for an association between bacterial presence, inflammatory signaling, and lesion development; however, findings remain inconsistent and are substantially influenced by methodological heterogeneity.

Limitations related to low-biomass sampling, contamination risk, patient selection, and variability in detection techniques preclude definitive conclusions regarding causality. Available data do not allow differentiation between a primary pathogenic role of Fusobacterium and secondary colonization of an already altered endometrial environment.

At present, there is insufficient evidence to support routine clinical testing or targeted antimicrobial treatment for Fusobacterium in women with endometriosis. Translation of microbiome-related findings into clinical practice should therefore be approached with caution.

Future research employing standardized protocols, well-defined clinical phenotypes, and integrated immunological and microbiological analyses will be essential to clarify the true role of Fusobacterium in endometriosis and to determine whether microbiome-targeted strategies may have therapeutic potential.

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