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Review Article

Gut Microbiome in Endometriosis: A Narrative Review of Human Evidence and Translational Challenges

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Abstract

The gut microbiome has been investigated as a possible contributor to the hormonal and inflammatory processes associated with endometriosis. However, human studies have produced inconsistent findings, and their clinical implications remain uncertain. This narrative review examines 15 publications addressing intestinal microbial composition, estrogen metabolism, immune associations, and microbiota-derived metabolites in endometriosis. Several small studies reported differences in microbial diversity or individual taxa, whereas a shotgun metagenomic study of 1,000 women found no significant differences in diversity, species, functional pathways, or estrobolome-related sequences after the relevant statistical analyses. Direct measurements of fecal β-glucuronidase activity have also failed to demonstrate a consistent disease-associated increase. Metabolomic research offers a complementary perspective: reduced fecal 4-hydroxyindole in affected women was accompanied by inhibitory effects on lesions and pain-related outcomes in preclinical models. These observations support further investigation but do not establish therapeutic efficacy in patients. Differences in participant selection, disease characteristics, sequencing methods, and statistical approaches limit comparisons across studies. Current evidence does not establish a reproducible gut microbial signature of endometriosis or a validated microbiome-based diagnostic test. Progress depends on clinically well-characterized cohorts, direct functional measurements, and independent validation of candidate biomarkers.

Keywords: Endometriosis, Gut Microbiome, Estrobolome, Inflammation, Microbial Metabolites

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Introduction

Endometriosis is an estrogen-dependent inflammatory disorder associated with pelvic pain, infertility, and gastrointestinal symptoms. Its heterogeneous presentation has encouraged investigation of biological processes that might connect reproductive disease with intestinal physiology. The gut microbiome is relevant to this question because of its involvement in hormone metabolism and immune regulation. Nevertheless, biological plausibility does not establish that intestinal microorganisms initiate or sustain endometriosis [1, 2].

The literature contains two related but distinct questions: whether women with endometriosis have a distinguishable gut microbial profile, and whether microbial activities influence disease-related processes. Compositional studies address the first question, whereas enzyme assays, metabolomics, and experimental interventions provide different levels of evidence for the second. Treating these approaches as interchangeable can obscure both negative findings and the limits of mechanistic inference. This review therefore considers human observations alongside functional evidence, with particular attention to inconsistent results and the requirements for diagnostic or therapeutic translation.

Scope and approach

This focused narrative review examined 15 selected publications, including observational human studies, two reviews, a reanalysis of sequencing datasets, a case report, and research combining human sampling with preclinical experiments. Evidence was organized by microbial composition, proposed mechanisms, and clinical applications. Primary studies were distinguished from secondary syntheses, and observations from different anatomical sites were considered separately. No independent systematic search or quantitative pooling was undertaken; the review consequently does not claim exhaustive coverage.

Human Evidence and Inconsistent Microbial Signatures

Diversity and taxonomic composition

Early human studies suggested altered intestinal communities in endometriosis. Shan et al. compared 12 women with stage III/IV disease and 12 healthy controls, reporting lower alpha diversity, a higher Firmicutes/Bacteroidetes ratio, and differences in several taxa [3]. Svensson et al., studying 66 patients and 198 matched population controls, also identified differences in diversity and bacterial abundance; 12 bacterial taxa differed after false discovery rate correction [4]. These findings support an association within the populations studied, but they do not identify a universally applicable microbial profile.

The largest investigation in this collection reached a different conclusion. Pérez-Prieto et al. analyzed shotgun metagenomic data from 136 women with endometriosis and 864 controls in the Estonian Microbiome cohort [5]. Neither alpha nor beta diversity differed significantly. Species-level and functional differences did not remain significant after adjustment for multiple testing, and estrobolome-associated sequence reads were also comparable. Sensitivity analyses excluding women older than 50 years did not materially change the findings. Although inclusion of heterogeneous disease phenotypes could obscure subgroup-specific associations, these results challenge the assumption that endometriosis consistently produces detectable fecal dysbiosis.

Other studies further illustrate the distinction between community-wide differences and selected taxonomic associations. Pai et al. found similar overall microbial diversity in 27 patients and 24 controls, despite enrichment of selected bacterial groups [6]. Guo et al. reported compositional differences in 22 patients and 18 controls, including reduced *Roseburia* and increased Proteobacteria [7]. In a Spanish cohort of 30 patients and 43 controls, Martínez-Lara et al. identified differential taxa, but the modestly higher diversity at family and genus levels was not statistically significant [8]. Together, these findings do not support a single direction of diversity change across populations.

Clinical context and sampling site

Participant selection is central to interpretation. Hicks et al. included 21 women with confirmed endometriosis, 24 surgical patients without endometriosis, and 19 healthy controls [9]. Stool composition differed across the three cohorts, demonstrating the relevance of the comparator population. Their reported enrichment of *Fusobacterium* in moderate or severe disease concerned oral samples and should not be presented as a fecal finding. Similarly, Dong et al. compared 32 infertile women with endometriosis against 13 women whose infertility was attributed to a male factor [10]. They found taxonomic and inflammatory-marker associations without a significant difference in alpha diversity. These observations concern a defined reproductive population rather than all women with endometriosis.

Zhao et al. reported gut and vaginal microbial differences using metagenomic sequencing, but the study involved only five patients and six controls [11]. Its 22 specimens represented paired anatomical samples from

11 participants, not 22 independent individuals. Torraco et al. reanalyzed 79 fecal and 103 vaginal sequencing samples and identified disease-associated fecal, but not vaginal, patterns [12]. This secondary analysis provides complementary evidence, although incomplete clinical metadata limited subgroup assessment. An uncontrolled nine-patient stool-profile study and a single case report contribute descriptive observations but cannot establish disease specificity [13, 14]. Table 1 summarizes the comparative human studies underlying these contrasts.

Proposed Mechanistic Links

Estrobolome and estrogen metabolism

The estrobolome comprises microbial genes involved in estrogen metabolism. Bacterial deconjugation of estrogens, including reactions mediated by β-glucuronidase, provides a proposed connection between intestinal microorganisms and enterohepatic estrogen recycling [2]. In endometriosis, however, the supporting measurements are not uniform. Shan et al. observed higher serum estradiol and correlations between estradiol and the abundance of *Blautia* and *Dorea* [3]. Such correlations are compatible with a relationship but cannot determine whether microbial changes precede hormonal differences or follow them.

Pai et al. directly measured fecal β-glucuronidase activity and found no significant difference between groups[6]. Fecal estriol, 16-epiestriol, 16α-hydroxyestrone, and 2-methoxyestradiol were higher in patients, whereas urinary estrogen metabolites did not differ significantly. The absence of differences in estrobolome-related sequences in the Estonian study adds further uncertainty [5]. Consequently, the presence of taxa associated with estrogen metabolism cannot, by itself, demonstrate enhanced enzyme activity or increased systemic estrogen exposure. Gene abundance, enzyme activity, and metabolite concentrations address different parts of the proposed pathway and require separate interpretation.

Immune associations and intestinal barrier mechanisms

Inflammatory signaling offers another possible link. Shan et al. reported higher serum IL-8 and an association between IL-8 and *Subdoligranulum* abundance [3]. Dong et al. identified correlations involving microbial taxa and macrophage migration inhibitory factor, TNF-α, and IL-6 [10]. For example, *Streptococcus* and *Veillonella* correlated positively with macrophage migration inhibitory factor, while *Bilophila* and *Enterococcus* correlated positively with TNF-α and IL-6. These findings connect intestinal profiles with systemic inflammatory measurements, but their observational design leaves the direction and specificity of the associations unresolved.

The reviewed mechanistic literature discusses intestinal barrier disruption and lipopolysaccharide-related signaling through TLR4 and NF-κB as possible contributors to inflammatory responses [1, 2]. These pathways provide a framework for interpreting human observations rather than proof that the measured fecal changes cause lesion development. Evidence from the genital tract also cannot establish an intestinal origin for bacteria or bacterial products. Likewise, functional profiles inferred from 16S data, as in the Guo and Torraco studies, represent predicted capacities rather than direct measurements of pathway activity [7, 12].

Microbial metabolites and experimental evidence

Talwar et al. combined stool microbiome analysis and untargeted metabolomics in 18 women with endometriosis and 31 controls [15]. They identified 61 differential metabolites among 371 detected compounds: 50 were reduced and 11 increased in patients. Fecal 4-hydroxyindole was reduced, and its abundance correlated positively with *Faecalibacterium*, Lachnospiraceae, and *Peptoniphilus*, but negatively with *Dorea*. Another indole derivative, 4-indolecarbaldehyde, was also reduced and correlated positively with *Bacteroides* and *Parabacteroides*. The investigators subsequently confirmed the reductions in these two compounds using targeted liquid chromatography–mass spectrometry. This combination of microbial profiling and metabolite measurement provides a more detailed account of the intestinal environment than taxonomic analysis alone [15]. Subsequent experiments showed that 4-hydroxyindole inhibited disease-related outcomes in cell-based and murine models, including models using human-derived endometriotic cells. Effects included reduced lesion growth, inflammation, and hyperalgesia [15]. This study links a human metabolic observation to an experimentally testable candidate, providing evidence beyond taxonomic association alone. Its interpretation nevertheless remains bounded by the models used. Experiments involving immortalized patient-derived cells and mouse xenografts do not establish clinical efficacy, and the human cohort was small. Moreover, reported metabolic similarities with inflammatory bowel disease were not tested through a simultaneous comparison with an independently recruited inflammatory bowel disease group [15]. The findings therefore support further study of 4-hydroxyindole without establishing diagnostic specificity or a treatment for patients (Table 1).

Table 1: Comparative human studies of the gut microbiome in endometriosis

Study	Participants	Main approach	Main finding and interpretive limit
Shan et al. [3]	12 cases; 12 controls	16S rRNA sequencing; serum assays	Lower alpha diversity; associations with estradiol and IL-8. Small cohort restricted to stage III/IV disease.
Svensson et al. [4]	66 cases; 198 controls	16S rRNA sequencing	Diversity and abundance differences; several subgroup findings lost significance after FDR correction.
Pérez-Prieto et al. [5]	136 cases; 864 controls	Shotgun metagenomics	No significant diversity differences; no differential species, pathways, or estrobolome sequences after multiple-testing adjustment.
Pai et al. [6]	27 cases; 24 controls	16S rRNA sequencing; enzyme and estrogen-metabolite assays	Similar diversity and β-glucuronidase activity; selected fecal estrogen metabolites increased.
Guo et al. [7]	22 cases; 18 controls	16S rRNA sequencing; PICRUSt2	Taxonomic differences and marker correlations; functional results were inferred.
Martínez-Lara et al. [8]	30 cases; 43 controls	16S rRNA sequencing	Differential taxa; family/genus diversity differences not significant. Age and comorbidity complicate interpretation.
Hicks et al. [9]	21 cases; 24 surgical non-cases; 19 healthy controls	Multisite 16S rRNA sequencing	Stool composition differed across groups; oral Fusobacterium finding must remain site-specific.
Dong et al. [10]	32 cases; 13 controls	16S rRNA sequencing ; inflammatory markers	Taxonomic and immune-marker associations; no significant alpha-diversity difference. Infertility-based recruitment.
Zhao et al. [11]	5 cases; 6 controls	Paired gut/vaginal metagenomics; machine learning	Compositional differences and candidate classifiers; 22 specimens came from only 11 participants.
Talwar et al. [15]	18 cases; 31 controls	16S rRNA sequencing ; metabolomics; linked preclinical experiments	Reduced fecal 4-hydroxyindole; experimental benefits do not establish efficacy in patients.

Diagnostic and Therapeutic Potential

Fecal microbial and metabolic profiles are attractive research candidates because stool sampling is non-invasive. However, separating study groups retrospectively or within a small discovery cohort is different from identifying disease reliably in clinical practice. Torraco et al. developed a microbial endometriosis index and evaluated classification models using internal cross-validation [12]. Zhao et al. reported promising discrimination using gut microbial features, but their analysis was based on 11 participants [11]. Such results require independent evaluation before their diagnostic performance can be generalized.

Comparator choice is particularly important when symptoms overlap with other conditions. Healthy controls, surgical controls with other gynecological disorders, and women undergoing infertility assessment are not equivalent populations [4, 9, 10]. A candidate marker must distinguish endometriosis in the setting where it would actually be used. Reported microbial associations with pain, infertility, or circulating markers may help formulate hypotheses, but do not demonstrate incremental diagnostic value over existing clinical assessment [7, 8, 10]. The available case report and uncontrolled stool-profile series cannot resolve this issue [13, 14].

Therapeutic proposals include probiotics, fecal microbiota transplantation, and interventions directed at microbial metabolites. The two reviews discuss these approaches while identifying unresolved questions concerning efficacy, microbial variability, and safety [12]. Evidence from other disease settings or experimental models should not be treated as proof of benefit in endometriosis. Within this collection, 4-hydroxyindole has direct preclinical support, but no demonstrated therapeutic efficacy in women [15]. The current evidence therefore supports targeted investigation rather than routine microbiome-directed treatment.

Methodological Limitations and Research Priorities

The disagreement between studies is partly a problem of comparability. Cohorts differ in age, disease stage, hormonal exposure, gastrointestinal symptoms, and control selection [2, 4, 5, 8].

Shan et al. restricted recruitment to advanced disease, whereas the Estonian study included a broader clinical population [3, 5]. The Spanish study discussed its older

cohort and potential effects of comorbidities and medication use [8]. These differences should be examined before interpreting inconsistent taxa as biological contradictions.

Analytical variation also matters. Most small studies used 16S rRNA sequencing, whereas others applied shotgun metagenomics, enzyme assays, or metabolomics. Predicted microbial functions cannot be equated with measured metabolites or enzyme activities. Multiple-testing correction is consequential: several apparent differences in the Estonian analysis disappeared after adjustment, and subgroup differences in the Svensson study did not remain significant after false discovery rate correction [4, 5]. A convincing synthesis must retain these null findings rather than emphasizing nominally significant associations alone.

Future studies should combine standardized sampling with detailed recording of diet, medication, menstrual or menopausal status, gastrointestinal conditions, and endometriosis phenotype [2, 5, 8, 12]. Longitudinal sampling would help establish whether microbial changes precede disease-related changes or accompany them. Functional investigations should connect microbial genes with measured enzyme activity, metabolites, and host responses, while diagnostic models require independent cohorts [2, 6, 12, 15]. These priorities follow directly from the limitations of the available studies; larger sample size alone will not address poorly defined clinical comparisons. Participant counts refer to the recruited or analyzed human cohorts described in the articles; availability may differ by specimen or assay. FDR, false discovery rate. The secondary sequencing reanalysis[12], uncontrolled series [13], and case report [14] are discussed in the text and excluded from this comparative primary-study table.

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Conflict of Interests

The authors declare no conflict of interest related to this study.

Author's contribution

All authors contributed to the conception and design of the study, data collection, data analysis, interpretation of the results, and preparation and revision of the manuscript. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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