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Research Article

Gut Microbiome and Gynecological Signatures in Women With Endometriosis and Chronic Pelvic Pain

Bushra Batool[1], Komal Javaid[2], Madiha Khan[3], Fauzia Tabbasum[4], Almas Raza[5], Sonia Tahir[6]

1. Gynaecologist and Health Manager, MNH Waan Bachran, District Mianwali, Pakistan.
2. Consultant Gynaecologist, Clinics and Diagnostic Hospital, Islamabad, Pakistan.
3. Women Medical Officer, Gynaecology and Obstetrics, CAT-B Hospital, Dargai, Malakand, Pakistan.
4. Assistant Professor, Gynaecology and Obstetrics Department, Islam Medical College Sialkot, Pakistan.
5. Associate Professor, Microbiology, Rashid Latif Medical College, Lahore, Pakistan.
6. Associate Professor, Microbiology/Pathology, Lahore Medical and Dental College, Lahore, Pakistan.

Corresponding author: Bushra Batool

Abstract: Endometriosis is a chronic estrogen-dependent inflammatory disorder characterized by the presence of endometrial-like tissue outside the uterine cavity and is frequently associated with chronic pelvic pain, dysmenorrhea, dyspareunia, infertility, and gastrointestinal symptoms. Emerging evidence suggests that alterations in the gut microbiome may influence estrogen metabolism, immune regulation, intestinal permeability, and inflammatory signaling in women with endometriosis. This case-control study compared gut microbial profiles and selected gynecological characteristics among women with surgically or clinically diagnosed endometriosis and healthy controls. A total of 120 women were enrolled, including 60 patients with endometriosis and chronic pelvic pain and 60 age-matched healthy controls. Clinical data included age, body mass index, menstrual characteristics, pain duration, dysmenorrhea severity, dyspareunia, infertility, bowel symptoms, and endometriosis stage. Stool samples were collected for bacterial DNA extraction and 16S rRNA gene sequencing. Relative abundance of selected bacterial taxa, microbial diversity indices, and fecal inflammatory markers were assessed. The mean age of patients was 32.4 ± 6.7 years compared with 31.8 ± 6.4 years among controls. Patients demonstrated significantly reduced microbial diversity and altered relative abundance of several bacterial groups. Increased abundance of potentially pro-inflammatory taxa and reduced

abundance of short-chain-fatty-acid-producing bacteria were observed among patients. Severe pelvic pain, bowel symptoms, and advanced-stage endometriosis were associated with greater microbial imbalance. Patients with severe pain had lower relative abundance of beneficial butyrate-producing bacteria than those with mild-to-moderate pain. Dysmenorrhea, dyspareunia, infertility, and bowel-related symptoms were significantly more frequent in the endometriosis group. The findings suggest that endometriosis-associated chronic pelvic pain may be accompanied by alterations in gut microbial composition and gynecological symptom patterns. Further longitudinal studies are required to determine whether microbiome changes contribute to disease development or occur secondary to inflammation, hormonal therapy, diet, and pain-related behavioral changes.

Keywords: Endometriosis; chronic pelvic pain; gut microbiome; dysbiosis; 16S rRNA sequencing; dysmenorrhea; dyspareunia; infertility; gynecological inflammation; microbiota.

Introduction

Endometriosis is a chronic gynecological disorder characterized by the presence of endometrial-like glands and stroma outside the uterine cavity. It commonly affects women during the reproductive years and may involve the ovaries, pelvic peritoneum, uterosacral ligaments, rectovaginal septum, bowel, and urinary tract. The disease is associated with chronic pelvic pain, severe dysmenorrhea, deep dyspareunia, infertility, fatigue, and impaired quality of life.[1-2]

The clinical presentation of endometriosis is heterogeneous. Some women remain asymptomatic, whereas others experience severe pain despite relatively limited anatomical disease. Conversely, extensive endometriotic lesions may be identified in women with minimal symptoms. This discrepancy suggests that disease burden is influenced not only by lesion size or anatomical distribution but also by inflammatory, neurological, hormonal, and immunological mechanisms.[3-4]

Chronic pelvic pain is one of the most disabling manifestations of endometriosis. It may be cyclical or continuous and can be associated with central sensitization, peripheral nerve involvement, pelvic floor

dysfunction, adhesions, and inflammatory mediator release. Gastrointestinal symptoms such as bloating, constipation, diarrhea, painful defecation, and altered bowel habits are also frequently reported.[5-6]

The gut microbiome consists of a complex community of bacteria, archaea, viruses, and fungi that contribute to digestion, immune regulation, metabolic homeostasis, and maintenance of intestinal barrier function. Alterations in microbial composition or function, commonly referred to as dysbiosis, have been associated with inflammatory, metabolic, autoimmune, and gynecological disorders.[7-8]

The gut microbiome may influence endometriosis through several biological pathways. Certain intestinal bacteria participate in estrogen metabolism through enzymes such as β-glucuronidase. These microbial activities may influence the enterohepatic circulation of estrogen and alter the availability of biologically active estrogen. Since endometriosis is an estrogen-dependent disease, changes in estrogen metabolism may be clinically relevant.

The microbiome may also influence immune responses. Dysbiosis can increase intestinal permeability, promote endotoxin exposure, and activate inflammatory pathways involving toll-like receptors, nuclear factor kappa B, and pro-inflammatory cytokines. These mechanisms may contribute to the persistence of pelvic inflammation and the development of pain.

In addition, gut bacteria produce short-chain fatty acids, including acetate, propionate, and butyrate. These metabolites influence epithelial integrity, regulatory T-cell activity, macrophage function, and mucosal immune balance. A reduction in short-chain-fatty-acid-producing bacteria may therefore contribute to an inflammatory environment.

Women with endometriosis frequently report gastrointestinal symptoms, including constipation, diarrhea, bloating, and abdominal discomfort. These symptoms may be related to bowel endometriosis, pelvic adhesions, altered intestinal motility, visceral hypersensitivity, or changes in gut microbial composition. However, the relationship between gastrointestinal symptoms and microbiome alterations remains incompletely understood.[9-10]

Gynecological signatures of endometriosis include dysmenorrhea, chronic pelvic pain, deep dyspareunia, infertility, abnormal menstrual bleeding, and pelvic tenderness.

These features may reflect different clinical phenotypes of the disease. Understanding the relationship between microbiome characteristics and gynecological symptoms may help identify clinically meaningful disease subgroups.

Previous research has suggested that women with endometriosis may have altered microbial diversity and differences in the relative abundance of specific bacterial taxa. However, findings have not been completely consistent, partly because of differences in sample size, diet, geographical population, antibiotic exposure, hormonal treatment, disease stage, and sequencing methodology.

There remains a need for clinical studies that evaluate gut microbial characteristics together with detailed gynecological symptoms and disease severity. A combined clinical and microbiological approach may improve understanding of the biological factors associated with chronic pelvic pain in endometriosis.

The present study was designed to compare gut microbiome characteristics between women with endometriosis and chronic pelvic pain and healthy controls. The study also assessed the association between microbial patterns, endometriosis stage, pain severity, bowel symptoms, dysmenorrhea, dyspareunia, and infertility.

Methodology

Study Design and Setting

This hospital-based case-control observational study was conducted at MNH Waan Bachran.

The study duration was six months.

A total of 120 women were enrolled:

- 60 women with endometriosis and chronic pelvic pain
- 60 healthy controls

Study Population

Women attending the gynecology outpatient department with a clinical or laparoscopic diagnosis of endometriosis were screened for eligibility.

Healthy controls were recruited from women attending the hospital for routine gynecological assessment or accompanying relatives, provided they had no history of endometriosis or chronic pelvic pain.

Inclusion Criteria for Cases

Women were included if they:

- Were aged 18–45 years.
- Had clinically, radiologically, or laparoscopically diagnosed endometriosis.

- Reported chronic pelvic pain for at least three months.
- Were willing to provide a stool sample.
- Provided written informed consent.

Exclusion Criteria for Cases

Patients were excluded if they had:

- Pregnancy.
- Active pelvic inflammatory disease.
- Inflammatory bowel disease.
- Known colorectal malignancy.
- Chronic liver disease.
- Chronic kidney disease.
- Current systemic infection.
- Antibiotic use within the previous eight weeks.
- Probiotic supplementation within the previous four weeks.
- Major gastrointestinal surgery.
- Current chemotherapy or immunosuppressive treatment.
- Other diagnosed causes of chronic pelvic pain.
- Incomplete clinical information.

Inclusion Criteria for Controls

Controls were included if they:

- Were aged 18–45 years.
- Had no history of endometriosis.
- Had no chronic pelvic pain.
- Had no active gynecological or gastrointestinal inflammatory disease.
- Had not used antibiotics within the previous eight weeks.
- Provided informed consent.

Clinical Assessment

A structured proforma was used to record:

- Age
- BMI
- Age at menarche
- Menstrual cycle characteristics
- Duration of pelvic pain
- Dysmenorrhea
- Dyspareunia
- Chronic non-cyclical pelvic pain
- Bowel symptoms
- Urinary symptoms
- Infertility
- Previous pelvic surgery
- Hormonal treatment
- Family history of endometriosis

Pain severity was assessed using a numerical rating scale from 0 to 10.

Pain was categorized as:

- Mild: 1–3
- Moderate: 4–6
- Severe: 7–10

Assessment of Endometriosis

Diagnosis and staging were based on available clinical, ultrasound, MRI, or laparoscopic findings.

Endometriosis was categorized as:

- Minimal/mild disease
- Moderate disease
- Severe/advanced disease

Where laparoscopic staging was available, the revised American Society for Reproductive Medicine classification was used.

Gynecological Signatures

The following gynecological features were considered major clinical signatures:

1. Severe dysmenorrhea.
2. Chronic pelvic pain.
3. Deep dyspareunia.
4. Infertility.
5. Menstrual irregularity.
6. Chronic fatigue.
7. Bowel-related menstrual symptoms.
8. Pelvic tenderness.
9. Previous endometriosis-related surgery.
10. Hormonal treatment history.

Stool Sample Collection

Participants provided a fresh stool sample in a sterile, labeled container.

Samples were transported to the laboratory under controlled conditions and stored at −80°C until DNA extraction.

Participants were instructed to avoid contamination with urine or menstrual blood.

Gut Microbiome Analysis

Bacterial DNA was extracted using a commercial microbial DNA extraction kit.

The V3–V4 region of the bacterial 16S rRNA gene was amplified using polymerase chain reaction.

Sequencing was performed using a next-generation sequencing platform.

Bioinformatic analysis included:

- Operational taxonomic unit or amplicon sequence variant identification.
- Taxonomic classification.
- Relative abundance analysis.
- Alpha-diversity analysis.
- Beta-diversity analysis.
- Differential abundance analysis.

Microbial Diversity

Alpha diversity was assessed using:

- Shannon diversity index.
- Simpson diversity index.
- Observed taxonomic features.

Beta diversity was evaluated using Bray–Curtis dissimilarity and visualized through principal coordinate analysis.

Selected Bacterial Groups

The analysis focused on selected bacterial groups, including:

- Lactobacillus species.
- Bifidobacterium species.
- Faecalibacterium species.
- Roseburia species.
- Bacteroides species.
- Prevotella species.
- Escherichia-Shigella group.
- Enterobacteriaceae.
- Ruminococcaceae.

The selected taxa were interpreted as exploratory microbial signatures rather than definitive diagnostic markers.

Fecal Inflammatory Markers

Where available, fecal calprotectin was measured using an enzyme-linked immunosorbent assay.

Fecal calprotectin was used as an exploratory marker of intestinal inflammatory activity.

Sample Size

Sample size was calculated using Epi Info version 7 based on an anticipated difference in microbial diversity between women with endometriosis and healthy controls, with a 95% confidence level and 80% power.

The minimum estimated sample size was 108 participants.

To compensate for possible sample loss and sequencing failure, 120 participants were enrolled.

Statistical Analysis

Data were analyzed using SPSS version 27 and suitable microbiome analysis software.

Continuous variables were presented as mean ± standard deviation or median with interquartile range.

Categorical variables were presented as frequencies and percentages.

Independent-samples t-test or Mann–Whitney U test was used for continuous variables.

Chi-square test or Fisher's exact test was used for categorical variables.

Spearman correlation was used to assess associations between microbial abundance and pain severity.

Beta-diversity differences were assessed using permutational multivariate analysis of variance.

Multivariable regression analysis was used to assess independent associations between microbial signatures and severe pelvic pain.

Potential confounders included:

- Age
- BMI
- Hormonal treatment
- Disease stage
- Antibiotic exposure
- Dietary pattern
- Constipation
- Previous pelvic surgery

Results:

Table 1. Demographic and clinical characteristics of study participants

Variable	Endometriosis with chronic pelvic pain (n=60)	Control group (n=60)	p-value
Age, years	32.4 ± 6.8	31.7 ± 6.2	0.56
BMI, kg/m²	25.8 ± 4.1	24.9 ± 3.7	0.21
Nulliparity, n (%)	29 (48.3)	25 (41.7)	0.47
Previous pregnancy, n (%)	31 (51.7)	35 (58.3)	0.47
Duration of pelvic pain, years	4.2 ± 2.6	—	—
Dysmenorrhea, n (%)	56 (93.3)	18 (30.0)	<0.001
Deep dyspareunia, n (%)	35 (58.3)	12 (20.0)	<0.001
Chronic bowel symptoms, n (%)	29 (48.3)	11 (18.3)	0.001
Constipation, n (%)	25 (41.7)	10 (16.7)	0.003
Menstrual irregularity, n (%)	17 (28.3)	9 (15.0)	0.08
Endometriosis stage III–IV, n (%)	35 (58.3)	—	—
Mean pelvic pain score (VAS)	6.8 ± 1.5	2.1 ± 1.2	<0.001
Fecal calprotectin, µg/g	118.6 ± 54.3	63.4 ± 29.7	<0.001

Table 2. Comparison of gut microbiome diversity and selected bacterial taxa

Microbiome parameter	Endometriosis with chronic pelvic pain (n=60)	Control group (n=60)	p-value
Shannon diversity index	3.42 ± 0.71	4.18 ± 0.66	<0.001
Simpson diversity index	0.78 ± 0.09	0.87 ± 0.06	<0.001
Faecalibacterium, relative abundance (%)	3.8 ± 1.7	6.2 ± 2.1	<0.001
Roseburia, relative abundance (%)	2.1 ± 1.1	3.7 ± 1.5	<0.001
Bifidobacterium, relative abundance (%)	1.9 ± 1.0	3.1 ± 1.3	<0.001
Escherichia-Shigella, relative abundance (%)	4.6 ± 2.3	2.1 ± 1.2	<0.001
Enterobacteriaceae, relative abundance (%)	3.2 ± 1.8	1.6 ± 0.9	<0.001
Prevotella, relative abundance (%)	5.1 ± 2.4	3.4 ± 1.7	<0.001
Fecal calprotectin, µg/g	118.6 ± 54.3	63.4 ± 29.7	<0.001

Table 3. Association of microbiome characteristics with severity of pelvic pain and gynecological symptoms

Variable	Mild–moderate pain (n=24)	Severe pain (n=36)	p-value
Shannon diversity index	3.76 ± 0.62	3.19 ± 0.68	0.002
Dysmenorrhea, n (%)	21 (87.5)	35 (97.2)	0.18

Variable	Mild–moderate pain (n=24)	Severe pain (n=36)	p-value
Deep dyspareunia, n (%)	10 (41.7)	25 (69.4)	0.035
Bowel-related symptoms, n (%)	7 (29.2)	22 (61.1)	0.017
Constipation, n (%)	6 (25.0)	19 (52.8)	0.036
Fecal calprotectin, µg/g	91.3 ± 39.5	136.8 ± 58.1	0.001
Faecalibacterium, %	4.5 ± 1.8	3.3 ± 1.5	0.008
Escherichia-Shigella, %	3.7 ± 1.9	5.2 ± 2.4	0.012
Advanced-stage endometriosis (III–IV), n (%)	7 (29.2)	22 (61.1)	0.015

Discussion: The present case-control study demonstrated significant differences in gut microbial diversity and selected bacterial taxa between women with endometriosis and chronic pelvic pain and healthy controls. Patients with endometriosis had lower alpha diversity, altered microbial community structure, reduced abundance of selected short-chain-fatty-acid-producing bacteria, and increased abundance of potentially pro-inflammatory bacterial groups.[11-13]

The observed reduction in microbial diversity suggests that endometriosis may be associated with a state of intestinal dysbiosis. Although reduced diversity is not specific to endometriosis, it may reflect an altered intestinal ecosystem influenced by chronic inflammation, hormonal exposure, dietary factors, medications, and gastrointestinal symptoms.[14-15]

Faecalibacterium and Roseburia were less abundant among women with endometriosis. These bacterial groups are commonly associated with the production of short-chain fatty acids, particularly butyrate. Butyrate contributes to intestinal epithelial integrity and has immunomodulatory effects. Reduced abundance of these organisms may therefore

be associated with impaired mucosal homeostasis and increased inflammatory activity.[16]

The higher abundance of Escherichia-Shigella and Enterobacteriaceae observed in the endometriosis group may indicate an increase in bacterial groups capable of contributing to inflammatory signaling. Some members of these groups may produce lipopolysaccharide, which can activate innate immune pathways and promote cytokine release.

However, the presence of a bacterial taxon does not necessarily indicate pathogenicity. Microbial function depends on strain-level characteristics, host immunity, diet, intestinal environment, and interactions with other microorganisms. Therefore, the observed bacterial differences should be interpreted as associations rather than direct evidence of causation.[17-19]

The relationship between gut microbiome and estrogen metabolism is particularly relevant to endometriosis. Certain intestinal bacteria participate in the deconjugation of estrogen metabolites, potentially influencing estrogen reabsorption and systemic estrogen availability. Altered microbial composition may therefore affect the hormonal environment that supports endometriotic lesion persistence.

The current study also demonstrated a significant association between lower microbial diversity and severe pelvic pain. Patients with severe pain had lower Shannon diversity and reduced abundance of Faecalibacterium and Roseburia. They also had higher abundance of Escherichia-Shigella.

Several mechanisms may explain this relationship. Microbial metabolites can influence immune activation, intestinal permeability, visceral sensitivity, and neuroinflammatory pathways. Chronic pelvic inflammation may also affect gastrointestinal function and microbial composition. The relationship is therefore likely bidirectional.[20]

Bowel symptoms were common among patients with endometriosis and were particularly frequent in women with severe pain and lower microbial diversity. Bloating, constipation, diarrhea, and painful defecation may arise from bowel endometriosis, adhesions, pelvic floor dysfunction, visceral hypersensitivity, or microbiome-related intestinal changes.

Fecal calprotectin was higher among patients with endometriosis, especially those with bowel symptoms. This finding may suggest increased intestinal inflammatory activity in a subset of patients. However, fecal calprotectin is nonspecific and may be

influenced by infection, inflammatory bowel disease, medications, and other gastrointestinal conditions.

The study identified several gynecological signatures associated with reduced microbial diversity, including severe dysmenorrhea, deep dyspareunia, advanced-stage disease, and higher pain scores. These associations suggest that microbiome changes may be more pronounced in clinically severe disease phenotypes.

The association between infertility and lower microbial diversity was not statistically significant in the present illustrative dataset. Infertility in endometriosis is influenced by multiple factors, including ovarian reserve, tubal distortion, adhesions, inflammatory mediators, altered follicular environment, and anatomical disease. Larger studies may be required to clarify whether specific microbial patterns are associated with reproductive outcomes.

Advanced-stage endometriosis was independently associated with severe pelvic pain. This finding is clinically plausible, although the relationship between anatomical stage and pain is not always linear. Some women with minimal disease may experience severe pain because of nerve sensitization, inflammatory mediator release, pelvic floor dysfunction, or central pain amplification.

Low microbial diversity remained independently associated with severe pain after adjustment for selected clinical variables. This suggests that microbial characteristics may provide additional information beyond anatomical disease stage. Nevertheless, residual confounding cannot be excluded.

Hormonal treatment may influence the gut microbiome through changes in estrogen exposure, intestinal motility, and immune regulation. The present study attempted to account for hormonal therapy, but detailed treatment duration, adherence, and type of hormonal medication may influence microbial findings.

Diet is another important confounder. Dietary fiber, fermented foods, fat intake, refined carbohydrates, and probiotic consumption can substantially influence gut microbial composition. Future studies should include detailed dietary assessment and preferably use standardized dietary protocols.

The present study has several strengths. It combined clinical gynecological assessment with microbiome analysis and included detailed evaluation of pain severity, bowel symptoms, disease stage, and reproductive characteristics. The inclusion of healthy controls also allowed direct comparison of microbial diversity and selected taxa.

However, several limitations must be considered. First, the case-control design cannot establish temporal or causal relationships. Second, the sample size was relatively small. Third, 16S rRNA sequencing provides information about bacterial composition but does not fully assess microbial function. Fourth, strain-level identification and metabolomic analysis were not performed. Fifth, diet, medication exposure, and hormonal therapy may have influenced microbial composition. Sixth, fecal microbiome findings may not reflect the microbiome of the female genital tract or endometriotic lesions. Finally, the numerical findings in this draft are hypothetical and must be replaced with actual data.

Future studies should include larger multicenter cohorts, longitudinal sampling, metagenomic and metabolomic analysis, assessment of estrogen-metabolizing bacterial genes, and evaluation of the vaginal and endometrial microbiome. Interventional studies involving dietary modification, probiotics, prebiotics, or targeted microbiome-based therapies may help determine whether microbiome manipulation can improve pain and quality of life.

Strengths and Limitations

Strengths

- Case-control comparison with healthy women.
- Combined assessment of microbiome and gynecological symptoms.
- Evaluation of pain severity and disease stage.
- Assessment of bowel symptoms and fecal inflammatory activity.
- Use of microbial diversity and relative abundance measures.

Limitations

- Cross-sectional case-control design.
- Small sample size.
- Potential dietary and medication-related confounding.
- Limited strain-level microbial information.
- No direct assessment of microbial metabolites.
- No vaginal or endometrial microbiome analysis.
- Lack of longitudinal follow-up.
- Hypothetical numerical results in the present draft.

Conclusion

Women with endometriosis and chronic pelvic pain demonstrated altered gut microbial diversity and differences in selected bacterial taxa compared with healthy controls.

Reduced abundance of selected short-chain-fatty-acid-producing bacteria and increased abundance of potentially pro-inflammatory

bacterial groups were associated with severe pelvic pain, bowel symptoms, and advanced-stage disease.

Lower microbial diversity was independently associated with severe pelvic pain, suggesting that gut microbiome alterations may represent a clinically relevant feature of endometriosis-associated pain. However, the direction of this relationship remains uncertain because inflammation, hormonal treatment, diet, and pain-related behavioral changes may also influence the microbiome.

The gut microbiome may have future value in clinical phenotyping and research into personalized treatment strategies for endometriosis. Larger prospective studies using functional microbiome analysis and longitudinal clinical assessment are required before microbiome-based diagnostic or therapeutic approaches can be recommended.

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