

**RESEARCH ARTICLE****Gut Microbiota Profile in Endometriosis Patients at Dr. M. Djamil Padang, West Sumatra, Indonesia**Haviz Yuad^{1,*}, Bobby Indra Utama², Nur Indrawaty Lipoeto³, Andani Eka Putra⁴¹ Endocrinology And Reproductive Fertility Division, Department Of Obstetrics And Gynecology, Faculty Of Medicine, Andalas University, Dr. M. Djamil Hospital, Padang, West Sumatra, Indonesia² Sub Division of Urogynecology, Obstetrics and Gynecology Department, Faculty of Medicine, Andalas University, Dr. M. Djamil Hospital, Padang, West Sumatra, Indonesia³ Department of Nutrition, Faculty of Medicine, Andalas University, Padang, West Sumatra, Indonesia⁴ Department of Biomedical, Faculty of Medicine, Andalas University, West Sumatra, Indonesia**Correspondence:** Haviz Yuad; yuadhaviz@gmail.com ; +62 813-6313-5810**Doi :** <https://doi.org/10.25077/aoj.9.1.134-145.2025>**Abstract****Objective:** Endometriosis (EMS) is a chronic gynecological condition affecting up to 10% of women worldwide. The pathogenesis associated with hormonal imbalance, immune dysregulation, and changes in the gut microbiota. Gut microbiota dysbiosis may drive chronic inflammation that contributes to the progression of EMS. This study hypothesizes that certain gut microbiota profiles are associated with these factors in EMS patients, potentially developing non-invasive diagnostics and more targeted therapies.**Methods:** This is an observational analytical study with a case-control design conducted at Dr. M. Djamil Padang General Hospital in May 2024 with a sample size of 44 people. Case samples were women aged 18–40 years who were diagnosed with endometriosis based on the inclusion criteria, while the control group were women of reproductive age without a diagnosis of endometriosis. Data testing used the Next Generation Sequencing method, microbiome analysis test, and SPSS test.**Results:** The majority of EMS patients were aged 30-37 years, married, and had Nullipara obstetric status. In addition, the gut microbiota was dominated by the phyla Bacteroidetes and Firmicutes.**Conclusion:** There is a relationship between gut microbiota dysbiosis and the incidence of endometriosis, namely an increase in Bacteroidetes and a decrease in Firmicutes**Keywords:** endometriosis, dysbiosis, bacteroides, firmicutes, gut microbiota

INTRODUCTION

Endometriosis is a gynecological disease characterized by the formation of ectopic endometrial implants in the peritoneal cavity and other estrogen-dependent body parts. The prevalence is estimated at 10% worldwide and increases to 50% in women with infertility or chronic pain. Endometriosis (EMS) is chronic so it can affect women's health and quality of life.¹ EMS usually affects women aged 15-49 years. This disease is a heterogeneous disease that can appear in various forms, including superficial peritoneal disease, ovarian endometrioma, and deep infiltrating endometriosis.² The recurrence rate of EMS is quite high, namely 23-56% with diagnosis often being delayed for up to 7-9 years. This is influenced by a number of factors, such as the onset or early attack of symptoms, pain that is considered normal, to misdiagnosis. The incidence of EMS in Indonesia cannot be estimated because there have been no specific epidemiological studies on EMS cases in Indonesia.³

Deregulation of immune homeostasis due to microbiological disorders can cause chronic inflammation, thus creating an environment conducive to increased adhesion and angiogenesis involved in the development of endometriosis.⁴ Gut microbiota plays an important role in the development of many diseases, including endometriosis associated with changes in the composition and function of the gut microbiota, such as dysbiosis.⁵ Changes in the gut and reproductive tract microbiota can cause changes in the immune response. Dysbiosis disrupts immune function causing an increase in proinflammatory cytokines that interfere with immune surveillance and change the profile of immune cells, so that immune dysregulation can develop into a state of chronic inflammation, creating an environment that maintains a vicious cycle, the onset, and development of EMS.⁶

Laparoscopic procedures followed by histopathological examination are still the standard diagnosis in EMS, but this has the disadvantage of being invasive. So it is necessary to develop a non-invasive diagnostic that can help reduce the incidence of late diagnosis and anticipate before the disease reaches a more advanced stage. Identifying the composition of the microbiome that is specific to the disease will allow the development of non-invasive diagnostics that can help reduce the incidence of delayed diagnosis and anticipate before the disease is at a more advanced stage.⁷ Characteristic findings from laparoscopy are typical lesions resembling powder burn or gunshot on the surface of the serous peritoneum and infection carefully of both ovaries. Management of endometriosis can be in the form of medical therapy, operative, and a combination of medical and operative therapy.⁸

Therefore, further research on the gut microbiota will deepen the understanding of EMS and provide a theoretical basis for becoming a new treatment method. In addition, it is necessary to recognize the gut microbiota profile so that it can be used as a new parameter in controlling EMS cases. Based on the background above, the author is interested in examining how the gut microbiota profile is in EMS patients and those without EMS, and how the relationship between the microbiota dibiosis is.

This study is an analytical observational study with a case-control study design. This study will be conducted in May 2024 which is estimated to last around 2-3 months until the required number of samples is met as many as 44 samples. This study was conducted at Dr. M. Djamil General Hospital, Padang City and sample examination will be carried out at the Infectious Disease Diagnostic and Research Center Laboratory (PDRPI) of the Faculty of Medicine, Andalas University. The sample in this study were endometriosis patients at Dr. M. Djamil General Hospital, Padang who met the inclusion and exclusion criteria, while the control group were women of reproductive age who were not diagnosed with endometriosis and met the control criteria.

The inclusion criteria for cases include fertile women aged 18-40 years who are diagnosed with EMS with a BMI of 18.50-22.9 kg/m² and agree to the informed consent form. No history of bowel surgery, bowel treatment in the last 6 months, and no family history of colon disease such as colon cancer or IBD. Not taking probiotics, antibiotics, or glucocorticoids in the last 3 months. Not using any hormone therapy in the last 6 months. Not having a special dietary habit, such as a vegan or meat-free diet, spicy foods, or an acidophilic diet. While the exclusion criteria for cases are postmenopausal women, pregnant and lactating women, and those with immune disorders.

The samples were selected by consecutive sampling and the examinations carried out were anamnesis, clinical and gynecological examinations, and filling out the research questionnaire. The research tools and materials were ELISA Kit, Biberoglu - Behrman score, 2-8 ° C refrigerator, vacuum sterile tube, miSeq illumina Next Generation Sequencing, sterile Handscoon, cotton, feces pot, feces, and QIAamp DNA Mini Kit. Bivariate analysis was carried out to determine the relationship between two variables, namely the dependent and independent variables. The relationship between variables will be significant if the p-value ≤ 0.05 with 95% CI (Confidence Interval). The data analysis used was the T-test if the data was normally distributed or the Man Whitney test if the data was not normally distributed.

RESULT AND DISCUSSION

Based on Table 1, it was found that women with endometriosis were mostly aged 30-37 years (45%), had a high school and bachelor's degree (36%), worked as housewives (36%), had a cesarean birth (55%), did not receive breast milk (55%), were married (91%), and had a nulliparous obstetric status (86%). Meanwhile, women without endometriosis were mostly aged 30-37 years (41%), had a bachelor's degree (59%), were private (27%), had a normal birth (64%), received breast milk (73%), were married (86%), and had a multiparous obstetric status (55%).

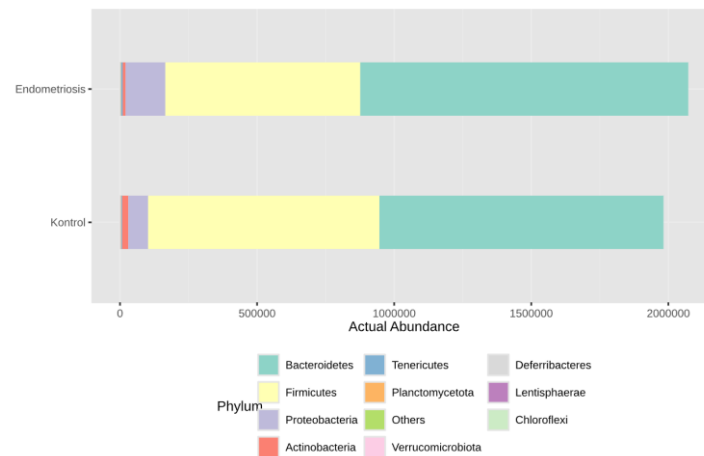


Figure 1. Gut Microbiota Based on Phylum

Figure 1 shows a graph of microbiota diversity in women with endometriosis and without endometriosis. It can be seen that Bacteroidetes are more abundant in endometriosis patients compared to control patients, while Firmicutes are more abundant in controls compared to endometriosis.

Table 1. Overview of Gut Microbiota Based on Phylum

Microbiota	Total Reads	
	Control	Endometriosis
Actinobacteria	22.478	10.286
Bacteroidetes	1.036.362	1.196.836
Chloroflexi	344	299
Deferribacteres	625	646
Firmicutes	843.803	710.983
Lentisphaerae	416	320
Others	995	1.195
Planctomycetota	1.350	926
Proteobacteria	71.864	144.673
Tenericutes	3.245	6.001
Verrucomicrobiota	774	541

Table 1 shows a list of the ten most abundant microbiota in the intestines of EMS sufferers based on phyla, including Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, Tenericutes, Planctomycetota, Deferribacteres, Verrucomicrobiota, Lentisphaerae, and Chloroflexi. The intestinal microbiota of this group is dominated by the Bacteroidetes phylum. Bacteroidetes microbiota in the study sample was found to be more abundant in women with endometriosis, 1,196,836 compared to control 1,036,362. The second most abundant microbiota that dominates is Firmicutes. In the Firmicutes microbiota, it was found that more women without endometriosis had Firmicutes microbiota, 843,803 compared to cases 710,983. It can be seen that there are other microbiota found in the intestines of women with and without endometriosis in general. The following are details of the gut microbiota found in each sample.

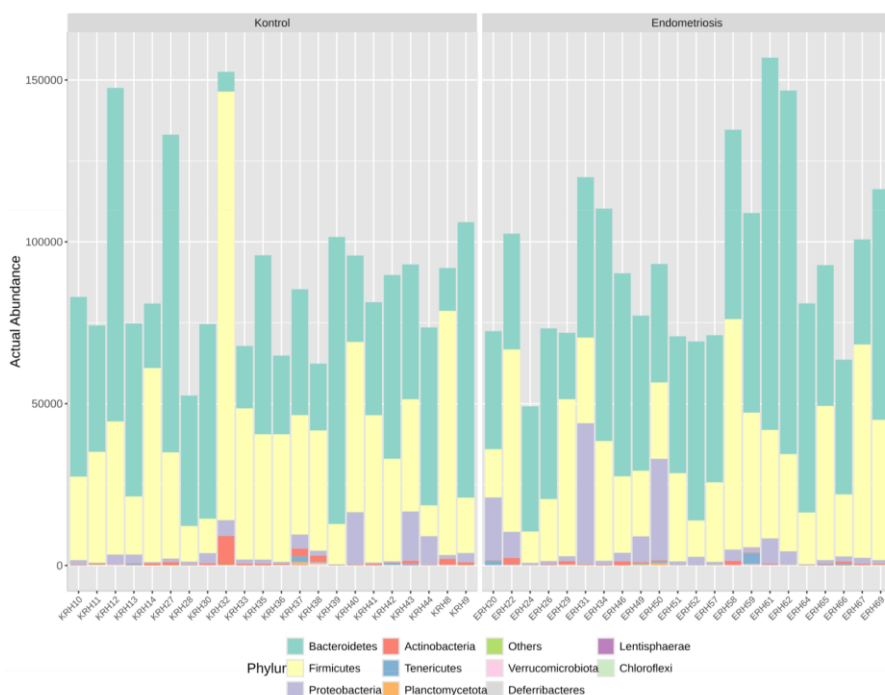


Figure 1. Comparison of Microbiota in Samples

Table 2. Overview of Gut Microbiota by Species

No.	Filum	Spesies	EMS	Bukan EMS
1	<i>Bacteroides</i>	<i>Prevotella copri</i>	465705	428121
2	<i>Firmicutes</i>	<i>Faecalibacterium prausnitzii</i>	150164	182763
3	<i>Bacteroides</i>	<i>Bacteroides fragilis</i>	94129	5236
4	<i>Bacteroides</i>	<i>Bacteroides coprocola</i>	56192	7704
5	<i>Bacteroides</i>	<i>Bacteroides vulgatus</i>	49244	69782
6	<i>Bacteroides</i>	<i>Bacteroides paurosaccharolyticus</i>	34857	2143
7	<i>Firmicutes</i>	<i>Flavonifractor plautii</i>	34516	27214
8	<i>Firmicutes</i>	<i>Pseudobutyrvibrio ruminis</i>	31301	32808
9	<i>Bacteroides</i>	<i>Alistipes senegalensis</i>	29052	22611
10	<i>Bacteroides</i>	<i>Prevotellamassilia timonensis</i>	28246	18783
11	<i>Firmicutes</i>	<i>Roseburia faecis</i>	18445	39606
12	<i>Firmicutes</i>	<i>Gemmiger formicilis</i>	18127	17592
13	<i>Bacteroides</i>	<i>Alloprevotella rava</i>	15504	13749
14	<i>Bacteroides</i>	<i>Bacteroides eggerthii</i>	13495	652
15	<i>Bacteroides</i>	<i>Bacteroides thetaiotaomicron</i>	13293	6787
16	<i>Firmicutes</i>	<i>Ruminococcus albus</i>	12426	14998
17	<i>Bacteroides</i>	<i>Barnesiella intestinihominis</i>	11156	8563
18	<i>Bacteroides</i>	<i>Bacteroides caccae</i>	10169	10319
19	<i>Bacteroides</i>	<i>Odoribacter splanchnicus</i>	8910	7607
20	<i>Firmicutes</i>	<i>Megamonas funiformis</i>	8895	29914
21	<i>Bacteroides</i>	<i>Dysgonomonas sp</i>	8415	9374
22	<i>Firmicutes</i>	<i>Eubacterium hallii</i>	6434	7820
23	<i>Firmicutes</i>	<i>Acidaminococcus intestini</i>	5892	6009
24	<i>Firmicutes</i>	<i>Roseburia inulinivorans</i>	2628	9279
25	<i>Firmicutes</i>	<i>Eubacterium eligens</i>	2619	11843

Table 3 lists the 25 most abundant microbiota in the intestines of endometriosis sufferers based on species, including *Prevotella copri*, *Faecalibacterium prausnitzii*, *Bacteroides fragilis*, *Bacteroides coprocola*, and *Bacteroides vulgatus*. The intestinal microbiota of this group is dominated by the species *Prevotella copri*. *Prevotella copri* (Phylum Bacteroides) in the study sample was found to be more abundant in women with endometriosis, namely 465,705 compared to women without endometriosis 428,121.

The second most abundant microbiota that dominates is *Faecalibacterium prausnitzii*. In *Faecalibacterium prausnitzii* (Phylum Firmicutes), it was found to be more abundant in women without endometriosis, namely 182,763 compared to women with endometriosis 150,164. The following is a comparison of the significance between the Bacteroidetes and Firmicutes microbiota found in women with and without endometriosis.

Tabel 3. Comparison of Significance of Microbiota Based on Phylum

Microbiota	Total Reads		P-value	Mean	
	Control	EMS		Control	EMS
Bacteroidetes	1.036.362	1.196.836	0,001	15,82	29,18
Firmicutes	843.803	710.983	0,027	26,77	18,23

Changes in the ratio of Firmicutes to Bacteroides (F/B) can indicate changes in gut health. In the control group, the F/B ratio was 1:1.23, while in the EMS group, this ratio decreased to 1:1.68. This decrease in the ratio indicates that the relative amount of Firmicutes is lower than Bacteroidetes in endometriosis cases. With a decrease in the F/B ratio in the control and F/B in the case of 0.8:0.6, the ratio of Firmicutes to Bacteroidetes (F/B) is greater in the control group than in the EMS group, thus proving that there is a change in the balance of the microbiota.

After statistical testing, it was found that Bacteroides and Firmicutes both had a significant relationship to changes in the microbiota in EMS and non-EMS women. In Bacteroides, a p-value of 0.001 was obtained with a mean of 29.18 in endometriosis and a mean of 15.82 in controls, proving that Bacteroides is more dominant in Endometriosis than in controls. Meanwhile, in Firmicutes, a p-value of 0.027 was obtained with a mean of 18.23 in endometriosis and 26.77 in controls, which proves that Firmicutes are more dominant in controls compared to EMS.

Comparison of ratios is also done based on species, the following is a comparison of microbiota ratios based on species.

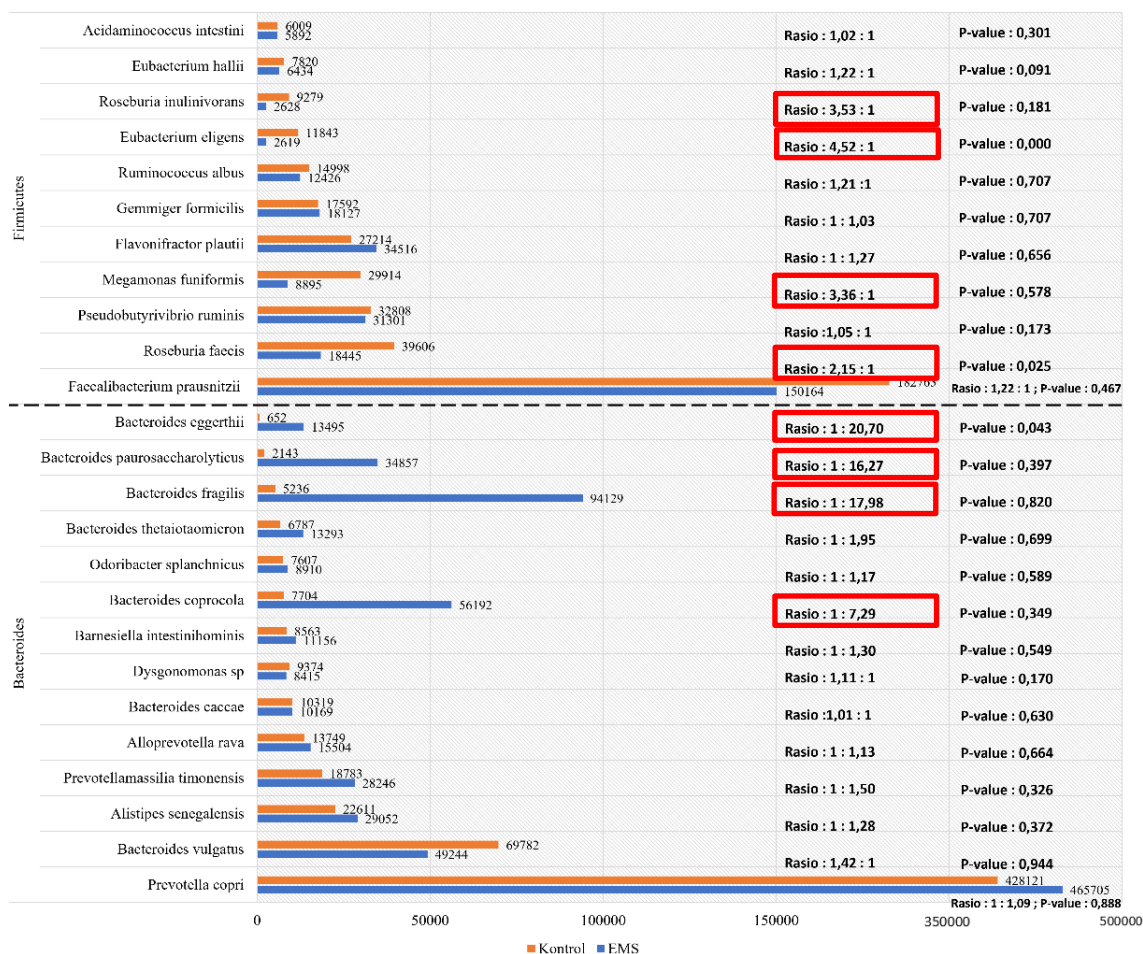


Figure 3. Comparison of Microbiota by Species

In Figure 3 there is a comparison of the ratio of microbiota based on species. In Firmicutes, species that have a high ratio difference between non-endometriosis and endometriosis are Eubacterium eligens, Roseburia inulinivorans, Megamonas fumiformis, and Roseburia faecis, while in Bacteroides, species that have a high ratio difference between non-endometriosis and endometriosis are Bacteroides eggerthii, Bacteroides fragilis, Bacteroides paurosaccharolyticus, and Bacteroides coprocola.

Table 4. Comparison of Significance of Microbiota Based on Species

No	Phylum	Species	EMS	Control	p	Mean	
						EMS	Control
1	Bacteroidetes	Bacteroides_eggerthii	13.495	652	0,043	26,36	18,64
2	Firmicutes	Eubacterium_eligens	2.619	11.843	0,000	15,43	29,57
3	Firmicutes	Roseburia_faecis	18.445	39.606	0,025	18,16	26,84

After conducting a significance test on 25 species, 3 species were found to contribute to dysbiosis in women with endometriosis compared to controls. In Bacteroides eggerthii, a p-value of 0.043 was obtained with a mean of 26.36 in women with endometriosis, which means that Bacteroides eggerthii was more abundant in women with endometriosis. Meanwhile,

Eubacterium eligens ($p = 0.000$ mean 29.57) and *Roseburia faecis* ($p = 0.025$ mean 26.84) were more abundant in controls than in women with endometriosis. With the microbiota profile above, it can be seen that patients with endometriosis experience an imbalance or disruption of the microbiota caused by an increase or decrease in microbes called dysbiosis.

Bacteriodes and Firmicutes are two major groups of bacteria found in the human gut microbiota. Bacteriodes mycobiota are a group of gram-negative bacteria that generally play a role in the metabolism of complex carbohydrates and can influence the immune response.⁹ In cases of endometriosis, increased numbers of Bacteriodes bacteria are associated with changes in metabolism and increased inflammation.¹⁰ Meanwhile, Firmicutes gut microbiota include *Lactobacillus* which play a role in digestion and the production of short-chain fatty acids (SCFA) which have anti-inflammatory effects. Gut microbiota plays a pivotal role in the regulation of metabolic, endocrine, and immune functions. Bacterial metabolites include the short chain fatty acids (SCFAs) acetate (C2), propionate (C3), and butyrate (C4), which are the most abundant SCFAs in the human body and the most abundant anions in the colon.¹¹ A certain dysbiosis of the gut microbiota is known as the “estrobolom” which has the ability to metabolize estrogen and increase circulating estrogen levels in the body.¹² This estrobolome is known to produce the enzymes β -glucuronidase and β -glucosidase, which conjugate estrogen and increase the reabsorption of free estrogen in the intestine. This condition can cause a state of hyperestrogenism that plays a role in the development of endometriosis.¹³

The enzyme β -Glucuronidase was first identified in 1934 in *Escherichia coli* and other Enterobacteriaceae. After that, other bacteria were detected in the intestinal microbiota, namely Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria. The enzyme β -Glucuronidase is an enzyme that can remove glucuronic acid from glucuronide, reversing phase II metabolism carried out by liver enzymes on endobiotics and xenobiotics to facilitate their excretion from the body.¹⁴ Estrogen in the human body comes from the ovaries, adrenal glands and adipose tissue, and then enters the blood circulation until it is metabolized in the liver.¹⁵ In the liver, estrogen combines with its metabolites to produce conjugated estrogen, which is then metabolized into water-soluble molecules that are excreted in urine and feces.¹⁶ Imbalance of intestinal flora produces beta-glucuronidase, which prevents the combination of estrogen and glucuronic acid to reduce estrogen inactivation and to increase the level of estrogen circulation through enterohepatic circulation, thereby significantly stimulating the growth of ectopic lesions and participating in the pathological process of endometriosis periodic bleeding.¹⁷

A study conducted by Chadchan et al in mice, by providing surgically induced endometriosis treatment intervention, found increased levels of Bacteriodes and decreased levels of Firmicutes in the composition of the gut microbiota compared to the control group.¹⁸ This study is also in line with the research of Anjeza Xholli et al which showed that endometriosis is associated with a decrease in the number of *Lactobacilli* bacteria and an increase in the concentration of gram-negative bacteria.¹⁹ The increased presence of Bacteriodes in patients with endometriosis may be related to its role in modulating the immune response. These bacteria can affect T cell differentiation, which drives the Th1/Th2 balance that may be skewed

towards inflammation in endometriosis patients.⁴ Bacteroides are also involved in estrogen metabolism, potentially leading to higher local estrogen levels. Since endometriosis is an estrogen-dependent condition, these interactions may exacerbate the growth of ectopic endometrial tissue, further perpetuating the cycle of inflammation and dysbiosis.^{5,19}

The human oestrobolome and microbiome have the potential to contribute to hormonal dysregulation that may lead to estrogen-mediated diseases.²⁰ Estrogen is a key factor contributing to the pathogenesis of EMS. Endometriosis is fundamentally an estrogen-dependent condition. High levels of estrogen, particularly estradiol (E2), promote the proliferation and survival of endometriotic tissues, leading to the growth of lesions and associated symptoms such as pain and inflammation.^{21,22} Therefore, when estrogen metabolism is dysregulated, estrogen-mediated diseases will be negatively impacted, and this may contribute to disease pathogenesis. The oestrobolome may alter circulating estrogen levels through deconjugation of its conjugate (glucuronic acid), thereby potentially influencing estrogen-mediated disorders. In addition, the microbiome may alter an individual's metabolism and levels of systemic/local inflammation.²³

The decrease in Firmicutes, which are commonly associated with anti-inflammatory effects and metabolic health, suggests a loss of protective microbiota in endometriosis patients. This decrease may lead to decreased production of beneficial short-chain fatty acids (SCFAs), which are critical for maintaining gut barrier integrity and regulating immune function.^{5,19} The lower abundance of Firmicutes leads to an impaired immune response, resulting in increased pro-inflammatory cytokines that may exacerbate the inflammatory environment associated with endometriosis. This dysregulation may impair immune surveillance, allowing the persistence and growth of ectopic endometrial tissue. Dysbiosis causes changes in the immune profile characterized by increased Th17 cells and pro-inflammatory cytokines such as IL-17, which have been correlated with disease severity in endometriosis patients.^{4,5}

In addition, gut microbiota dysbiosis can also cause immune system dysfunction, resulting in activation of innate and adaptive immune responses and decreased immunity and increased pro-inflammatory cytokines, proangiogenic/growth factors. Increased pro-inflammatory cytokines can also be caused by retrograde menstruation, in which the backflow of menstrual blood containing endometrial tissue through the fallopian tubes spills out and implants in the peritoneal cavity, this is also known to be the cause of endometriosis. Management of endometriosis involves conservative or radical surgery, or medical therapy. Therefore, finding a safe and effective way to prevent and treat endometriosis has become a global focus, especially for women of childbearing age with endometriosis. Imbalance of gut microbiota has many adverse effects on the body, so it is necessary to regulate gut microbiota through antibiotics, fecal bacterial transplantation, probiotics, nutrition, and others can provide new ideas for clinical treatment of endometriosis.^{24,25}

CONCLUSION

The majority of endometriosis patients are aged 30-37 years, married and have a Nullipara obstetric status. In addition, the intestinal microbiota is dominated by the phyla Bacteroidetes and Firmicutes. There is a relationship between intestinal microbiota dysbiosis and the incidence of endometriosis, and also increase in Bacteroidetes and a decrease in Firmicutes. There are 3 species were found to contribute to dysbiosis in women with endometriosis, it's *Bacteroides eggerthii* ($p = 0.043$), *Eubacterium eligens* ($p = 0.0002$) and *Roseburia faecis* ($p = 0.025$).

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