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## Gut microbiota and female health

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### Abstract

The gut microbiota is recognized as an endocrine organ with the capacity to influence distant organs and associated biological pathways. Recent advancements underscore the critical role of gut microbial homeostasis in female health; with dysbiosis potentially leading to diseases among women such as polycystic ovarian syndrome, endometriosis, breast cancer, cervical cancer, and ovarian cancer *etc.* Despite this, there has been limited discussion on the underlying mechanisms. This editorial explores the three potential mechanisms through which gut microbiota dysbiosis may impact the development of diseases among women, namely, the immune system, the gut microbiota-estrogen axis, and the metabolite pathway. We focused on approaches for treating diseases in women by addressing gut microbiota imbalances through probiotics, prebiotics supplementation, and fecal microbiota transplantation (FMT). Future studies should focus on determining the molecular mechanisms underlying associations between dysbiosis of gut microbiota and female diseases to realize precision medicine, with FMT emerging as a promising intervention.

**Key Words:** Gut microbiota; Female health; Estrogen; Polycystic ovarian syndrome; Endometriosis

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**Core Tip:** Maintaining intestinal microbial homeostasis is essential for human health. Dysbiosis of gut microbiota has been demonstrated in patients with polycystic ovarian syndrome, endometriosis, breast cancer, cervical cancer, and ovarian cancer, disordered gut microbiota may affect the occurrence and development of these diseases through the immune system, estrogen, or metabolite pathways. In the future, maintaining gut microbiota homeostasis may be a promising treatment.

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## INTRODUCTION

The human body contains trillions of microbes, rapidly diversifying after birth. Recent developments in genome sequencing, transcriptome analysis, and metabolomics have enabled researchers to explore the microbiota in more detail, particularly their functions. The gut microbiota plays a pivotal role in nutrient transformation and absorption, maintaining vital interactions with multiple tissues and organs, an indispensable factor for human health. The primary bacteria found in the gut are *Firmicutes* and *Bacteroidetes*, accounting for 90% of the flora in the gut[1], other bacterial constituents include *Actinobacteria* and *Proteobacteria*.

While a universally healthy gut microbiota remains undefined, dysbiosis has been associated with diseases ranging from irritable bowel syndrome to cancer. Previous studies have reported sex differences in the distribution of gut microbiota and disease prevalence[2], of which, the female gut microbiota emerges as a compelling area for investigation. Marano *et al*[3] underscore the strategic role of gut microbiota in crucial life stages for women, from childhood through adolescence, fertile age to pregnancy-partum, and up to menopause. This editorial aimed to discuss the potential mechanisms and therapeutic targets associated with the impact of gut microbiota dysbiosis on female diseases.

## POSSIBLE MECHANISMS OF GUT MICROBIOTA DYSBIOSIS AFFECTING FEMALE HEALTH

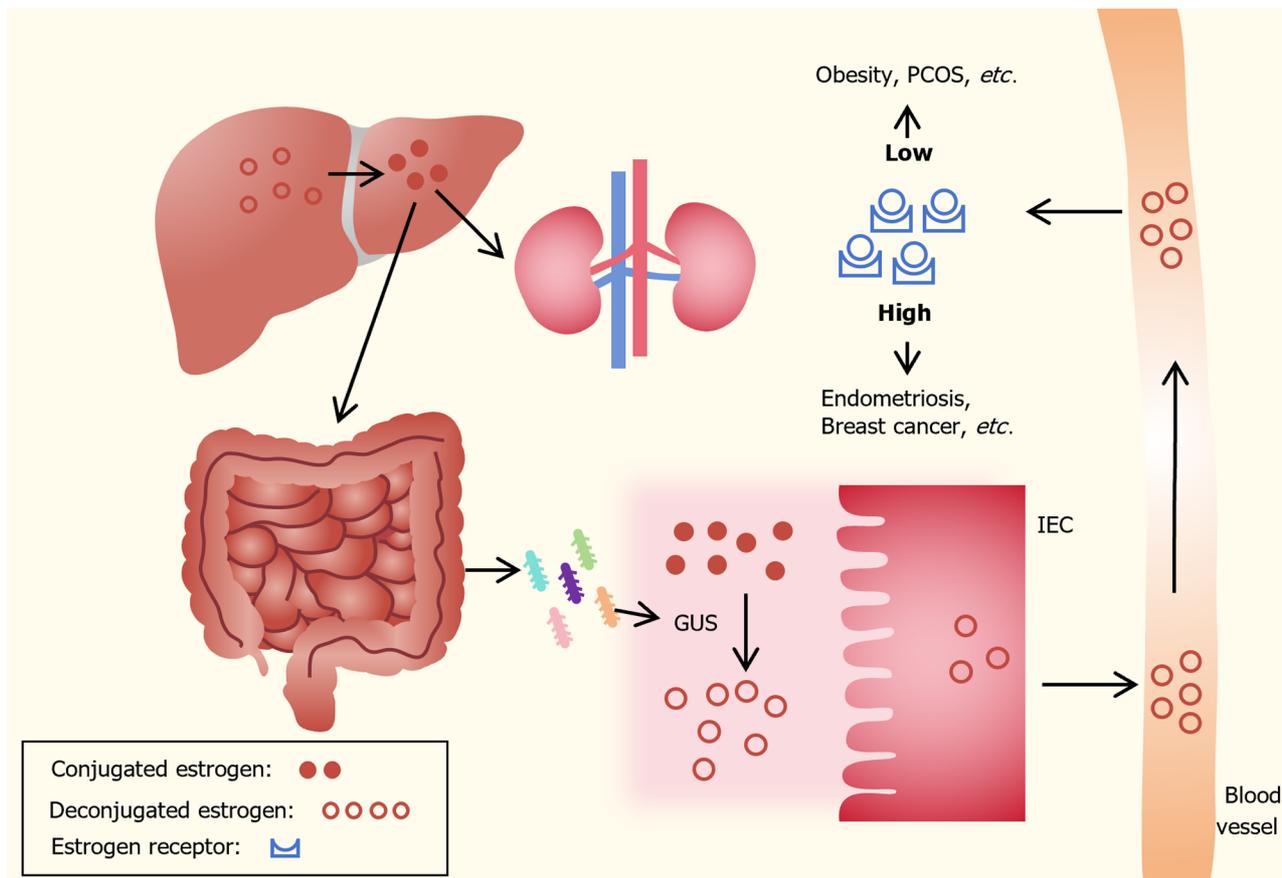
### Immune system

The gut microbiota can both promote and inhibit inflammatory response by influencing inflammatory factors, thus affecting the onset and progression of female diseases. In a study by Xu *et al*[4], ovarian cancer cells transplanted into mice with gut microbiota dysbiosis demonstrated increased xenograft tumor sizes. This dysbiosis stimulated macrophages, resulting in increased circulating levels of interleukin (IL)-6 and tumor necrosis factor- $\alpha$ , thus inducing the progression of ovarian cancer epithelial-mesenchymal transition[4]. One study examined the gut microbiota in patients with preeclampsia, revealing that *Akkermansia muciniphila* significantly suppressed inflammation and alleviated preeclamptic symptoms in rats by promoting autophagy and M2 polarization of macrophages in the placental bed[5]. Dysbiotic shifts in the gut microbiota are associated with increased gut permeability, leading to increased translocation of bacterial endotoxins, primarily lipopolysaccharide (LPS)[6]. The activation of the innate immune system through toll-like receptor 4 by LPS increases the expression of proinflammatory cytokines *via* nuclear factor  $\kappa$ B translocation[7].

### Gut microbiota - estrogen axis

In premenopausal women, ovaries use cholesterol derived from saturated fats for estrogen synthesis. Following menopause, adipose tissue, adrenal glands, and other organs convert circulating androgens into estrogens through the aromatase enzyme[8,9]. As shown in Figure 1, circulating estrogens undergo conjugation in the liver through glucuronidation or sulfonation, facilitating their excretion in bile, urine, and stool. The gut microbiota significantly influences estrogen levels by secreting  $\beta$ -glucuronidase (GUS), an enzyme that converts conjugated estrogen into deconjugated estrogen in the gastrointestinal tract. This transformation allows it to bind to estrogen receptors, initiating downstream signaling and physiological effects[10,11]. In the lower female reproductive tract, estrogen regulates the microenvironment by increasing epithelial thickness, glycogen levels, mucus secretion, and indirectly lowering vaginal pH through the promotion of *Lactobacilli* abundance and lactic acid production[12]. Additionally, estrogen can modify gut epithelial barrier integrity[13].

Decreased GUS activity may lead to reduced deconjugation of estrogen, resulting in decreased circulating estrogen levels and contributing to pathologies such as obesity and polycystic ovarian syndrome (PCOS). In contrast, increased GUS activity can elevate estrogen levels, leading to conditions such as endometriosis and cancer[14,15]. Endogenous estrogen is a major factor in the development of postmenopausal breast cancer. Certain bacterial genera and species in the human gut, including *Bacteroides*, *Escherichia*, and *Lactobacillus*, contain genes encoding GUS[16]. In a study on mice with letrozole-induced PCOS, serum estradiol levels positively correlated with the abundance of *Bifidobacterium* and *Bacteroides*, while negatively correlating with the abundance of *Prevotella*[17]. The investigation by Shin *et al*[18] on 26 healthy women revealed that those in the high-estradiol group harbored a more diverse gut microbiota compared to the low- and medium-estradiol groups. The drop in serum estradiol concentration was attributed to the relative overabundance of *Slackia* and *Butyrivimonas*[18]. Another study found a significant and positive association between non-ovarian urine



**Figure 1 Effects of gut microbiota on estrogen metabolism.** Estrogens are primarily produced in the ovaries, adrenal glands, and adipose tissue and circulate in the bloodstream and first undergo metabolism in the liver, where estrogens are conjugated. Conjugated estrogens are eliminated from the body by metabolic conversion to water-soluble molecules, which are excreted in urine or bile into the gut. The gut microbiota significantly influences estrogen levels by secreting  $\beta$ -glucuronidase (GUS), an enzyme that converts conjugated estrogen into deconjugated estrogen in the gastrointestinal tract. This transformation allows it to bind to estrogen receptors, initiating downstream signaling and physiological effects. Decreased GUS activity may lead to reduced deconjugation of estrogen, resulting in decreased circulating estrogen levels and contributing to pathologies such as obesity and polycystic ovarian syndrome. In contrast, increased GUS activity can elevate estrogen levels, leading to conditions such as endometriosis and cancer. IEC: Intestinal epithelial cell; GUS:  $\beta$ -glucuronidase; PCOS: Polycystic ovarian syndrome.

estrogen levels and *Clostridia* taxa in the *Firmicutes* (including *non-Clostridiales* and three genera in the family *Ruminococcaceae*)[19].

### Metabolite pathway

Through the breakdown of organic matter, gut microbiota produces metabolites such as short-chain fatty acids (SCFA) and bile acids. SCFAs, including acetic acid, propionic acid, and butyric acid, provide energy for colon cells, regulate the intestinal barrier, and influence the inflammatory response[20-23]. *Firmicutes* predominantly synthesize butyrate[24], while *Bacteroides* are major producers of acetate and propionate[25]. Butyric acid has been shown to regulate progesterone and estradiol secretion through the cAMP signaling pathway in porcine granulosa cells[26]. The study by Liu *et al*[27] demonstrated that supplementing with butyrate can alleviate nonalcoholic fatty liver disease in ovariectomized mice. One study found that SCFAs have anti-inflammatory properties mediated through the G protein-coupled receptor pathway and histone acetylase[28]. Notably, SCFAs may have anti-cancer properties in cervical cancer through the activation of free fatty acid receptor 2[29].

Bile acid plays an important role in maintaining intestinal homeostasis, regulating lipid and carbohydrate metabolism, and influencing immune function. The study by Qi *et al*[30] reported that elevated levels of *Bacteroides vulgatus* were observed in the gut microbiota of individuals with PCOS, and this elevation was accompanied by reduced levels of glycodeoxycholic acid and tauroursodeoxycholic acid. The study found that glycodeoxycholic acid induced intestinal group 3 innate lymphoid cell IL-22 secretion through GATA binding protein 3. IL-22, in turn, improved the PCOS phenotype[30]. In an *in vitro* experiment, it was demonstrated that urolithin A reduces the Rac1 and PAK1 activity, leading to a decrease in actin polymerization and consequently reducing cell migration in human endometrial carcinoma cells[31], urolithin A may offer new avenues for the development of novel cancer therapeutics.

## CHANGES OF GUT MICROBIOTA IN PATIENTS

### PCOS

PCOS is a prevalent endocrine disorder in women, characterized by symptoms such as anovulation, obesity, insulin resistance, and hyperandrogenism. Tremellen and Pearce[32] highlighted that disturbances in the gut microbiota resulting from a poor diet can lead to increased gut mucosal permeability. Subsequently, this allows LPS from Gram-negative colonic bacteria to enter the systemic circulation. The subsequent activation of the immune system interferes with insulin receptor function, elevating serum insulin levels, consequently contributing to increased androgen production by the ovaries and disruption of normal follicle development[32]. A study involving 18 obese patients with PCOS and 15 obese women without PCOS revealed that the richness and diversity of gut microbiota were lower in the obese PCOS group compared to the control group, *Lachnospirillum*, *Fusobacterium*, *Coprococcus\_2*, and *Tyzzera* 4 were identified as the characteristic genera in obese patients with PCOS[33]. Additionally, mice transplanted with stool from women with PCOS exhibited fewer pups compared to mice transplanted with stool from healthy controls[30]. Modulating gut microbiota could hold significant value for the treatment of PCOS[34,35].

### Endometriosis

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial tissue (glands and stroma) outside the uterus, significantly impacting the quality of life of women of childbearing age[36]. Although endometriosis is known to be estrogen-dependent, studies have revealed that the growth of ectopic lesions persists even in ovariectomized animals. This suggests that in addition to ovarian steroids, the innate immune system of the pelvic environment can also regulate the growth of ectopic lesions in endometriosis[37]. Notably, gut microbiota dysbiosis has been associated with the occurrence and development of endometriosis. A study involving 14 women with histologically confirmed stage 3/4 endometriosis and 14 healthy controls demonstrated significant decreases in the genera *Sneathia*, *Barnesiella*, and *Gardnerella* in stool samples of the endometriosis group[38]. Two patients in the endometriosis group exhibited higher levels of *Escherichia/Shigella* in stool, and subsequent follow-up revealed severe bowel involvement by endometriosis in these patients[38]. Moreover, a study using antibiotic-induced microbiota-depleted (MD) mice to investigate endometriosis progression demonstrated that MD mice exhibited reduced endometriotic lesion growth, and the transplantation of gut microbiota through oral gavage of feces from mice with endometriosis caused the endometriotic lesion growth[39]. Thus, these findings underscore the close relationship between the occurrence and development of endometriosis and gut microbiota.

### Cancer

Dysbiosis of microbiota can impact the occurrence and progression of tumors by regulating host immune response and inflammatory pathways. Breast cancer is one of the most prevalent malignant tumors among women worldwide and is closely linked to estrogen levels. The gut microbiota plays a role in deconjugating estrogens through the bacterial secretion of GUS, enabling estrogens to bind to estrogen receptors. Subsequently, the activation of estrogen receptors increases the number of G0/G1 cells entering the cell cycle, promoting cell proliferation, which is particularly well-defined in breast cancer[40]. The study conducted by Bobin-Dubigeon *et al*[41] demonstrated a reduction in gut microbiota diversity, a relative enrichment in *Firmicutes*, and a depletion in *Bacteroidetes* among patients with breast cancer as compared to those of healthy women. In another controlled study, patients with breast cancer exhibited a lower abundance of some microbial taxa, including *Bacteroidetes* phylum, *Firmicutes* phylum, *Verrucomicrobia* phylum, *Clostridium* genus, *Shigella* genus, *Bifidobacterium* genus, *Akkermansia muciniphila*, *Clostridium perfringens*, *Escherichia coli*, *Bacteroides uniformis*, *Clostridium hathewayi*, and *Faecalibacterium prausnitzii*[42].

Cervical cancer ranks as the fourth most common cancer in terms of morbidity and mortality, primarily attributed to human papillomavirus infection. In a study involving 42 patients with cervical cancer, gut microbiota 16S rDNA analysis revealed differences in both  $\alpha$  and  $\beta$  diversity between the patient group and the control group[43]. The patient group exhibited a higher abundance of *Prevotella*, *Porphyromonas*, and *Dialister*, while the control group showed a higher abundance of *Bacteroides*, *Alistipes*, and members of the *Lachnospiracea* family[43]. Additionally, Chang *et al*[44] conducted an enrichment analysis of gut microbiota from patients with cervical cancer patients and healthy controls and found that the functions of the differentially expressed genes in the two groups, primarily associated with REDOX reactions, biosynthesis of other secondary metabolites, and amino acid transport and metabolism.

Ovarian cancer, with the highest mortality among female genital tract malignancies, is often diagnosed at advanced stages with metastasis. Endoscopic ultrasound is a non-invasive and accurate method for the early diagnosis of early carcinoma in the upper gastrointestinal tract and liver diseases[45,46]. Additionally, this tool is effective in detecting ovarian cancer infiltration of surrounding organs[47]. Xu *et al*[4] demonstrated *in vitro* that gut microbiota dysbiosis can promote the growth of ovarian cancer cells and induce epithelial-mesenchymal transition. This underscores the need for further exploration of the role of gut microbiota in the occurrence and development of various tumors. Table 1 summarizes the list of studies that highlighted the gut microbiota changes in patients with PCOS, endometriosis, breast cancer, cervical cancer, and ovarian cancer.

## THERAPY

Probiotics have emerged as a modulator of gut microbiota. Recently, probiotics have been successfully used in the regulation of disrupted gut microbiota and the improvement of diseases such as gestational diabetes mellitus (GDM) and

**Table 1 Gut microbiota alterations in polycystic ovarian syndrome, endometriosis, breast cancer, cervical cancer, and ovarian cancer of the human studies**

Diseases	Changes in gut microbiota (human studies)
PCOS	Increase: <i>Lachnospirillum</i> , <i>Fusobacterium</i> , <i>Coprococcus_2</i> , and <i>Tyzzereia 4</i> [33]; <i>Bacteroides</i> , <i>Escherichia/Shigella</i> , and <i>Streptococcus</i> [48] Decrease: <i>Tenericutes</i> and <i>Firmicutes/Bacteroides ratio</i> [33]; <i>Akkermansia</i> and <i>Ruminococcaceae</i> [48]
Endometriosis	Increase: <i>Bacteroides</i> , <i>Parabacteroides Oscillospira</i> , and <i>Coprococcus</i> [49] Decrease: <i>Paraprevotella</i> and <i>Lachnospira</i> [49]; <i>Clostridia Clostridiales</i> , <i>Lachnospiraceae Ruminococcus</i> , <i>Clostridiales</i> , <i>Lachnospiraceae</i> , and <i>Ruminococcaceae Ruminococcus</i> [50]
Breast cancer	Increase: <i>Firmicutes</i> , <i>Clostridium cluster IV</i> , and <i>cluster XIVa</i> [41] Decrease: <i>Bacteroidetes</i> [41]; <i>Bacteroidetes phylum</i> , and <i>Verrucomicrobia phylum</i> [42]
Cervical cancer	Increase: <i>Prevotella</i> , <i>Porphyromonas</i> , and <i>Dialister</i> [43]; <i>Succinivibrio</i> , <i>Ruminococcus</i> , <i>Morganella</i> , <i>Shewanella</i> , and <i>Proteus</i> [51] Decrease: <i>Bacteroides</i> , <i>Alistipes</i> , and <i>Lachnospiraceae</i> [43]; <i>Phascolarctobacterium</i> and <i>Halomonas</i> [51]
Ovarian cancer	Increase: <i>Proteobacteria</i> [52] Decrease: <i>Actinobacteria</i> , <i>Bifidobacterium</i> , and <i>Coprococcus</i> [52]

PCOS: Polycystic ovarian syndrome.

endometriosis. In a prospective study involving 256 pregnant women randomized to receive probiotics or a placebo during the first trimester, the probiotic intervention resulted in a reduced incidence of GDM[53]. Additionally, oral administration of lactic acid bacteria was found to alleviate endometriosis-related pain[54]. In a study by He *et al*[34], a PCOS-induced rat model treated through letrozole treatment showed that a 4-wk strain intervention, particularly with *Lactobacillus plantarum* HL2, was protective against PCOS-like pathological changes in the ovaries. Prebiotics are defined as a nondigestible food ingredient that selectively stimulates the growth and/or activity of specific bacteria in the colon; thus, improving host health[55]. Prebiotics improve the balance of gut microbiota and produce various beneficial effects on the human host, such as improving insulin resistance[56] and regulating intestinal immunity[57].

The technology of fecal microbiota transplantation (FMT) has gradually matured and found applications in various complex intestinal diseases. However, there has been limited research on the use of FMT for the treatment of gynecological diseases. In a study, rats with PCOS were observed to have lower levels of *Lactobacillus* and *Clostridium*, and higher levels of *Prevotella* compared to control rats[35]. Following treatment with FMT and *Lactobacillus* from healthy rats, the abnormal estrous cycle improved, and androgen biosynthesis decreased in all rats in the FMT group and 75% of the rats in the *Lactobacillus* group. Moreover, ovarian morphology normalized, and the composition of the recovered gut microbiota in the FMT and *Lactobacillus*-treated groups demonstrated an increase in *Lactobacillus* and *Clostridium* and a decrease in *Prevotella*[35]. Huang *et al*[2] performed ovariectomy on 12-wk-old mice and subsequent follow-up revealed vaginal atrophy and disrupted intestinal microbial balance at 4 wk post-operation. Subsequent transplantation of gut microbiota from normal female mice to ovariectomized mice resulted in enhanced proliferation of vaginal epithelium and significant alleviation of epithelial atrophy. The abundance of bacteria positively influencing vaginal epithelial regeneration (*Proteobacteria*, *Verrucomicrobia*, *Akkermansia*) increased as observed in the study. Therefore, further research on FMT could offer a new alternative treatment for gynecological diseases.

## CONCLUSION

The impact of gut microbiota on the body's immune system and hormonal balance is significant, dysbiosis of gut microbiota has been associated with the promotion of common gynecological diseases, such as PCOS, endometriosis, and malignant tumors. Conversely, these diseases can further disrupt the balance of gut microbiota. Interventions targeting the imbalanced gut microbiota, including the use of probiotics, prebiotics, and FMT, have shown promising results in animal experimental models. This approach offers a new perspective on the treatment of gynecological diseases, although further clinical studies are necessary to validate these findings. In the future, exploring the possibility of "matching" FMT donors and recipients or using bioengineering to synthesize bacterial solutions for precise disease treatment is worth further exploration.

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