

## Therapeutic potential of gut microbiome interventions in reproductive disorders



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### Abstract

The gut microbiome has literally become the master controller of the whole body's physiological balance, and its impact has even reached reproductive health, placing fertility, metabolism, and immunity among the impacted areas. A gut-reproductive axis has been proposed and is gaining support from an ever-increasing body of evidence complicated, two-way communication network between the microbes and the metabolites, the immune mediators, and the endocrine pathway. An imbalance in gut flora, which is called dysbiosis, can block the regulatory and signalling mechanisms and eventually result in an increase in the incidence of different reproductive disorders such as polycystic ovary syndrome (PCOS), endometriosis, recurrent pregnancy loss in women, and infertility in men. All these reproductive disorders have been associated with microbial imbalance and immune dysfunction. The review through its signalling pathways reveals the mechanistic interplay of gut microbiota with reproductive physiology and especially emphasizes pathways of short-chain fatty acid signalling, lipopolysaccharide-induced inflammation, and sex steroid metabolism modulation as the main ones. Furthermore, it evaluates both established and emerging microbiome-targeted interventions, including dietary modulation, prebiotics, probiotics, synbiotic, and faecal microbiota transplantation (FMT), as potential therapeutic strategies. The review discusses potentially utilizing gut microbiota modulation to enhance reproductive homeostasis based on preclinical and human investigations. Altering the gut-reproductive axis represents a new option for non-invasive interventions to improve fertility, decrease pregnancy complications, and may be used to treat reproductive disease.

**Keywords:** Gut-reproductive axis, Dysbiosis, Fertility, Microbiome modulation, Probiotics

## **1. Introduction**

Millions of people all over the world suffer from reproductive disorders. In general, these challenges may result in infertility, a decreased quality of life, or a broad health burden. Recent works suggest that gut microbiota can be implicated in the immune, endocrine and metabolic systems, as well modulate the hypothalamic-pituitary-gonadal (HPG) axis [1]. The estrobolome, which designates the diverse collection of gut bacterial genes that are associated with estrogen metabolism, is another important system for hormonal homeostasis. Furthermore, the disruption of gut microbiota may lead to reproductive hormone metabolism availability, causing direct influence on the HPG axis. Dysbiosis may promote the translocation of bacterial products into systemic circulation (termed, medically, metabolic endotoxemia), which is often characterized by decreased overall diversity in the microbiome, a lack of health promoting bacteria (notably *Lactobacillus* and *Bifidobacterium*), and an increase in pro-inflammatory species [2].

The basis of microbiome-based interventions attempting to treat these conditions that may arise from stress is to specifically intervene with gut microbiota through diet and probiotic, prebiotic, synbiotic, postbiotic, antibiotic, or faecal microbiota transplantation (FMT), thereby aiming to emphasize a balanced microbiome ecosystem. Recently emerging novel therapies, especially live biotherapeutics and phage therapy, are starting to intervene in the treatment of the disease [3]. Probiotics help restore the microbial balance, increase insulin sensitivity, and alter levels of sex hormones. For example, some strains of *Lactobacillus* have been shown to improve ovulatory function and lower androgen levels in women with polycystic ovary syndrome (PCOS). Additionally, the gut microbiome's influence extends to male reproductive health, where dysbiosis has been linked to altered sperm parameters, oxidative stress, and hormonal imbalances [4]. Collectively, these findings suggest that gut microbiome interventions may complement existing therapeutic strategies and represent a novel, systems-level approach to addressing reproductive dysfunction.

## **2. The Gut–Reproductive Axis**

Disruption of the gut-reproductive axis due to either dysbiosis of the gut microbiome and/or metabolic scarring have been increasingly associated with reproductive conditions including, but not limited to, polycystic ovary syndrome (PCOS), endometriosis, infertility and male subfertility. The implications of the various mechanistic and sex-dependent systems on this axis could potentially be an area for new therapeutic interventions.

### **2.1 Mechanistic Pathways**

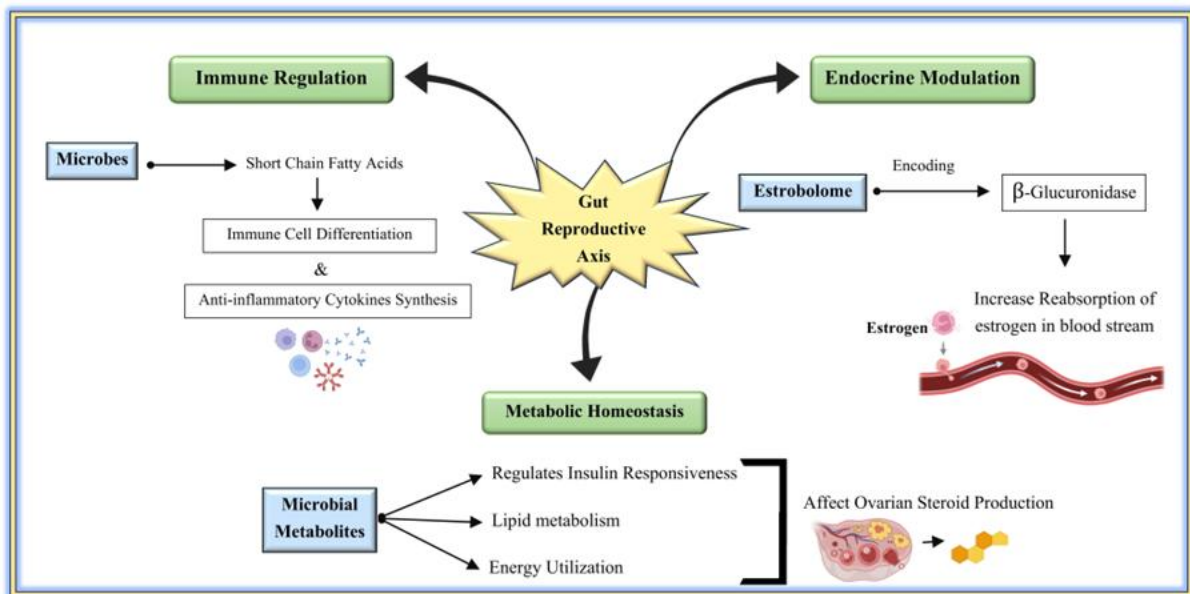
#### **2.1.1 Endocrine modulation**

The gut microbiome plays a significant role in modifying a host's endocrine system, including the modulation of estrogen, primarily through the estrobolome-made up of bacterial genes that code for enzymes that metabolize estrogen, including the important enzyme  $\beta$ -glucuronidase, which in turn influences the availability of estrogen. Dysbiosis that alters the abundance of  $\beta$ -glucuronidase-producing organisms (e.g., *Escherichia coli*, *Bacteroides* species, and *Clostridium* species), can disrupt estrogen homeostasis which can result in hypoestrogenic or hyper estrogenic states [5].

#### **2.1.2 Immune regulation**

The intestinal microbiota continuously interacts with the host immune system in order to regulate immune responses both locally and globally. Dysbiosis, or reduced microbial richness, is associated with higher abundance of proinflammatory microbes like *Enterobacteriaceae*, leading to increased intestinal permeability ("leaky gut") and subsequent efflux of

lipopolysaccharide (LPS) into circulation. Moreover, the gut microbiota regulates the balance between regulatory T cells (Tregs) and Th17 cells, shaping local immune tolerance at the maternal–fetal interface—an essential process for embryo implantation and pregnancy continuation [6]. Figure 1 shows the mechanistic pathways of gut–reproductive axis.



**Figure 1.** Mechanistic Pathways of Gut–Reproductive Axis

### 2.1.3 Metabolic homeostasis

Furthermore, the gut microbiome's contribution to metabolic regulation is massive and tightly intertwined with reproductive wellness. Dysbiosis has been recognized as a primary cause of metabolic disorders, such as obesity, insulin resistance, and type 2 diabetes—all of which are closely linked to reproductive dysfunctions [7]. PCOS is one such clear example where alterations in gut microbes, hirsutism, insulin resistance, and leaky gut have been significantly correlated. The decrease of *Akkermansia muciniphila* and *Bifidobacterium* spp. has been implicated in glucose metabolism difficulties and chronic inflammation [8].

### 2.2 Sex-Specific Considerations

In women, the gut microbiota influences ovarian function, menstrual cycles, and reproductive processes through hormone and immune mechanisms that regulate estrogen, progesterone, and androgen levels [9]. In the case of men, the influence of the gut flora on reproductive health is either negative or positive depending on how it affects hormones, metabolism, and the immune system. The gut microbiota synthesizes compounds that take part in testicular steroidogenesis and gonadotropin secretion, whereas dysbiosis is linked to reduced testosterone, poor sperm production, and oxidative stress [10].

## 3. Dysbiosis and Reproductive Disorders

### 3.1 Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is a disorder that is very often accompanied by gut dysbiosis, which is a condition that can be characterized by the absence of various types of bacteria, a change in the Firmicutes to Bacteroidetes ratio, and a decrease in the number of two specific genera called *Akkermansia* and *Bifidobacterium*. These factors are linked to the impaired insulin action of the cells and to the inflammation present which worsens the process of hyperandrogenism and anovulation. Thus, the inflammation has made insulin resistance stronger, which in turn has caused the production of androgens by theca cells to increase due

to the activation of LPS–TLR4 signaling as a result of the loss of barrier integrity and metabolism being disrupted by the lower production of short-chain fatty acids [11].

### **3.2 Endometriosis**

Endometriosis is a disease that demands a lot of estrogen and is an inflammatory disorder linked with gut dysbiosis and dysbiosis that not only goes along with the proliferation of pro-inflammatory taxa but also with the reduction of microbial diversity. This condition causes the immune system to be more active in the whole body and the pelvic area, thus leading to the emergence of pain-related pathology [12]. The unhealthy intestinal microflora that was responsible for the dysbiosis is in fact driving the activity of the estrobolome, which then increases the level of  $\beta$ -glucuronidase and facilitates the enterohepatic estrogen recycling process, thus allowing ectopic endometrial tissue to grow [13].

### **3.3 Infertility and Pregnancy Complications**

One of the reasons for infertility and pregnancy complications is the dysbiosis of gut flora, as it disrupts the immune tolerance process, raises the body's level of chronic inflammation, and changes the metabolic state which is very important for implantation and placental development, thus causing infertility and pregnancy complications [11].

### **3.4 Male Infertility**

The gut microbiome has been implicated in various ways in the production of testosterone, sperm quality, and even the whole process of fertility. The couple's microflora is defined by their microbiome; the so-called good genera (*Lactobacillus*, *Streptococcus*, and *Corynebacterium*) not only have a positive effect on sperm viability and antioxidant but also defense, while on the other hand, the genera of *Prevotella* and *Pseudomonas*, which are antagonistic to sperm, have an indirect connection to DNA fragmentation and thus, the lowering of fertility potentials [16].

## **4. Therapeutic Interventions Targeting the Gut Microbiome**

The concept of gut microbiome as an influential factor in reproductive health is slowly but surely overcoming the doubts; the medical profession will have to find ways to control or modify the microbial communities and their activities as part of the new treatment for infertility.

### **4.1 Dietary Interventions**

Diet is one of the most significant determinants that can alter the intestinal flora. The live microbes in the guts, mainly *Bifidobacterium* and *Lactobacillus*, are known to be powerful agents in the production of SCFAs and preservation of intestinal factors, and they are fed by the consumption of foods that are rich in fibers, complex carbohydrates, and polyphenols. SCFAs, especially butyrate, are capable of exerting anti-inflammatory actions and enhancing the effectiveness of insulin, which are both very necessary in treating conditions like PCOS and endometriosis [17].

### **4.2 Probiotics and Synbiotics**

Probiotics are live microorganisms that produce health benefits in sufficient doses, and are gaining attention due to health benefits in restoring gut microbial disruption and promoting reproductive health. Synbiotics, which combine probiotics with prebiotic substrates, may offer synergistic benefits by supporting the survival and activity of beneficial microbes. Synbiotic formulations have been shown to improve lipid metabolism, reduce oxidative stress, and normalize reproductive hormone profiles in PCOS and other metabolic reproductive disorders [18].

### **4.3 Fecal Microbiota Transplantation**

Fecal microbiota transplantation (FMT) is a procedure in which fecal matter is obtained from a healthy donor and transplanted into the gastrointestinal microbiome of a recipient with the aim of restoring a healthy ecosystem of microbes. Although FMT is mostly used to modify *Clostridioides difficile* infections, preclinical work is emerging from animal models that may show possible efficacy in reproductive disorders[19].

### **4.4 Emerging Biotherapeutics**

In addition to well-known probiotics and fecal microbiota transplant (FMT), a growing number of microbiome-based therapies are emerging. Advances in synthetic biology are making the engineering of probiotics possible in such a way that they can be guided towards selected therapeutic molecules, or alter host pathways. For example, specific strains of *Lactobacillus* could be engineered to produce anti-inflammatory agents, or could promote estrogens through localized action [20]. Table 1 shows the summary of clinical trials investigating key microbiomes in reproductive health

## **5. Challenges and Future prospectives**

There are barriers to sourcing microbiome-targeted therapies in reproductive medicine because of the variability in individual microbe composition that results in variability in the effects of normalizing probiotics, diets or FMT on reproductive health. Safety issues will always raise their head with these types of interventions especially with FMT or live microbial interventions to enclose the development of highest standards and oversight of the application of interventions to prevent infection or other unwanted adverse side effects. Future aims in this space would be to establish a precision microbiome therapy framework that utilizes an individual microbial, hormonal and metabolic rubric. One methodology worth exploring that houses mixed microbial communities that differentiate reproductive health is merging metabolomics, metagenomics and transcriptomics.

## **6. Conclusion**

The gut microbiome has been recognized more and more as a factor influencing the reproductive health through various means of communication: hormonal, immunological, and metabolic. Microbiome modulation through dietary means (diet, probiotics, synbiotics) and new interventions (fecal microbiota transplantation and postbiotics) have been considered some of the most preferable options in the area concerning control over hormonal balance, inflammation regulation, and thus, the prevention of reproductive health issues. Common beneficial gut bacteria that help improve reproductive problems include *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus fermentum*, *Lactobacillus jensenii*, *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Blautia*, *Clostridium*, *Parabacteroides*, *Adlercreutzia*, *Bacillus coagulans*, and *Streptococcus thermophilus*. In brief, the microbiome modification therapy may offer a competitive edge over traditional reproductive health treatments, such as shifting the attention to be more systemic on causes rather than isolated symptoms, and thus leading to a more continuous and personalized approach to reporting and resolving reproductive source disorders.

**Table 1.** Summary of Clinical Trials Investigating key microbiomes in reproductive health

Sr. No.	Title	Id	Status	Conditions	Phase	Measures	Target Hormones	Ref.
1.	Influence of Probiotics on the Vaginal Microbiota	NCT04471116	Active/Recruiting (registry)	Vaginal dysbiosis; infertility	NA	Lactobacillus dominance; microbiome shift; safety	Estrogen	[21]
2.	Effect of a Probiotic on the Female Genital Tract Microbiota	NCT06122207	Recruiting (planned RCT)	IVF candidates	Phase 2/3	Dysbiosis criteria at ET; implantation; pregnancy	Estrogen, FSH, LH, Progesterone	[22]
3.	Probiotic and Antibiotic Modulation of Vaginal Microbiota	NCT04955574	Recruiting/Active	Vaginal dysbiosis in fertility care	NA	Safety; feasibility; microbiome composition	Estrogen	[23]
4.	Modulating the Vaginal Microbiome After Implantation Failure	NCT03843112	Complete	Recurrent implantation failure	NA/ Interventional	Pregnancy rate; vaginal microbiota change	Progesterone, Estrogen, LH	[24]
5.	Microbiome and Endometrial Receptivity in Obese Infertile Women	NCT03493529	Unknown/Active	Obesity; infertility	Observational	Endometrial receptivity gene panel; microbiome	LH, Insulin, Androgens (e.g., testosterone), Estrogen	[25]
6.	New Strategies to Evaluate the Reproductive Tract Microbiome	NCT06920797	Not yet recruiting/ Recruiting	Endometrial microbiome	Observational	Sampling concordance; profiles	Estrogen, Progesterone, FSH, LH	[26]
7.	Donor vs Autologous FMT in Metabolic Syndrome (signal for fertility)	NCT04691544	Active/Completed	Metabolic syndrome	Phase 2	Insulin sensitivity; exploratory reproductive markers	Insulin, Testosterone, LH, FSH	[27]

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