PIBB 生物化学与生物物理进展
*Progress in Biochemistry and Biophysics*
XXXX, XX(XX): 1~13
www.pibb.ac.cn

# 肠道菌群通过肠道–性腺轴影响生殖功能的机制*

赵亚琪[1,2)] 齐莉莉[2)**] 王进波[2)**] 胡徐琦[2)] 王梦婷[2)] 毛海光[2)] 孙秋珍[3)]

([1)] 浙江理工大学生命科学与医药学院，杭州 310018；[2)] 浙大宁波理工学院生物与化学工程学院，宁波 315100；[3)] 浙江大学明州医院，宁波 315000）

**摘要** 生殖系统疾病是导致社会生育率下降、老龄化加剧的原因之一，严重危害人们的身心健康和生活质量。近年来的研究揭示，肠道菌群（GM）在改善生殖系统疾病方面表现出巨大的潜力。健康状况下，GM处于动态平衡，而失衡会引起免疫炎症反应、代谢紊乱等，进而诱发生殖系统疾病。肠道菌群组成与男女生殖系统具有密切的因果关系，短链脂肪酸、胆汁酸等典型GM代谢产物通过调控免疫反应、内分泌系统、维生素代谢以及下丘脑-垂体-性腺轴等多种机制影响生殖系统。微生态制剂、粪便微生物群移植以及药物通过调控GM及肠道免疫功能，发挥治疗生殖疾病的作用。本综述主要概括了GM变化与生殖系统疾病的相关性，GM通过肠道-性腺轴影响机体繁殖能力的内在机制及其在生殖疾病治疗领域的研究进展。

**关键词** 肠道菌群，肠道-性腺轴，不孕不育，生殖功能
**中图分类号** R339.38 **DOI**：10.16476/j.pibb.2024.0462 **CSTR**：32369.14.pibb.20240462



人体肠道菌群（gut microbiota，GM）种类繁多，主要由厚壁菌门（Firmicutes）与拟杆菌门（Bacteroidetes）等构成，两者的比值可作为评估机体健康状况的指标[1]。GM及其代谢物是构建肠道化学屏障的关键，对于维持肠道稳态平衡至关重要[2]。GM参与脂质及胆汁酸（bile acids，BA）代谢、维生素合成以及短链脂肪酸（short-chain fatty acids，SCFAs）的合成等多个生理过程，GM产生的代谢产物对免疫调节及抗炎功能至关重要。此外，许多研究发现，GM组成变化还与生殖系统疾病存在一定的关联性。那么，GM通过什么机制调控生殖系统？GM能否作为生殖系统疾病的治疗靶标？本文将针对这些问题进行探讨，以期为生殖疾病治疗、恢复机体繁殖能力方面提供新思路。

## 1 GM与生殖疾病

越来越多的研究发现，GM在生殖健康领域的作用日益显著，GM失衡与生殖系统疾病存在一定的关联性。

### 1.1 GM与女性生殖疾病的相关性

多囊卵巢综合征（polycystic ovary syndrome，PCOS）是一种由雄激素过多和雌二醇不足所诱发的疾病，患者卵泡发育异常，进而影响生育能力和内分泌系统的平衡[3]；子宫内膜异位症（endometriosis，EMS）是另一种常见的女性生殖疾病，发病机理复杂，患者不仅性激素水平紊乱，且细胞因子表达异常，是一种典型的慢性疾病[4]；宫颈癌在全球范围内位居女性恶性肿瘤发病率的第四位[5]，其高发病率和致死率引起了广泛关注。研究发现，在这些女性生殖系统疾病中，患者GM组成存在显著异常（表1）。

* 国家重点研发计划（2022YFD1300301），宁波市重大科技计划项目（2021Z112，2024Z180），宁波市科技特派员项目（2022S225）和宁波市自然科学基金（2022J151，2023J270）资助。
** 通讯联系人。
齐莉莉 Tel：0574-88130130，E-mail：qll@nbt.edu.cn
王进波 Tel：0574-88130130，E-mail：wjb@nbt.edu.cn
收稿日期：2024-11-06，接受日期：2025-02-27

**Table 1　Changes in gut microbiota abundance in infertility related diseases**

**表1　女性生殖相关疾病的肠道菌群丰度变化**

| 疾病 | 研究模型 | 疾病相关肠道菌群丰度变化 | 参考文献 |
|---|---|---|---|
| PCOS | 人 | 普雷沃氏菌属（*Prevotella*）丰度增加，乳杆菌属（*Lactobacillus*）、瘤胃球菌属（*Ruminococcus*）和梭状芽胞杆菌属（*Clostridium*）丰度降低 | [3] |
| | 小鼠 | Firmicutes丰度增加，Bacteroidetes丰度降低 | [6] |
| | 人 | 肠球菌属（*Enterococcus*）丰度增加 | [7] |
| | 人 | 活泼瘤胃球菌（*Ruminococcus gnavus*）、普雷沃氏菌斯特克雷亚亚种（*Prevotella stercorea*）、丁二酸杆菌（*Dialister succinatiphilus*）和脆弱拟杆菌（*Bacteroides fragilis*）丰度增加，克里斯滕森菌科（Christensenellaceae）丰度降低 | [8] |
| | 人 | 拟杆菌科（Bacteroidaceae）丰度增加，普雷沃氏菌科（Prevotellaceae）丰度降低 | [9] |
| EMS | 人 | 志贺氏菌属（*Shigella*）和埃希氏菌属（*Escherichia*）丰度增加，纤毛菌属（*Sneathia*）、巴恩斯氏菌属（*Barnesella*）和加特纳菌属（*Gardnerella*）丰度降低 | [10] |
| | 恒河猴 | 革兰氏阴性菌丰度增加，乳酸杆菌（*Lactobacilli*）丰度降低 | [11] |
| | 人 | 迟缓埃格特菌（*Eggerthella lenta*）和长真杆菌（*Eubacterium dolichum*）丰度增加，梭菌纲梭菌目（Clostridia Clostridiales）、毛螺菌科瘤胃菌属（*Lachnospiraceae Ruminococcus*）、梭菌目毛螺菌科（Clostridiales Lachnospiraceae）和瘤胃球菌科瘤胃球菌属（*Ruminococcaceae Ruminococcus*）丰度降低 | [12] |
| | 人 | Firmicutes/Bacteroidetes比值升高，放线菌门（Actinobacteria）、蓝菌门（Cyanobacteria）、糖细菌门（Saccharibacteria）、梭杆菌门（Fusobacteria）和酸杆菌门（Acidobacteria）丰度增加，软壁菌门（Tenericutes）丰度降低 | [13] |
| 宫颈癌 | 人 | Bacteroidetes丰度增加，Firmicutes丰度降低 | [14] |
| | 人 | *Prevotella*、卟啉菌属（*Porphyromonas*）和戴阿利斯特杆菌属（*Dialister*）丰度增加 | [15] |
| | 人 | 胶膜菌科（Tissierellaceae）、普雷沃氏菌科（Prevotellaceae）、放线菌科（Actinomycetaceae）和*Prevotella*丰度增加，*Ruminococcus*和梭菌属（*Clostiridium*）丰度降低 | [16] |
| | 人 | 拟杆菌属（*Bacteroides*）、*Prevotella*丰度增加，粪杆菌属（*Faecalibacterium*）、罗氏菌属（*Roseburia*）丰度降低 | [17] |

PCOS：多囊卵巢综合征；EMS：子宫内膜异位症

### 1.2　GM与男性生殖疾病的相关性

不育症是指因男方因素导致男女双方在规律性生活一年以上且未避孕情况下女方未能受孕的病症，常见症状包括精子数量减少和活力低下，GM失衡与不育症密切相关。许多环境污染物，如聚苯乙烯微塑料（polystyrene microplastics，PS-MPs）可能导致GM失衡。小鼠暴露于PS-MPs后，肠道*Bacteroidetes*呈上升趋势，*Firmicutes*呈下降趋势，且小鼠的精子活力与数量显著下降[18]。将高脂饮食（high-fat diet，HFD）小鼠的粪便菌群移植到正常饮食的小鼠中，正常小鼠肠道中*Bacteroides*和*Prevotella*丰度显著增加，同时引发局部炎症和内毒素血症，导致生殖细胞数量减少及精液质量下降；人粪便中*Bacteroides-Prevotella*的联合丰度与精子活力呈负相关，循环内毒素水平与*Bacteroides*丰度呈正相关，说明GM可能参与了不育疾病的发生和发展[19]。

上述研究结果揭示了GM组成变化与生殖系统疾病之间存在一定的关联性，但两者之间的因果关系尚不明确，需更深层次的研究明确二者的关系[20]。

## 2　GM通过肠道–性腺轴影响生殖功能

肠道-性腺轴揭示了肠道与生殖系统间的关联，GM及其代谢物通过调节免疫、内分泌以及下丘脑-垂体-性腺（hypothalamic-pituitary-gonadal，HPG）轴等多种机制影响生殖系统疾病的发生与发展。

### 2.1　GM通过肠道–卵巢轴影响女性生殖功能

肠道-卵巢轴影响女性生殖功能表现为：GM及其代谢物通过调控免疫炎症反应、内分泌系统及下丘脑-垂体-卵巢（hypothalamic-pituitary-ovarian，HPO）轴三种机制，影响生殖功能。

**2.1.1** 介导免疫反应

GM及其代谢物可能通过介导炎症细胞因子的表达，改善卵巢功能并减少炎症反应。GM失衡时，EMS患者肠道中革兰氏阴性菌的丰度增加，释放的脂多糖（lipopolysaccharide，LPS）激发巨噬细胞的活化，促进炎症细胞因子和趋化因子的生成[12]。EMS患者血清中的白介素-17A（interleukin-17A，IL-17A）浓度显著低于健康女性，且血清IL-17A水平与Bacteroides丰度呈正相关，与链球菌（*Streptococcus*）和双歧杆菌（*Bifidobacterium*）丰度呈负相关，而IL-8浓度则高于健康女性，并与罕见小球菌属（*Subdoligranulum*）的丰度呈负相关[13]；此外，IL-6、肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）浓度也显著升高[21]。细胞实验揭示了GM代谢物，如SCFAs在改善卵巢功能与抗炎保护方面的独特机制：SCFAs通过与G蛋白偶联受体4（g protein-coupled receptor 4，GPR4）相互作用、控制细胞代谢并抑制组蛋白脱乙酰酶（histone deacetylases，HDAC），促进$CD4^+$T细胞产生IL-22，保护小鼠免受炎症损伤[22]。作为SCFAs中的重要成分，丁酸能够通过抑制METTL3（一种m6A甲基转移酶）的表达，降低转录因子FOSL2 m6A甲基化水平及其mRNA表达，有效改善PCOS小鼠的卵巢功能并减少卵巢局部炎症因子的表达[23]。

GM及其代谢物通过传递免疫刺激信号，诱导细胞免疫反应，从而调控癌细胞的极化和凋亡。肠道Bacteroides通过修饰的BA激活两类免疫细胞：调节性T细胞（regulatory T cells，Tregs）和效应辅助T（helper T，Th）细胞，这些细胞通过抑制或促进炎症来调控免疫反应[24]。阿克曼氏菌（*Akkermansia*）通过激活T细胞的信号途径并增加干扰素γ（interferon γ，IFN γ）来增强对肿瘤细胞的杀伤效应，进而抑制卵巢癌细胞的生长和扩散[25]。丁酸和丙酸作为GM重要的代谢产物，在调控免疫细胞功能和诱导癌细胞凋亡方面发挥关键作用。丁酸不仅能上调Tregs相关的叉头盒蛋白P3（forkhead box P3，FoxP3）的表达，抑制Th17细胞分泌RORγt和IL-17，进而促进初始宫颈癌细胞CD4+T细胞中的Th17细胞极化[26]，还通过调控GPR43、GPR109A、HDAC以及肿瘤抑制因子RAP1GAP的表达，调节细胞免疫反应，从而有效抑制子宫内膜异位细胞的存活和病变生长[27]。丙酸通过产生活性氧类（reactive oxygen species，ROS）以及抑制AKT/mTOR和核因子-κB（nuclear factor-kappa B，NF-κB）信号通路，诱导HeLa宫颈癌细胞凋亡[28]。

**2.1.2** 调控内分泌系统

GM失衡扰乱了机体内环境的稳态，影响内分泌系统，导致类固醇激素、胰岛素等分泌紊乱，影响女性生殖系统。

GM失调可能导致雌激素水平异常，增加生殖系统疾病发生的风险。肠道*Bacteroides*、*Bifidobacterium*和*Lactobacillus*等通过产生β葡萄糖醛酸酶（β-Glucuronidase，β-GUS）等激素代谢酶，解离并重新激活雌激素，影响雌激素循环水平[29]。GM通过代谢物SCFAs调控雌激素的合成，如丁酸通过cAMP信号通路以及增加组蛋白H3K9的乙酰化，经由PPAR-γ和PGC1-α途径激活卵巢颗粒细胞中孕酮和雌二醇等类固醇激素的合成[30-31]。GM还可通过调控HPO轴间接影响雌激素的分泌。乙酸治疗PCOS大鼠能够有效降低血清促黄体生成素（luteinizing hormone，LH）与T水平，同时促使促性腺激素释放激素（gonadotropin-releasing hormone，GnRH）和卵泡刺激素（follicle-stimulating hormone，FSH）水平升高[32]。

雄激素与胰岛素也是影响女性生殖系统的关键激素。高雄激素与血脂异常、胰岛素抵抗（insulin resistance，IR）等代谢障碍的发生密切相关，50%~70%的PCOS患者，尤其是肥胖患者，存在不同程度的IR。GM能够调控雄激素和胰岛素的分泌与代谢，肠道放线菌属（*Actinomyces*）和变形菌门（Proteobacteria）可降解雄激素，裂解梭菌（*Clostridium scindens*）能将糖皮质激素转化为雄激素[33]，以及粪便普雷沃氏菌（*Prevotella copri*）能够诱发IR[34]。GM及其代谢物还能够通过调控糖代谢与脂质代谢，从而改善卵巢功能和卵细胞质量，如GM可以通过*Bacteroides*-BA-法尼醇X受体信号通路加剧PCOS患者糖代谢紊乱[35]。丁酸可能通过上调葡萄糖摄取、脂肪合成以及诱导葡萄糖转运蛋白（glucose transporter，GLUT）4/PPAR-γ等多种机制来增强脂肪生成和脂质积累、改善人卵巢颗粒细胞凋亡状况和葡萄糖代谢过程[36-37]；丁酸还能通过上调ARHGAP10（一种促进细胞死亡的蛋白质）表达和靶向调控RBM3/SLC7A11轴，降低细胞活力、增加脂质过氧化物和铁含量的积累，诱导氧化应激，从而诱导卵巢癌与子宫内膜癌

细胞铁死亡[38-39]。

### 2.1.3　调控HPO轴

下丘脑炎症被认为是PCOS代谢、生殖及临床异质性的病理基础。GM能够通过肠-脑轴影响PCOS患者垂体和下丘脑的脂质代谢过程及免疫功能，并调控神经系统炎症因子的表达[40-41]。如丁酸可以通过改善γ氨基丁酸（gamma-aminobutyric acid，GABA）系统缓解PCOS患者内分泌紊乱相关的下丘脑炎症[42]，而乙酸则通过抑制NLRP3炎症小体的免疫反应恢复PCOS大鼠模型下丘脑脂肪组织中Kisspeptin表达状态[43]，并通过调节NrF2/HIF1-α信号通路改善PCOS模型中下丘脑的脂毒性和促炎性损伤[44]，同时还能降低血浆低密度脂蛋白、甘油三酯含量以及下丘脑甘油三酯水平[32]。

## 2.2　GM通过肠道–睾丸轴影响男性生殖功能

肠道-睾丸轴通过GM及其代谢物调控免疫炎症反应、内分泌系统、维生素代谢及下丘脑-垂体-睾丸（hypothalamus-pituitary-testes，HPT）轴等过程，影响睾丸精子生成及质量。

### 2.2.1　介导免疫反应

GM及其代谢物通过调控促炎因子和免疫细胞影响睾丸的免疫微环境（图1）。高异常精子率和低精液利用率的公猪肠道内含有较高的内毒素和促炎因子，以及较低的抗炎因子[45]。肠道Proteobacteria能够产生支链脂肪酸及其他有毒代谢物诱发炎症反应，进而降低精液质量[46]。Round等[47]发现，*Bacteroides Fragilis*产生的免疫调节分子多糖A能激活TLR2信号通路，诱导FoxP3$^{+}$ Tregs产生，促进IL-10的分泌并抑制Th17细胞的功能。GM失调导致肠道通透性增加，促进内毒素渗漏到血液中，激活Toll样受体，介导多种IL、TNF-α等多种促炎因子的表达，从而降低精子活力及数量[48]。

GM代谢物能够通过调控免疫细胞，进而影响生育能力。巨噬细胞是睾丸中最丰富的免疫细胞，其数量与精子发生过程密切相关，睾丸间质组织中的M2型巨噬细胞通过分泌抗炎因子，促进Th2细胞分化，参与生精过程[49-51]。GM代谢物通过调控胰岛素样生长因子1（insulin-like growth factor 1，IGF-1）的产生影响精子生成和精子质量。SCFAs能够促进前列腺中IGF-1的产生，而IGF-1通过激活其受体下游信号转导促进前列腺癌的进展[52]，丁酸能够促进M2巨噬细胞的分化[53]。GM还能够激活特异性T细胞，睾丸中的Tregs上调抗炎因子IL-10、IL-35和TGF-β，形成免疫抑制微环境，当睾丸中效应T细胞的数量高于Tregs时，会扰乱免疫抑制环境，进而激活自身免疫反应[54]。SCFAs能够抑制LPS诱导的巨噬细胞产生促炎因子，促进IL-10的分泌，并抑制NF-κB信号通路，从而抑制炎症反应[55]。

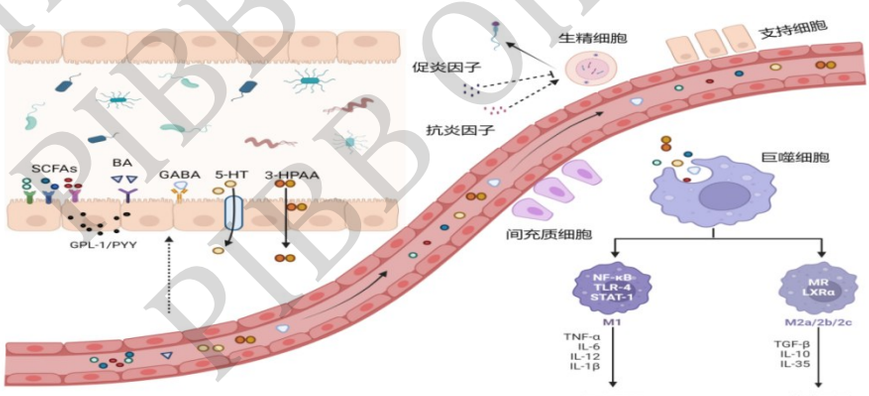



**Fig. 1　Schematic diagram of intestinal bacterial metabolites influencing spermatogenesis by mediating inflammatory responses and modulating the immune systems (https://App.biorender.com)**

**图1　肠道细菌代谢产物通过介导炎症反应，调节免疫系统来影响精子发生 (https://App.biorender.com)**

SCFAs：短链脂肪酸；BA：胆汁酸；GABA：γ-氨基丁酸；5-HT：5-羟色胺；3-HPAA：3-羟基苯乙酸；GLP-1：胰高糖素样肽-1；PYY：肽YY；NF-κB：核因子-κB；TLR-4：Toll样受体-4；STAT-1：信号转导与转录激活因子-1；MR：盐皮质激素受体重组蛋白；LXRα：肝X受体α重组蛋白；TNF-α：肿瘤坏死因子-α；IL：白细胞介素；TGF-β：转化生长因子-β。

**2.2.2** 介导激素代谢

GM能够调节睾丸激素水平，睾酮（testosterone，T）是睾丸中的主要雄激素，*Clostridium scindens*、*Ruminococcus*等能够将糖皮质激素、孕烯醇酮和羟基孕烯醇酮转化为雄激素，导致肠道内T、二氢睾酮（dihydrotestosterone，DHT）水平增加[33]。GM主要依赖于GUS活性促进雄性动物T和DHT的去糖醛酸化，并增加游离T和DHT的水平[56]，从而促进雄性动物第二性征的发育。

胰岛素在男性生殖的发展中也发挥重要作用，研究显示IR与GM密切相关。Zhu等[57]发现，IR不育小鼠的GM丰度和多样性较低，糖杆菌（*Saccharobacillus*）水平较高，*Actinomyces*和疣微菌门（Verrucomicrobia）显著减少。GM和IR之间的联系涉及胃肠道激素，该激素通过调节胰岛素分泌和食欲来影响IR，同时也可以通过调节GM的组成和功能来进一步影响代谢健康。瘦素和生长素释放肽都与IR呈负相关[58]。高水平的瘦素对类固醇的产生有抑制作用[59]，生长素释放肽抑制T分泌，并可能调节生精小管功能[60]。GM代谢产生的乙酸能够通过抑制氧化应激反应和上调PPAR-γ的表达，进而增加脂肪瘦素浓度，从而改善HFD诱导的肥胖雄性大鼠的脑脂肪代谢功能障碍及葡萄糖稳态异常[32]。

**2.2.3** 介导维生素吸收

GM失调引发维生素代谢紊乱，可导致精子发生和精子活力受损[61]。

生殖细胞再生障碍与维生素A代谢失调有关[61]，*Bacteroides*、*Bifidobacterium*和*Lactobacillus*等在维生素的吸收和代谢中起关键作用。Zhang等[61]发现，GM紊乱时*Ruminococcaceae NK4A214*的丰度急剧下降，维生素A代谢异常并通过血液循环转移到睾丸细胞，从而损害机体的生精能力。维生素A缺乏导致A型精原干细胞不能向A1型分化，减慢了精子的产生[62]。研究表明，雄性啮齿类动物不育的主要原因是缺乏维生素A的酸化衍生物维甲酸[63]，维甲酸促进了与精子发生相关的两个基因（*Stra8*和*Rec8*）的表达；当*Stra8*不表达或低表达时，未分化精原细胞难以积累和分化，导致减数分裂失败，从而导致无精症[64]。

GM合成的B族维生素与男性生殖细胞和精子形成密切相关。肠道乳杆菌（*Lactobacillus reuteri*）合成的维生素B9能够通过影响细胞分裂所必需的组蛋白甲基化来影响染色质结构，保护生殖细胞免受氧化损伤[65-66]。附睾是哺乳动物促进精子成熟、储存和保护精子的重要器官，维生素K在大鼠附睾的微环境调节中扮演重要角色。*Bifidobacterium*与*Bacteroides fragilis*合成的维生素K能够改善大鼠的精子活力，增加附睾尾部精子数量，降低精子形态异常比例[67-68]。维生素K依赖性酶γ谷氨酰羧化酶可以促进支持细胞中维生素K依赖性雄激素受体γ羧化，有助于维持血睾丸屏障结构，促进生殖细胞发育和精子释放[69]。

**2.2.4** 调控HPT轴

GM通过调控5-羟色胺（5-HT）和GABA等神经递质的合成与释放[70]，从而影响HPT轴对生殖系统的作用。肠道梭状芽胞杆菌（*Clostridium ramosum*）的细胞成分可以刺激宿主内皮细胞分泌5-HT[71]，5-HT可能与HPT轴中的某些激素或受体相互作用，从而影响性激素的分泌。GM分泌的5-HT、GABA等信号分子还能够通过调节血钙浓度以维持精子活力，并直接对精子的激活与功能产生影响[46]。*Bacteroides*、副拟杆菌（*Parabacteroides*）和大肠杆菌（*Escherichia coli*）等积极表达GABA，GABA通过抑制5-HT与5-HT受体的结合来减少精子的过度激活，从而与5-HT共同调节精子的激活[72]。GM还能通过NO信号通路调控HPT轴，*Lactobacillus*、*Bifidobacterium*、金黄色葡萄球菌（*Staphylococcus aureus*）和芽孢杆菌（*Bacillus*）等可通过精氨酸代谢过程影响NO的产生[73]，NO可促进神经递质的释放以维持性欲，并促进促黄体激素释放激素和GnRH的分泌以增加性激素水平[46]。

## 3　调控GM治疗生殖疾病

随着GM与宿主生殖之间的关系越来越清晰，可靶向调节GM，恢复机体繁殖能力。GM治疗生殖疾病主要有三条途径：微生态制剂干预、粪便微生物群移植（fecal microbiota transplantation，FMT）和药物治疗。

### 3.1　微生态制剂干预

微生态制剂是指通过收集、培养和应用具有有益微生物特性的生物材料来维持或改良人体的正常微生态系统，以达到预防和治疗疾病的目的。

**3.1.1** 益生菌

益生菌通过竞争肠道内的空间和资源，有效抑

制致病菌的生长，进而维持肠道微生态平衡[74]。临床研究多应用*Lactobacillus*与*Bifidobacterium*来治疗生殖系统疾病，通过对EMS患者的研究发现，乳酸杆菌（*Lactobacillus gasseri OLL 2809*）能够激活小鼠自然杀伤细胞抑制EMS的发生以及印度Unic Biotech Ltd生产的Femina Probiz益生菌（含有*Lactobacillus*的药片）能够抑制NLRP3炎症小体的mRNA表达，患者临床症状得到显著改善[75-76]。对PCOS患者的临床研究发现，服用乳双歧杆菌V9（*Bifidobacterium lactis V9*）以及硒+益生菌（*Lactobacillus*和*Bifidobacterium*）联合补充剂后，能够有效改善GM组成，与糖、脂代谢相关的PPAR及脂肪细胞因子信号通路被下调[77]，性激素结合蛋白水平升高，多毛症评分降低，胰岛素敏感性增强，脂蛋白水平降低[78-79]。

就益生菌与雄性生殖的关系而言，口服益生菌能够调节激素平衡、缓解精子炎症反应和氧化应激状态，进而增加精子活力并提高精子质量[80-82]。Oliveira等[83]发现，患有特发性男性不育症（涵盖少精子症、畸精子症和弱精子症）的男性患者，经过益生菌（*Lactobacillus*、*Bifidobacterium*和嗜热链球菌（*Streptococcus thermophiles*））治疗后，精子脂质过氧化水平降低，DNA碎片减少，所有精子参数均得到显著改善。

**3.1.2** 益生元

益生元是指一类不被宿主消化吸收，但能选择性地促进体内有益菌代谢和增殖，从而改善宿主健康的有机物质，包括多不饱和脂肪酸（polyunsaturated fatty acids，PUFAs）、多酚以及碳水化合物等多种成分。Omega-3 PUFAs作为人体必需脂肪酸，参与肠道免疫功能的调节并维护肠道稳态[84]。水果、蔬菜、乳制品或Omega-3 PUFAs食用量较高的的女性患EMS的风险相对较低[85]。益生元能够有效缓解PCOS症状。小肠抗消化淀粉（小麦/玉米糊精）干预3个月能够有效调节PCOS患者的代谢参数、雄激素水平以及包括多毛症和月经周期不规律在内的临床表现[86]。PCOS患者接受为期12周的高纤维饮食（包含全谷物、中药食品和益生元）治疗后，显著改善了患者的临床症状，如减轻炎症状态、降低体重指数、减少瘦素水平及空腹血浆胰岛素水平[87]。在雄性生殖方面，益生元能够提高精子的质量和数量，Zhou等[88]通过喂食公猪海藻酸寡糖重塑其GM，可提高精液质量。

**3.1.3** 合生元

合生元作为益生菌与益生元的复合制剂，也表现出类似的治疗效果。PCOS患者服用多菌株益生菌（*Lactobacillus*、*Bifidobacterium*和*Streptococcus thermophiles*）与益生元（菊粉和低聚果糖）合生，并结合饮食与生活方式的调整，能够显著改善月经周期、体重、代谢和激素状况，并减少炎症标志物[89-90]。除此之外，连续补充合生元胶囊（嗜酸乳杆菌T16（*Lactobacillus acidophilus T16*）、干酪乳杆菌T2（*Lactobacillus casei T2*）、两歧双歧杆菌T1（*Bifidobacterium bifidum T1*）和菊粉）也能显著降低PCOS患者身体质量指数、血清胰岛素水平及血脂水平[91]。

在雄性生殖方面，副干酪乳杆菌B21060（*Lactobacillus paracasei B21060*）与益生元（Flortec、Bracco）结合能够显著改善特发性少弱精子症患者的精子质量和数量[92]。鼠李糖乳杆菌NCDC-610（*Lactobacillus rhamnosus NCDC-610*）、发酵乳杆菌NCDC-400（*Lactobacillus fermentum NCDC-400*）与低聚果糖合生对雄性小鼠的氧化应激具有保护作用，从而提高精子质量[93]。服用合生元FamiLact（*Lactobacillus*、短/长双歧杆菌（*Bifidobacterium breve/longum*）、*Streptococcus thermophiles*和低聚果糖）可改善精子的浓度和活力，并减少异常形态和精子DNA损伤[94]。

上述研究表明，微生态制剂对生殖疾病的治疗具有有效性，但因样本量小、人群同质和干预持续时间短等限制了研究结果的推广[90]。因此，临床研究还需要针对不同人群以及标准化方法进行更大规模、更长时间的多中心试验以及随机临床试验，来阐明作用机制，以明确此类治疗方法的有效性和安全性。

**3.2 FMT**

FMT通过将健康供体的粪便悬浮液移植到受体患者的肠道内，能够改善某些生殖系统疾病。对PCOS大鼠进行FMT治疗后发现，*Lactobacillus*和*Clostridium*丰度增加，*Prevotella*丰度减少，发情周期得到改善，雄激素生物合成减少，卵巢形态趋于正常化[3]，对EMS小鼠进行FMT治疗后发现子宫内膜异位病变的生长减少[95]。IR在PCOS患者中均较为普遍，相关临床试验显示，接受来自瘦型供体FMT治疗的肥胖患者在胰岛素敏感性方面表现出积极的变化[96]。通过FMT改善精子发生和男性不育的情况比较常见。通过移植海藻酸寡糖食用

小鼠的粪便微生物群，Zhang等[97-98]首次发现GM可以改善精液质量和精子发生，治疗白消安诱导的雄性不育。FMT还可以利用GM产生的3-羟基苯基乙酸，减轻了衰老导致的生精功能障碍，恢复精子发生[99]。

综上所述，FMT可能是生殖系统疾病的潜在治疗方法，然而这种策略受到移植粪便中存在未知微生物和致病菌的限制，在患者（尤其是免疫功能低下的患者）中研究性使用FMT还需要额外的安全和测试法规[100]，且因患者较难接受而少有应用。

### 3.3　药物治疗

目前，药物治疗仍旧是治疗生殖疾病的一种重要治疗手段。二甲双胍被应用于缓解PCOS患者的相关临床表现，非糖尿病性PCOS患者接受二甲双胍治疗后，肠道内丁酸盐产生菌及嗜粘蛋白阿克曼氏菌（*Bacterium Akkermansia muciniphila*）等抗炎细菌的丰度增加，显著提高了月经恢复率、排卵率和妊娠率[101-102]。近期研究发现，姜黄素能够调节GM中有益菌和有害菌之间的比例，在治疗女性生殖系统疾病中具有巨大潜力。姜黄素通过减少革兰氏阴性菌的数量，抑制TLR4/MyD88/NF-κB信号通路的激活及降低肠粘膜通透性，有效缓解PCOS患者的空腹血糖水平以及闭经、月经稀发和月经不规律等临床症状[103-104]。鉴于生殖系统疾病病因的复杂性，单一药物往往难以取得显著疗效，因此，临床上倾向于采用多种药物联合治疗，二甲双胍与姜黄素的联合应用在改善PCOS患者的血脂、葡萄糖代谢、激素参数和体重指数等方面表现出优异的功效[105]。在男性生殖健康领域，健脾补肾方药（聚精汤中药）与双歧杆菌三联活菌（*Bifidobacterium*、*Lactobacillus*、*Enterococcus*）胶囊联用能够显著改善精子质量，提升正常形态精子的百分比[106]。

## 4　总结和展望

综上所述，GM及其代谢物通过调控代谢、免疫反应、内分泌系统以及HPG轴等途径影响生殖系统，这些机制相互作用，共同通过“肠道-性腺轴”影响机体繁殖能力，深入研究这些机制有助于人们更好的理解GM在机体繁殖中的作用，为生殖疾病的诊治疗提供新思路。

GM有望作为生殖疾病的治疗靶标，但目前尚有许多困难需要克服。首先，GM与生殖疾病关联性研究还不够深入，无法明确两者的因果关系，这对提出针对GM的潜在治疗方法至关重要；其次，虽然GM代谢物能够通过各种信号通路影响脂质、葡萄糖以及激素等物质的合成和代谢，从而间接影响卵巢和睾丸功能，但对于GM代谢物直接影响生殖细胞或颗粒细胞的机制还需要更深入的研究；最后，运用GM治疗生殖疾病的具体疗效受到多种因素的影响，需要更加深入的机理研究，以及进一步的临床研究来验证和优化治疗方案。

## 参考文献


[1] Yañez C M, Hernández A M, Sandoval A M, *et al*. Prevalence of Blastocystis and its association with Firmicutes/Bacteroidetes ratio in clinically healthy and metabolically ill subjects. BMC Microbiol, 2021, **21**(1): 339

[2] Morrison D J, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes, 2016, **7**(3): 189-200

[3] Guo Y, Qi Y, Yang X, *et al*. Association between polycystic ovary syndrome and gut microbiota. PLoS One, 2016, **11**(4): e0153196

[4] Lee S R, Lee J C, Kim S H, *et al*. Altered composition of microbiota in women with ovarian endometrioma: microbiome analyses of extracellular vesicles in the peritoneal fluid. Int J Mol Sci, 2021, **22**(9): 4608

[5] Zhang W, Liu Y, Zhou X, *et al*. Applications of CRISPR-Cas9 in gynecological cancer research. Clin Genet, 2020, **97**(6): 827-834

[6] Lin W, Wen L, Wen J, *et al*. Effects of sleeve gastrectomy on fecal gut microbiota and short-chain fatty acid content in a rat model of polycystic ovary syndrome. Front Endocrinol: Lausanne, 2021, **12**: 747888

[7] He F, Li Y. The gut microbial composition in polycystic ovary syndrome with insulin resistance: findings from a normal-weight population. J Ovarian Res, 2021, **14**(1): 50

[8] Dong S, Jiao J, Jia S, *et al*. 16S rDNA full-length assembly sequencing technology analysis of intestinal microbiome in polycystic ovary syndrome. Front Cell Infect Microbiol, 2021, **11**: 634981

[9] Zeng B, Lai Z, Sun L, *et al*. Structural and functional profiles of the gut microbial community in polycystic ovary syndrome with insulin resistance (IR-PCOS): a pilot study. Res Microbiol, 2019, **170**(1): 43-52

[10] Ata B, Yildiz S, Turkgeldi E, *et al*. The endobiota study: comparison of vaginal, cervical and gut microbiota between women with stage 3/4 endometriosis and healthy controls. Sci Rep, 2019, **9**: 2204

[11] Bailey M T, Coe C L. Endometriosis is associated with an altered profile of intestinal microflora in female rhesus monkeys. Hum Reprod, 2002, **17**(7): 1704-1708

[12] Huang L, Liu B, Liu Z, *et al*. Gut microbiota exceeds cervical microbiota for early diagnosis of endometriosis. Front Cell Infect

Microbiol, 2021, **11**: 788836

[13] Shan J, Ni Z, Cheng W, *et al*. Gut microbiota imbalance and its correlations with hormone and inflammatory factors in patients with stage 3/4 endometriosis. Arch Gynecol Obstet, 2021, **304**(5): 1363-1373

[14] Wang Z, Wang Q, Zhao J, *et al*. Altered diversity and composition of the gut microbiome in patients with cervical cancer. AMB Express, 2019, **9**(1): 40

[15] Sims T T, Colbert L E, Zheng J, *et al*. Gut microbial diversity and genus-level differences identified in cervical cancer patients versus healthy controls. Gynecol Oncol, 2019, **155**(2): 237-244

[16] Kang G U, Jung D R, Lee Y H, *et al*. Dynamics of fecal microbiota with and without invasive cervical cancer and its application in early diagnosis. Cancers: Basel, 2020, **12**(12): E3800

[17] 韩梦真, 孙涛, 徐君南. 宫颈癌女性阴道、肠道菌群特征及微生物组作为宫颈癌诊断工具的临床潜力: 2024 中国肿瘤标志物学术大会暨CACA整合肿瘤学高峰论坛暨第十七届肿瘤标志物青年科学家论坛暨中国肿瘤标志物产业创新大会, 中国江苏南京, 2024
Han M Z, Sun T, Xu J N. 2024 China Tumor Markers Academic Conference & CACA Integrated Oncology Summit Forum & 17th Tumor Markers Young Scientists Forum & China Tumor Markers Industry Innovation Conference, Nanjing, Jiangsu, China, 2024

[18] 夏俭有, 刘波, 潘铁军. 聚苯乙烯微塑料通过重塑肠道微生物和上调 Claudin 1 蛋白表达诱导小鼠睾丸损伤. 生态毒理学报, 2024, **19**(3): 353-362
Xia J Y, Liu B, Pan T J. Asian J Ecotoxicol, 2024, **19**(3): 353-362

[19] Ding N, Zhang X, Zhang X D, *et al*. Impairment of spermatogenesis and sperm motility by the high-fat diet-induced dysbiosis of gut microbes. Gut, 2020, **69**(9): 1608-1619

[20] Uzuner C, Mak J, El-Assaad F, *et al*. The bidirectional relationship between endometriosis and microbiome. Front Endocrinol: Lausanne, 2023, **14**: 1110824

[21] Wang X M, Ma Z Y, Song N. Inflammatory cytokines IL-6, IL-10, IL-13, TNF-alpha and peritoneal fluid flora were associated with infertility in patients with endometriosis. Eur Rev Med Pharmacol Sci, 2018, **22**(9): 2513-2518

[22] Yang W, Yu T, Huang X, *et al*. Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. Nat Commun, 2020, **11**: 4457

[23] Liu K, He X, Huang J, *et al*. Short-chain fatty acid-butyric acid ameliorates granulosa cells inflammation through regulating METTL3-mediated N6-methyladenosine modification of FOSL2 in polycystic ovarian syndrome. Clin Epigenetics, 2023, **15**(1): 86

[24] Hang S, Paik D, Yao L, *et al*. Bile acid metabolites control TH17 and Treg cell differentiation. Nature, 2019, **576**(7785): 143-148

[25] Wang Z, Qin X, Hu D, *et al*. Akkermansia supplementation reverses the tumor-promoting effect of the fecal microbiota transplantation in ovarian cancer. Cell Rep, 2022, **41**(13): 111890

[26] McBride D A, Dorn N C, Yao M, *et al*. Short-chain fatty acid-mediated epigenetic modulation of inflammatory T cells *in vitro*. Drug Deliv Transl Res, 2023, **13**(7): 1912-1924

[27] Chadchan S B, Popli P, Ambati C R, *et al*. Gut microbiota-derived short-chain fatty acids protect against the progression of endometriosis. Life Sci Alliance, 2021, **4**(12): e202101224

[28] Pham C H, Lee J E, Yu J, *et al*. Anticancer effects of propionic acid inducing cell death in cervical cancer cells. Molecules, 2021, **26**(16): 4951

[29] Kumari N, Kumari R, Dua A, *et al*. From gut to hormones: unraveling the role of gut microbiota in (phyto)estrogen modulation in health and disease. Mol Nutr Food Res, 2024, **68**(6): e2300688

[30] Ye Q, Zeng X, Wang S, *et al*. Butyrate drives the acetylation of histone H3K9 to activate steroidogenesis through PPARγ and PGC1α pathways in ovarian granulosa cells. FASEB J, 2021, **35**(2): e21316

[31] Lu N, Li M, Lei H, *et al*. Butyric acid regulates progesterone and estradiol secretion *via* cAMP signaling pathway in porcine granulosa cells. J Steroid Biochem Mol Biol, 2017, 172: 89-97

[32] Olaniyi K S, Owolabi M N, Atuma C L, *et al*. Acetate rescues defective brain-adipose metabolic network in obese Wistar rats by modulation of peroxisome proliferator-activated receptor-γ. Sci Rep, 2021, **11**: 18967

[33] Ridlon J M, Ikegawa S, Alves J M P, *et al*. Clostridium scindens: a human gut microbe with a high potential to convert glucocorticoids into androgens. J Lipid Res, 2013, **54**(9): 2437-2449

[34] Jiang C, Xie C, Lv Y, *et al*. Intestine-selective farnesoid X receptor inhibition improves obesity-related metabolic dysfunction. Nat Commun, 2015, **6**: 10166

[35] Yang Y L, Zhou W W, Wu S, *et al*. Intestinal flora is a key factor in insulin resistance and contributes to the development of polycystic ovary syndrome. Endocrinology, 2021, **162**(10): bqab118

[36] Yu S Y, Luan Y, Xu P C, *et al*. Metabolic characteristics of granulosa cell tumor: role of PPARγ signaling. Biol Reprod, 2024, **110**(3): 509-520

[37] Sun D, Zhao Y, Wu X. Effects of tumor necrosis factor-alpha on glucose uptake in human granulosa cells under high androgen conditions. Iran J Basic Med Sci, 2023, **26**(8): 912-918

[38] Ke H, Shao J, Hu J, *et al*. ARHGAP10, transcriptionally regulated by sodium butyrate, promotes ferroptosis of ovarian cancer cells. Front Biosci: Landmark Ed, 2024, **29**(5): 167

[39] Wang Z, Shu W, Zhao R, *et al*. Sodium butyrate induces ferroptosis in endometrial cancer cells *via* the RBM3/SLC7A11 axis. Apoptosis, 2023, **28**(7): 1168-1183

[40] Li M, Yang H, Shao C, *et al*. Application of dominant gut microbiota promises to replace fecal microbiota transplantation as a new treatment for Alzheimer's disease. Microorganisms, 2023, **11**(12): 2854

[41] Mancilla V J, Braden-Kuhle P N, Brice K N, *et al*. A synthetic formula amino acid diet leads to microbiome dysbiosis, reduced colon length, inflammation, and altered locomotor activity in C57BL/6J mice. Microorganisms, 2023, **11**(11): 2694

[42] Eepho O I, Bashir A M, Oniyide A A, *et al*. Modulation of GABA

by sodium butyrate ameliorates hypothalamic inflammation in experimental model of PCOS. BMC Neurosci, 2023, **24**(1): 62

[43] Olaniyi K S, Areloegbe S E, Oyeleke M B. Acetate restores hypothalamic-adipose kisspeptin status in a rat model of PCOS by suppression of NLRP3 immunoreactivity. Endocrine, 2022, **78**(3): 628-640

[44] Olaniyi K S, Agan S U, Areloegbe S E, *et al*. Acetate attenuates hypothalamic pyroptosis in experimentally induced polycystic ovarian syndrome. BMC Res Notes, 2024, **17**(1): 260

[45] Guo L, Wu Y, Wang C, *et al*. Gut microbiological disorders reduce semen utilization rate in duroc boars. Front Microbiol, 2020, **11**: 581926

[46] Cai H, Cao X, Qin D, *et al*. Gut microbiota supports male reproduction *via* nutrition, immunity, and signaling. Front Microbiol, 2022, **13**: 977574

[47] Round J L, Mazmanian S K. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci USA, 2010, **107**(27): 12204-12209

[48] El-Baz A M, Shata A, Hassan H M, *et al*. The therapeutic role of lactobacillus and montelukast in combination with metformin in diabetes mellitus complications through modulation of gut microbiota and suppression of oxidative stress. Int Immunopharmacol, 2021, **96**: 107757

[49] Bhushan S, Theas M S, Guazzone V A, *et al*. Immune cell subtypes and their function in the testis. Front Immunol, 2020, **11**: 583304

[50] Rehman A, Pacher P, Haskó G. Role of macrophages in the endocrine system. Trends Endocrinol Metab, 2021, **32**(4): 238-256

[51] Liu K S, Mao X D, Pan F, *et al*. Application of leukocyte subsets and sperm DNA fragment rate in infertile men with asymptomatic infection of genital tract. Ann Palliat Med, 2021, **10**(2): 1021

[52] Matsushita M, Fujita K, Hatano K, *et al*. Connecting the dots between the gut-IGF-1-prostate axis: a role of IGF-1 in prostate carcinogenesis. Front Endocrinol: Lausanne, 2022, **13**: 852382

[53] Ji J, Shu D, Zheng M, *et al*. Microbial metabolite butyrate facilitates M2 macrophage polarization and function. Sci Rep, 2016, **6**: 24838

[54] Jacobo P. The role of regulatory T Cells in autoimmune orchitis. Andrologia, 2018, **50**(11): e13092

[55] Liu T, Li J, Liu Y, *et al*. Short-chain fatty acids suppress lipopolysaccharide-induced production of nitric oxide and proinflammatory cytokines through inhibition of NF-κB pathway in $RAW_{264.7}$ cells. Inflammation, 2012, **35**(5): 1676-1684

[56] Colldén H, Landin A, Wallenius V, *et al*. The gut microbiota is a major regulator of androgen metabolism in intestinal contents. Am J Physiol Endocrinol Metab, 2019, **317**(6): E1182-E1192

[57] Zhu Y, Du Q, Jiao N, *et al*. Catalpol ameliorates diabetes-induced testicular injury and modulates gut microbiota. Life Sci, 2021, **267**: 118881

[58] Lin T, Li S, Xu H, *et al*. Gastrointestinal hormone secretion in women with polycystic ovary syndrome: an observational study. Hum Reprod, 2015, **30**(11): 2639-2644

[59] Moreira B P, Monteiro M P, Sousa M, *et al*. Insights into leptin signaling and male reproductive health: the missing link between overweight and subfertility?. Biochem J, 2018, **475**(22): 3535-3560

[60] Barreiro M L, Tena-Sempere M. Ghrelin and reproduction: a novel signal linking energy status and fertility?. Mol Cell Endocrinol, 2004, **226**(1/2): 1-9

[61] Zhang T, Sun P, Geng Q, *et al*. Disrupted spermatogenesis in a metabolic syndrome model: the role of vitamin A metabolism in the gut-testis axis. Gut, 2022, **71**(1): 78-87

[62] Clagett-Dame M, Knutson D. Vitamin A in reproduction and development. Nutrients, 2011, **3**(4): 385-428

[63] Chung S S, Wolgemuth D J. Role of retinoid signaling in the regulation of spermatogenesis. Cytogenet Genome Res, 2004, **105**(2/3/4): 189-202

[64] Schleif M C, Havel S L, Griswold M D. Function of retinoic acid in development of male and female gametes. Nutrients, 2022, **14**(6): 1293

[65] Thomas C M, Saulnier D M A, Spinler J K, *et al*. FolC2-mediated folate metabolism contributes to suppression of inflammation by probiotic Lactobacillus reuteri. MicrobiologyOpen, 2016, **5**(5): 802-818

[66] Rad I, Saberi A, Koochakzadeh-Nematollahi N S, *et al*. The effects of folic acid on testicular histology, sperm quality, and spermatogenesis indices following 3, 4-methylenedioxymethamphetamine exposure in adult male rats. Addict Health, 2021, **13**(1): 36-44

[67] 马赫 . $VK_2$ 依赖的 GGCX/MGP 维持附睾管腔钙稳态的机制和对男性生育的影响[D]. 中国人民解放军空军军医大学, 2019
Ma H. The Mechanism by Which GGCX/MGP, Which VK2 Depends on, Maintains The Calcium Homeostasis in The Epididymal Lumen and Its Impact on Male Fertility [D]. Xi'an: Air Force Medical University of the People's Liberation Army of China, 2019

[68] 宋婷, 李佳, 张茜, 等 . 基于肠道菌群维生素 $K_2$ 调控肝脏胰岛素抵抗作用机制 . 中国微生态学杂志, 2024, **36**(10): 1117-1122
Song T, Li J, Zhang Q, *et al*. Chin J Microecol, 2024, **36**(10): 1117-1122

[69] Shiba S, Ikeda K, Horie-Inoue K, *et al*. Vitamin K-dependent γ-glutamyl carboxylase in Sertoli cells is essential for male fertility in mice. Mol Cell Biol, 2021, **41**(4): e00404-20

[70] 裴洋, 刘星吟 . 肠道菌群对卵巢衰老的影响及其潜在的机制 . 中国细胞生物学学报, 2024, **46**(4): 912-924
Pei Y, Liu X Y. Chin J Cell Biol, 2024, **46**(4): 912-924

[71] Mandić A D, Woting A, Jaenicke T, *et al*. Clostridium ramosum regulates enterochromaffin cell development and serotonin release. Sci Rep, 2019, **9**: 1177

[72] Fujinoki M, Takei G L. γ -Aminobutyric acid suppresses enhancement of hamster sperm hyperactivation by 5-hydroxytryptamine. J Reprod Dev, 2017, **63**(1): 67-74

[73] Dai Z, Wu Z, Hang S, *et al*. Amino acid metabolism in intestinal bacteria and its potential implications for mammalian reproduction. Mol Hum Reprod, 2015, **21**(5): 389-409

[74] Mohapatra S K, Ranvir S, Nikam P, *et al*. Alleviation of fertility disorders based on probiotics induced immune system improvement: a review. Crit Rev Biomed Eng, 2019, **47**(5): 427-436

[75] Bakun O V, Voloshynovych N S, Dyak K V, *et al*. Probiotics and NLRP3 mRNA inflammasome levels in women with endometriosis-related infertility undergoing assisted reproductive technologies. J Med Life, 2023, **16**(10): 1439-1444

[76] Itoh H, Sashihara T, Hosono A, *et al*. Lactobacillus gasseri OLL2809 inhibits development of ectopic endometrial cell in peritoneal cavity *via* activation of NK cells in a murine endometriosis model. Cytotechnology, 2011, **63**(2): 205-210

[77] 马臣臣, 彭倩楠, 姜帅铭, 等. 益生菌 Bifidobacterium lactis V9 对多囊卵巢综合征患者肠道微生物组的调节作用. 科学通报, 2019, **64**(3): 360-368
Ma C C, Peng Q N, Jiang S M, *et al*. Chin Sci Bull, 2019, **64**(3): 360-368

[78] Jamilian M, Mansury S, Bahmani F, *et al*. The effects of probiotic and selenium co-supplementation on parameters of mental health, hormonal profiles, and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome. J Ovarian Res, 2018, **11**(1): 80

[79] Mohammadparast V, Mohammadi T, Karimi E, *et al*. Effects of probiotic and selenium co-supplementation on lipid profile and glycemia indices: a systematic review and meta-analysis of randomized clinical trials. Curr Nutr Rep, 2023, **12**(1): 167-180

[80] Zhang Y, Hou B, Liu T, *et al*. Probiotics improve polystyrene microplastics-induced male reproductive toxicity in mice by alleviating inflammatory response. Ecotoxicol Environ Saf, 2023, **263**: 115248

[81] Cao T, Wang S, Pan Y, *et al*. Characterization of the semen, gut, and urine microbiota in patients with different semen abnormalities. Front Microbiol, 2023, **14**: 1182320

[82] Helli B, Kavianpour M, Ghaedi E, *et al*. Probiotic effects on sperm parameters, oxidative stress index, inflammatory factors and sex hormones in infertile men. Hum Fertil, 2022, **25**(3): 499-507

[83] Oliveira L C S L, Costa E C, Martins F D G, *et al*. Probiotics supplementation in the treatment of male infertility: a Systematic Review. JBRA Assist Reprod, 2024, **28**(2): 341-348

[84] Kaliannan K, Wang B, Li X Y, *et al*. A host-microbiome interaction mediates the opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia. Sci Rep, 2015, **5**: 11276

[85] Samaneh Y, ShahidehJahanian S, Azadeh M, *et al*. The association of food consumption and nutrient intake with endometriosis risk in Iranian women: a case-control study. Int J Reprod Biomed, 2019, **17**(9): 661-670

[86] Gholizadeh Shamasbi S, Dehgan P, Mohammad-Alizadeh Charandabi S, *et al*. The effect of resistant dextrin as a prebiotic on metabolic parameters and androgen level in women with polycystic ovarian syndrome: a randomized, triple-blind, controlled, clinical trial. Eur J Nutr, 2019, **58**(2): 629-640

[87] Wang X, Xu T, Liu R, *et al*. High-fiber diet or combined with acarbose alleviates heterogeneous phenotypes of polycystic ovary syndrome by regulating gut microbiota. Front Endocrinol: Lausanne, 2021, **12**: 806331

[88] Zhou Y, Wei Z, Gao Y, *et al*. The role of alginate oligosaccharide on boar semen quality: a research review. Int J Biol Macromol, 2024, **277**: 134492

[89] Kaur I, Suri V, Sachdeva N, *et al*. Efficacy of multi-strain probiotic along with dietary and lifestyle modifications on polycystic ovary syndrome: a randomised, double-blind placebo-controlled study. Eur J Nutr, 2022, **61**(8): 4145-4154

[90] Martinez Guevara D, Vidal Cañas S, Palacios I, *et al*. Effectiveness of probiotics, prebiotics, and synbiotics in managing insulin resistance and hormonal imbalance in women with polycystic ovary syndrome (PCOS): a systematic review of randomized clinical trials. Nutrients, 2024, **16**(22): 3916

[91] Samimi M, Dadkhah A, Haddad Kashani H, *et al*. The effects of synbiotic supplementation on metabolic status in women with polycystic ovary syndrome: a randomized double-blind clinical trial. Probiotics Antimicrob Proteins, 2019, **11**(4): 1355-1361

[92] Maretti C, Cavallini G. The association of a probiotic with a prebiotic (Flortec, Bracco) to improve the quality/quantity of spermatozoa in infertile patients with idiopathic oligoasthenoteratospermia: a pilot study. Andrology, 2017, **5**(3): 439-444

[93] Akram M, Ali S A, Kaul G. Probiotic and prebiotic supplementation ameliorates chronic restraint stress-induced male reproductive dysfunction. Food Funct, 2023, **14**(18): 8558-8574

[94] Abbasi B, Abbasi H, Niroumand H. Synbiotic (FamiLact) administration in idiopathic male infertility enhances sperm quality, DNA integrity, and chromatin status: a triple-blinded randomized clinical trial. Int J Reprod Biomed, 2021, **19**(3): 235-244

[95] Chadchan S B, Naik S K, Popli P, *et al*. Gut microbiota and microbiota-derived metabolites promotes endometriosis. Cell Death Discov, 2023, **9**: 28

[96] Aron-Wisnewsky J, Clément K, Nieuwdorp M. Fecal microbiota transplantation: a future therapeutic option for obesity/diabetes?. Curr Diabetes Rep, 2019, **19**(8): 51

[97] Zhang C, Xiong B, Chen L, *et al*. Rescue of male fertility following faecal microbiota transplantation from alginate oligosaccharide-dosed mice. Gut, 2021, **70**(11): 2213-2215

[98] Zhang P, Feng Y, Li L, *et al*. Improvement in sperm quality and spermatogenesis following faecal microbiota transplantation from alginate oligosaccharide dosed mice. Gut, 2021, **70**(1): 222-225

[99] Jin Z, Yang Y, Cao Y, *et al*. The gut metabolite 3-hydroxyphenylacetic acid rejuvenates spermatogenic dysfunction in aged mice through GPX4-mediated ferroptosis. Microbiome, 2023, **11**(1): 212

[100] Łaniewski P, Ilhan Z E, Herbst-Kralovetz M M. The microbiome and gynaecological cancer development, prevention and therapy. Nat Rev Urol, 2020, **17**(4): 232-250

[101] Zhang J, Si Q, Li J. Therapeutic effects of metformin and

clomiphene in combination with lifestyle intervention on infertility in women with obese polycystic ovary syndrome. Pak J Med Sci, 2017, **33**(1): 8-12

[102] Ouyang J, Lin J, Isnard S, *et al*. The bacterium *Akkermansia muciniphila*: a sentinel for gut permeability and its relevance to HIV-related inflammation. Front Immunol, 2020, **11**: 645

[103] Yang Q, Wan Q, Wang Z. Curcumin mitigates polycystic ovary syndrome in mice by suppressing TLR4/MyD88/NF-κB signaling pathway activation and reducing intestinal mucosal permeability. Sci Rep, 2024, **14**: 29848

[104] Ghanbarzadeh-Ghashti N, Ghanbari-Homaie S, Shaseb E, *et al*. The effect of Curcumin on metabolic parameters and androgen level in women with polycystic ovary syndrome: a randomized controlled trial. BMC Endocr Disord, 2023, **23**(1): 40

[105] Feghhi F, Ghaznavi H, Sheervalilou R, *et al*. Effects of metformin and curcumin in women with polycystic ovary syndrome: a factorial clinical trial. Phytomedicine, 2024, **135**: 156160

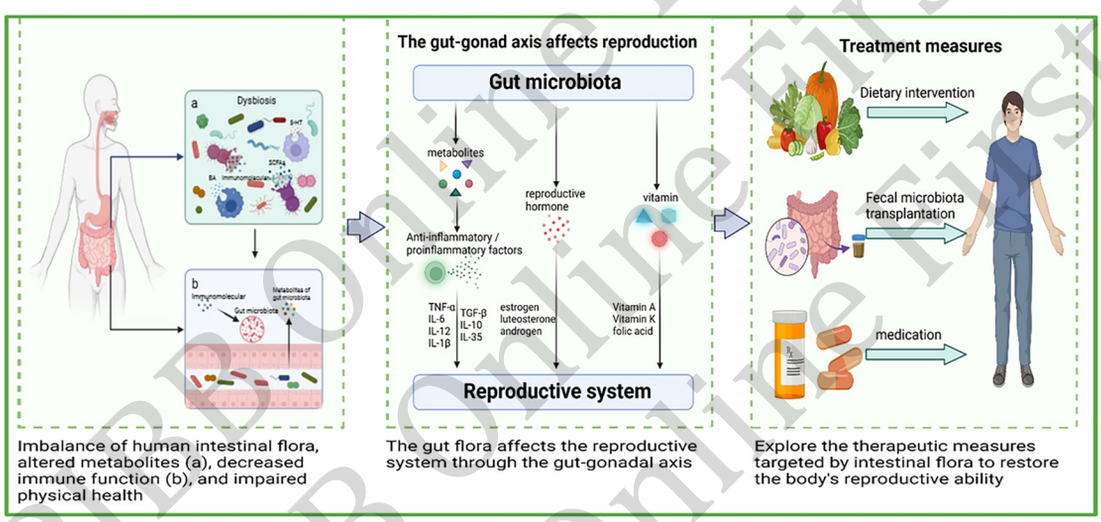
[106] 鄢盼 . 基于肠道菌群探讨从脾胃论治脾肾两虚型特发性少弱畸形精子症的临床研究[D]. 南京中医药大学, 2022
Yan P. Clinical Study on The Treatment of Idiopathic Oligoasthenoteratozoospermia With Spleen-kidney Deficiency Syndrome Based on The Intestinal Flora From The Perspective of Spleen and Stomach Therapy[D]. Nanjing: Nanjing University of Chinese Medicine, 2022

# Mechanisms of Gut Microbiota Influencing Reproductive Function *via* The Gut−Gonadal Axis*

ZHAO Ya-Qi[1,2], QI Li-Li[2)**], WANG Jin-Bo[2)**], HU Xu-Qi[2)], WANG Meng-Ting[2)], MAO Hai-Guang[2)], Sun Qiu-Zhen[3)]

([1)]*College of Life Sciences and Medicine, Zhejiang Sci-Tech University, Hangzhou* 310018, China;
[2)]*School of Biological and Chemical Engineering, NingboTech University, Ningbo* 315100, China;
[3)]*Zhejiang University Mingzhou Hospital, Ningbo* 315000, China)

## Graphical abstract




**Abstract**　Reproductive system diseases are among the primary contributors to the decline in social fertility rates and the intensification of aging, posing significant threats to both physical and mental health, as well as quality of life. Recent research has revealed the substantial potential of the gut microbiota in improving reproductive system diseases. Under healthy conditions, the gut microbiota maintains a dynamic balance, whereas dysfunction can trigger immune-inflammatory responses, metabolic disorders, and other issues, subsequently leading to reproductive system diseases through the gut-gonadal axis. Reproductive diseases, in turn, can exacerbate gut microbiota imbalance. This article explores the impact of the gut microbiota and its metabolites on both male and female reproductive systems, analyzing changes in typical gut microorganisms and their metabolites related to reproductive function. The composition, diversity, and metabolites of gut bacteria, such as *Bacteroides*, *Prevotella*, and *Firmicutes*, including short-chain fatty acids, 5-hydroxytryptamine, γ-aminobutyric acid, and bile acids, are closely linked to reproductive function. As reproductive diseases develop, intestinal immune function typically undergoes changes, and the expression levels of immune-related factors, such as Toll-like receptors and inflammatory cytokines (including IL-6, TNF-α, and TGF-β), also vary. The gut microbiota and its metabolites influence reproductive hormones such as estrogen, luteinizing hormone, and testosterone, thereby affecting folliculogenesis and spermatogenesis. Additionally, the metabolism and absorption of vitamins can also impact spermatogenesis through the gut-testis axis. As the relationship between the gut microbiota and reproductive diseases becomes clearer, targeted regulation of the gut microbiota can be employed to address reproductive

system issues in both humans and animals. This article discusses the regulation of the gut microbiota and intestinal immune function through microecological preparations, fecal microbiota transplantation, and drug therapy to treat reproductive diseases. Microbial preparations and drug therapy can help maintain the intestinal barrier and reduce chronic inflammation. Fecal microbiota transplantation involves transferring feces from healthy individuals into the recipient's intestine, enhancing mucosal integrity and increasing microbial diversity. This article also delves into the underlying mechanisms by which the gut microbiota influences reproductive capacity through the gut-gonadal axis and explores the latest research in diagnosing and treating reproductive diseases using gut microbiota. The goal is to restore reproductive capacity by targeting the regulation of the gut microbiota. While the gut microbiota holds promise as a therapeutic target for reproductive diseases, several challenges remain. First, research on the association between gut microbiota and reproductive diseases is insufficient to establish a clear causal relationship, which is essential for proposing effective therapeutic methods targeting the gut microbiota. Second, although gut microbiota metabolites can influence lipid, glucose, and hormone synthesis and metabolism *via* various signaling pathways—thereby indirectly affecting ovarian and testicular function—more in-depth research is required to understand the direct effects of these metabolites on germ cells or granulosa cells. Lastly, the specific efficacy of gut microbiota in treating reproductive diseases is influenced by multiple factors, necessitating further mechanistic research and clinical studies to validate and optimize treatment regimens.

**Key words**　gut microbiota, gut-gonadal axis, sterility, reproductive function
**DOI**：10.16476/j.pibb.2024.0462　　**CSTR**：32369.14.pibb.20240462

* This work was supported by grants from National Key R&D Program(2022YFD1300301), Ningbo Major Science and Technology Research Project (2021Z112, 2024Z180), Ningbo Science and Technology Special Commissioner Project(2022S225)and Ningbo Natural Science Foundation (2022J151, 2023J270).
** Corresponding author.
QI Li-Li. Tel：86-574-88130130，E-mail：qll@nbt.edu.cn
WANG Jin-Bo. Tel：86-574-88130130，E-mail：wjb@nbt.edu.cn
Received：November 6，2024　Accepted：February 27，2025