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Gut Microbiota and Probiotics in Obesity-Associated Female Reproductive Dysfunction: Underlying Mechanisms and Therapeutic Potential

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ABSTRACT: Obesity adversely affects female reproductive health via metabolic dysregulation, chronic inflammation, and hormonal imbalances, leading to conditions such as ovulatory dysfunction, polycystic ovary syndrome (PCOS), and pregnancy complications. Emerging evidence identifies gut microbiota dysbiosis as a key mediator that transmits obesity-related metabolic and inflammatory signals to the reproductive system. Characteristic alterations in obesity—including an elevated Firmicutes/Bacteroidetes (F/B) ratio, reduced short-chain fatty acid (SCFA) production, and endotoxemia—promote reproductive dysfunction by activating inflammatory pathways and disrupting hormonal balance. Targeting the gut microbiota with probiotics offers a promising therapeutic approach through structural and functional remodeling of the microbiota, enhanced barrier integrity, and immunomodulation. Nevertheless, challenges such as insufficient understanding of strain-specific mechanisms, scarce clinical evidence, and the absence of personalized protocols persist. This review synthesizes the impact of obesity on female reproduction, outlines the gut microbiota's regulatory role, and explores the dual mechanisms of probiotic action. Future research should leverage multi-omics technologies, stratified population studies, and functional strain analysis to facilitate the translational application of probiotics in reproductive medicine.

Keywords: obesity, female reproduction, gut microbiota, probiotics

1. Introduction

Obesity represents a formidable and escalating challenge to global public health. According to the World Health Organization (WHO), the worldwide prevalence of obesity has risen steadily over recent decades, and it is estimated that by 2030, nearly one in three adults will be affected by this condition [1]. Beyond its well-established role as a major risk factor for cardiovascular disease, type 2 diabetes, and certain cancers, obesity exerts distinct effects on female reproductive health through sex-specific mechanisms—such as

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disruptions in estrogen metabolism and differences in adipose tissue distribution. Female reproductive dysfunction refers to structural, functional, or endocrine abnormalities of the reproductive system that compromise fertility, sexual health, or menstrual cyclicity. This broad category includes diseases such as polycystic ovary syndrome (PCOS), premature ovarian insufficiency (POI), and hyperprolactinemia [2]. Clinically, these conditions may present as ovulatory failure, recurrent pregnancy loss, amenorrhea, or other forms of hormonal imbalance [3]. Evidence indicated that obesity can promote hormonal dysregulation, leading to menstrual irregularities, anovulation, or PCOS, thereby substantially elevating the risk of infertility [4]. Moreover, obesity heightens the likelihood of pregnancy-related complications, including gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), and preterm birth, which pose significant threats to both maternal and fetal health [5, 6]. Women with obesity are more susceptible to reproductive endocrine disturbances than men, and they experience a greater metabolic burden during pregnancy, underscoring a particular vulnerability to obesity-related pathologies. Thus, elucidating the impact of obesity on female reproductive health is essential not only for individual patient care but also for broader public health initiatives.

In recent years, growing attention has been directed toward the involvement of the gut microbiota in obesity and its associated complications. Individuals with obesity often exhibit characteristic alterations in gut microbial composition, including an elevated Firmicutes/Bacteroidetes (F/B) ratio, reduced production of short-chain fatty acids (SCFAs), and increased endotoxemia [7, 8]. These changes are known to aggravate metabolic dysfunction via axes such as the gut–brain and gut–liver pathways, and may also directly influence female reproduction through a "gut microbiota–reproductive axis." For instance, studies demonstrated that gut microbiota dysbiosis can elevate circulating lipopolysaccharide (LPS) levels, activate the ovarian TLR4/NF-κB inflammatory pathway, suppress follicular development, and disrupt hormonal secretion [9, 10]. Conversely, other research showed that microbial metabolites such as SCFAs (e.g., butyrate) help improve insulin sensitivity and support ovulatory function via G protein-coupled receptors (GPR41/43) and epigenetic pathways [11, 12].

Interventions targeting the gut microbiota, particularly the use of probiotics, have opened new avenues for preventing and treating obesity-related reproductive conditions. Probiotics demonstrate dual potential—improving both metabolic and reproductive outcomes—by limiting pathogen colonization, reinforcing intestinal barrier function, and modulating host immune activity [13, 14]. Nevertheless, most current evidence derives from studies involving single bacterial strains or animal models. Clinical data across diverse human populations remain limited, and the complex interplay between strain specificity, intervention duration, and host genetic background has not been fully elucidated [15, 16]. This review seeks to summarize the pathological mechanisms linking obesity to female reproductive disorders, with an emphasis on the gut microbiota's regulatory influence and the intervention strategies employing beneficial microbes. This paper aims to systematically analyze the pathological processes of obesity-related female reproductive dysfunction, with a focus on exploring the regulatory role of gut microbiota and probiotic intervention strategies, in order to

provide theoretical support for precision nutritional intervention in the cross-field of food science and reproductive medicine.

2. Pathological mechanisms of obesity-related female reproductive dysfunction

2.1 Effects of obesity on ovulation dysfunction and PCOS

Ovulatory dysfunction represents a key diagnostic criterion for polycystic ovary syndrome (PCOS), which exhibits a complex bidirectional pathological relationship with obesity. Research has demonstrated that obesity disrupts the hypothalamic-pituitary-ovarian axis via the underlying pathways including insulin resistance (IR), hyperleptinemia, and chronic inflammation, thereby aggravating PCOS manifestations [17]. A central feature of obesity-associated PCOS is IR. Hyperinsulinemia stimulates the expression of androgen-synthesizing enzymes through activation of the insulin-like growth factor 1 receptor (IGF-1R) in ovarian theca cells, consequently elevating circulating androgen levels [18]. Concurrently, leptin secretion from adipose tissue is markedly increased in individuals with obesity, while the expression of leptin receptors in granulosa cells becomes downregulated, culminating in leptin resistance. This state further suppresses aromatase activity and impairs the conversion of androgens to estrogens [19, 20]. Such hormonal dysregulation not only contributes to anovulation and menstrual irregularities but may also induce follicular developmental arrest by activating pro-inflammatory pathways within the ovary, such as the nuclear factor kappa-B (NF-κB) cascade [21].

Notably, the interaction between obesity and PCOS forms a self-perpetuating vicious cycle. Patients with PCOS are predisposed to visceral fat accumulation as a result of hyperandrogenism and IR. Adipose tissue-derived inflammatory mediators, including TNF-α and IL-6, in turn exacerbate IR by impairing the phosphorylation of insulin receptor substrate 1 (IRS-1) [20]. Clinical evidence further indicates that the risk of spontaneous miscarriage is 1.5-fold higher among obese patients compared to those with normal body weight—a phenomenon potentially linked to hyperinsulinemia-induced impairment of endometrial receptivity and oxidative stress damage [22].

2.2 Effects of obesity on oocyte quality and embryo development

Obesity significantly impairs oocyte quality and embryo development through multiple interconnected pathological pathways. Hyperinsulinemia, for instance, disrupts the androgen-to-estrogen balance within the follicular microenvironment, thereby impairing normal oocyte maturation [23]. Clinical investigations have further revealed that obese women (BMI > 35 kg/m²) undergoing in vitro fertilization (IVF) exhibit a significantly higher incidence of meiotic spindle abnormalities and chromosomal misalignment in oocytes compared to normal-weight individuals, indicating that obesity adversely affects nuclear-cytoplasmic synchrony during oocyte development [24]. Concurrently, obesity induces alterations in the composition of follicular fluid, which exacerbate germ cell damage [25]. In obese patients, antioxidant levels in follicular fluid are markedly reduced, whereas pro-inflammatory factor concentrations rise, creating a state of redox imbalance. This compromised microenvironment promotes DNA damage and reduces mitochondrial

membrane potential in oocytes, ultimately diminishing the developmental competence of embryos following fertilization [26]. A metabolomic study involving women with PCOS reported that the follicular fluid metabolic profile was predominantly disturbed in pathways related to glycerophospholipid metabolism, ether lipid metabolism, and primary bile acid biosynthesis. Notably, overweight individuals showed significant alterations in lipid metabolites such as glycerophospholipids, underscoring an independent effect of obesity on follicular fluid metabolism [27]. Additional clinical observations have documented a substantial increase in $CD4^+$ T cells and Th2-type cytokines (e.g., IL-4, IL-13) within the pre-ovulatory follicular microenvironment of obese women, accompanied by a widened triglyceride concentration gradient between serum and follicular fluid, collectively contributing to impaired embryo quality [28]. Another study conducted in infertile women receiving assisted reproductive technology (ART) treatment observed a significant reduction in monocyte and macrophage subpopulations in the follicular fluid of obese patients (BMI > 25 kg/m^2) [29]. Together, these findings indicate that obesity compromises assisted reproduction outcomes by disrupting both immune homeostasis and metabolic equilibrium within the follicular niche.

2.3 Mechanisms of the association between obesity and pregnancy complications

Obesity significantly elevates the risk of pregnancy complications through multifaceted pathological processes involving metabolic dysregulation, chronic inflammation, and impaired placental function. Gestational diabetes mellitus (GDM) represents one of the most frequent metabolic dysfunction in obese pregnant women. Insulin resistance (IR) and elevated free fatty acids associated with obesity impair pancreatic β-cell compensatory capacity, while adipose tissue-derived inflammatory cytokines further disrupt glucose homeostasis by interfering with insulin receptor signaling [30]. Clinical studies have reported an increased incidence of GDM in obese pregnancies, wherein maternal hyperglycemia promotes macrosomia and neonatal hypoglycemia via activation of placental oxidative stress pathways [5, 6].

The development of gestational hypertension or preeclampsia (PE) is closely linked to obesity-induced vascular endothelial dysfunction. Elevated levels of leptin and angiopoietin-like protein 4 (ANGPTL4) in obese gravidas inhibit nitric oxide synthesis, leading to vasoconstriction and reduced placental perfusion [31]. Moreover, obesity drives endothelial dysfunction, placental ischemia, and systemic vascular injury through synergistic effects of adipokine imbalance, chronic inflammation, oxidative stress, IR, and aberrant placental angiogenesis. Regular exercise may mitigate these effects by promoting weight control and improving metabolic, vascular, and inflammatory parameters [32]. Epidemiological analyses have documented a graded increase in PE incidence with rising BMI: rates of 2.6%, 4.7%, 7.8%, and 10.3% were observed in normal-weight, overweight, obese, and severely obese pregnant women, respectively [6].

Preterm birth constitutes another significant adverse outcome in obese pregnancies, primarily driven by two mechanistic pathways. First, mechanical compression from excessive visceral adipose tissue alters uterine architecture, generating physical strain that may initiate premature labor. Second, dysregulated uterine contractility—marked by aberrant myometrial contractions—further elevates preterm delivery risk [33]. A comprehensive meta-analysis of 86 cohort studies (covering > 20 million pregnancies) quantified these

associations, revealing that overweight/obesity increased odds of cesarean delivery (OR: 1.40–1.98), GDM (OR: 2.10–4.10), and PE (OR: 1.89–3.57). Importantly, maternal obesity independently raised preterm birth risk (OR: 1.17), with a stronger effect size for extreme prematurity (OR: 1.40) [34]. Dose-response analyses further established that each 5 kg/m² increment in pre-pregnancy BMI increased preterm birth likelihood by 1.3-fold. Specifically, class III obesity (BMI ≥40 kg/m²) was associated with a 9.1% preterm birth rate—nearly double the 4.7% observed in normal-weight pregnancies [35, 36]. Emerging evidence indicates that obesity-related gut microbiota dysbiosis may exacerbate these risks via the gut-placenta axis. In obese pregnant women, increased intestinal Firmicutes abundance showed positive correlation with placental inflammatory markers (e.g., IL-1β), suggesting that microbial metabolites such as lipopolysaccharide (LPS) may translocate into circulation and directly compromise placental barrier integrity [37] (Figure 1).

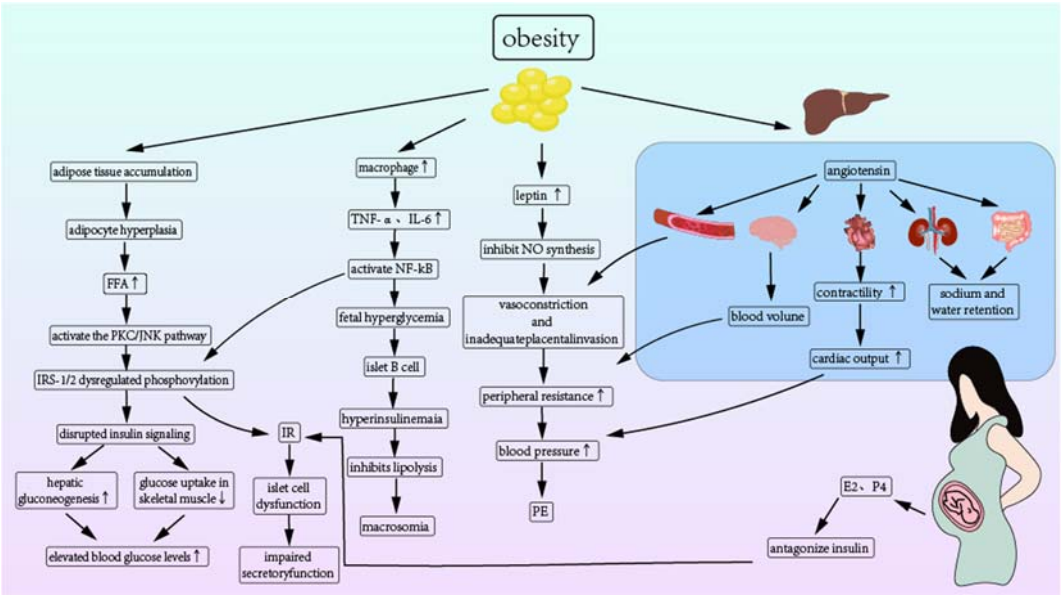

Figure 1. The impact of obesity on pregnancy and fetal development. Obesity triggers a cascade of pathological events that adversely affect pregnancy and fetal outcomes. These include chronic low-grade inflammation (elevated TNF-α and IL-6), insulin resistance, and vascular dysfunction. These derangements lead to placental dysfunction (e.g., hypoxia and impaired angiogenesis) and maternal metabolic and cardiovascular dysregulation (including hepatic steatosis, hypertension, and altered cardiac output). Collectively, these processes increase the risk of pregnancy complications, such as gestational diabetes mellitus and preeclampsia, and exert deleterious effects on fetal development.

In summary, obesity inflicts multi-dimensional and multi-target damage on the female reproductive system, driven by the interplay of hormonal imbalance, elevated oxidative stress, aberrant metabolic reprogramming, and disrupted immune homeostasis. These pathological mechanisms reinforce one another through metabolic–immune–endocrine crosstalk, forming a self-sustaining vicious cycle that markedly elevates the risk of ovulatory dysfunction, impaired embryonic development, and pregnancy-related complications. Notably, recent findings has revealed that obesity-associated gut microbiota dysbiosis may further amplify inflammatory and metabolic disturbances in the reproductive system via a microbial metabolite-mediated “gut–obesity–reproductive axis.” This microbiota-driven systemic regulatory network offers a novel conceptual framework for advancing our understanding of the pathological basis of obesity-related reproductive dysfunction.

3. Interactive regulation of obesity and reproductive health mediated by gut microbiota

3.1 Metabolic characteristics of obesity-related gut microbiota dysbiosis

Obesity-associated gut microbiota dysbiosis is characterized by reduced microbial diversity and functional imbalance. Through microbial metabolites, it establishes a complex bidirectional regulatory network with the host, ultimately aggravating energy metabolism dysfunction. Historically, an elevated Firmicutes/Bacteroidetes (F/B) ratio was considered a hallmark of dysbiosis in obesity, potentially linked to enhanced dietary energy harvest—such as through enrichment of genes encoding polysaccharide-degrading enzymes [38]. However, recent studies have cautioned that the clinical relevance of the F/B ratio must be interpreted with care. Population-based cohort investigations have revealed that the association between this ratio and obesity is significantly influenced by dietary patterns, geographic variations, and sequencing methodologies. For instance, an increased F/B ratio in high-fiber consumers may correlate with improved metabolic health, whereas the same shift in high-fat diet populations is often associated with heightened inflammation [39]. Nevertheless, substantial evidence supports the role of gut bacteria in mediating bidirectional gut–adipose tissue crosstalk. Even in the presence of a comparable F/B ratio, obese individuals may exhibit specific alterations in microbial functional gene profiles—such as those involved in SCFA synthesis and bile acid metabolism—implying that functional dysregulation of the microbiota holds greater pathological significance than compositional changes alone [40] (Figure 2).

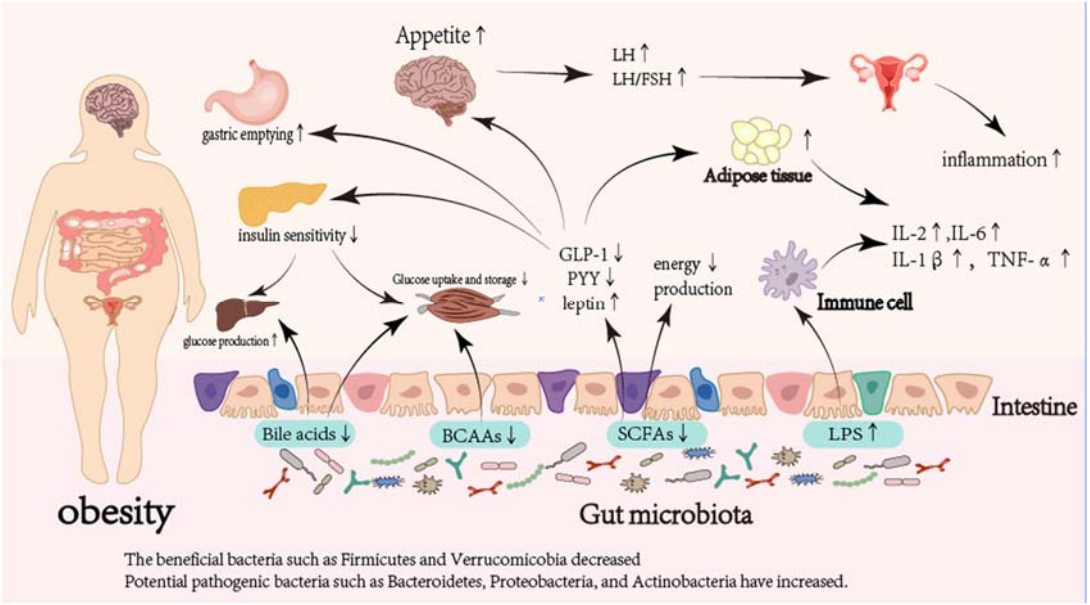

Figure 2. Mechanisms linking gut microbiota dysbiosis in obesity to host metabolism and female reproductive health. Obesity-associated gut dysbiosis (e.g., an increased F/B ratio) influences host metabolism through microbial metabolites, modulating gastric emptying, insulin sensitivity, glucose homeostasis, and bile acid metabolism. This dysbiosis also compromises the secretion of appetite-regulating hormones (e.g., GLP-1, PYY, leptin) and triggers a systemic inflammatory response, characterized by the release of pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α). Furthermore, these changes impact the female reproductive endocrine system, leading to elevated LH levels and an altered LH/FSH ratio, which are potential contributors to reproductive dysfunction such as PCOS.

In metabolite-mediated host energy regulation, the gut microbiota exerts a central influence through two key classes of molecules: SCFAs and bile acids [41]. SCFAs, such as acetate, propionate and butyrate, are primarily generated via microbial fermentation of dietary fiber. Acetate is produced through the acetyl-CoA

pathway, propionate via the succinate or acrylate pathways, and butyrate through the condensation of acetyl-CoA to butyryl-CoA. The final proportions of these metabolites are shaped by metabolic interactions among microbial species, such as cross-feeding [42]. These microbiota-derived SCFAs modulate host inflammatory responses and lipid metabolism via G protein-coupled receptor (GPCR)-mediated immune regulation, playing a pivotal role in the pathogenesis and progression of obesity [43]. Clinical observations have indicated that reduced colonization of SCFA-producing genera such as *Faecalibacterium* and *Roseburia* in obese individuals leads to impaired acetate and butyrate synthesis. This deficiency compromises intestinal epithelial energy supply and barrier function, thereby disrupting normal fat storage regulation and promoting obesity [44]. Additionally, SCFAs stimulate enteroendocrine cells to release glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) through activation of GPR41/GPR43, which in turn suppresses appetite and enhances insulin sensitivity [11, 45].

In addition, bile acid metabolism undergoes significant reprogramming influenced by the gut microbiota. Microbes contribute to the biotransformation of primary bile acids into secondary bile acids and modulate their enterohepatic recycling, processes intimately linked to obesity development [46]. Specifically, gut bacteria convert primary bile acids to secondary forms via 7α-dehydroxylase activity. These secondary bile acids regulate lipid oxidation and energy expenditure by activating the farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor TGR5 [47]. Furthermore, microbial functional alterations can reduce bile salt hydrolase (BSH) activity, leading to elevated circulating levels of taurodeoxycholic acid (TDCA) and tauroursodeoxycholic acid (TUDCA). These metabolites have been shown to reduce body weight and fasting blood glucose by inhibiting intestinal carbonic anhydrase 1 (Car1) expression and limiting intestinal lipid and energy absorption [48].

Critically, obesity and gut microbiota dysbiosis engage in a mutually reinforcing vicious cycle. Specific bacterial taxa promote adipose tissue inflammation and insulin resistance by degrading the mucosal layer, releasing endotoxins such as lipopolysaccharide (LPS), and activating the Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) pathway [44, 49]. Obesity-associated dietary habits—such as high-fat, low-fiber diets—along with the resulting metabolic-inflammatory microenvironment, favor the expansion of conditional pathogens while suppressing beneficial SCFA-producing bacteria. This creates a positive feedback loop that perpetuates microbial imbalance [41] (Figure 3). Such bidirectional interactions not only amplify metabolic dysregulation but may also indirectly perturb hormonal balance and endocrine homeostasis in individuals with obesity.

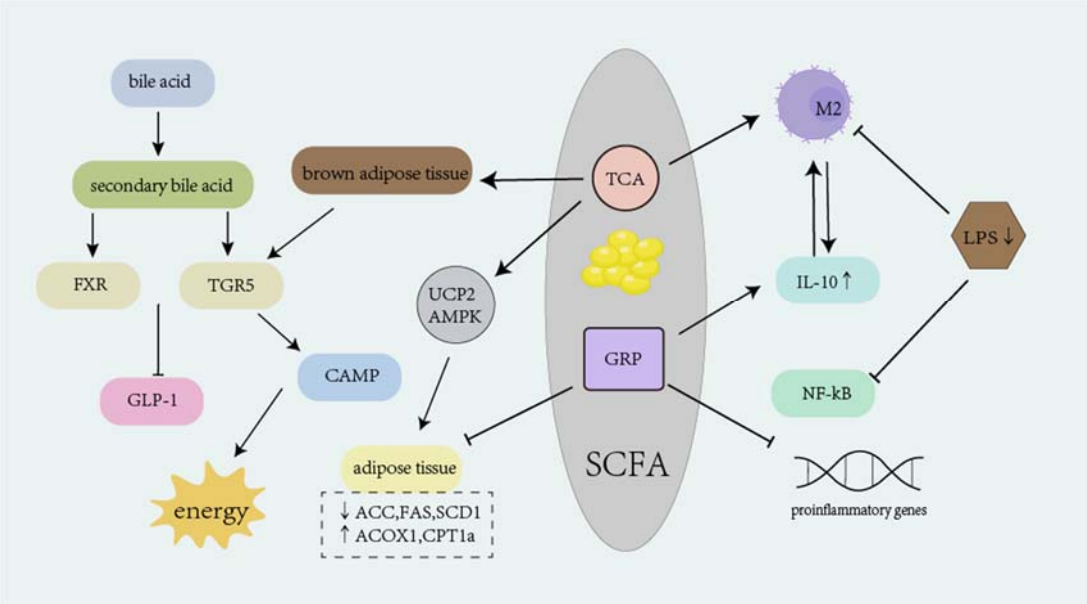

Figure 3. Metabolic and signaling pathways of microbial metabolites (SCFAs and BAs) in adipose tissue and inflammatory regulation. Gut microbiota-derived SCFAs and secondary BAs play crucial roles in energy metabolism and inflammation. Secondary BAs activate the FXR and the G protein-coupled bile acid receptor TGR5, influencing GLP-1 secretion and energy expenditure in brown adipose tissue via pathways involving UCP2 and AMPK. SCFAs interact with receptors such as GPR41/GPR43, modulating cAMP levels and downstream signaling. Additionally, SCFAs promote anti-inflammatory M2 macrophage polarization through IL-10 and inhibit the LPS-induced NF-κB pathway, thereby suppressing the expression of pro-inflammatory genes. *Abbreviations: ACC, acetyl-CoA carboxylase; ACOX1, acyl-CoA oxidase 1; AMPK, AMP-activated protein kinase; CPT1a, carnitine palmitoyltransferase 1a; FAS, fatty acid synthase; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; IL, interleukin; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPAR-γ, peroxisome proliferator-activated receptor gamma; SCD1, stearoyl-CoA desaturase-1; SCFAs, short-chain fatty acids; TGR5, Takeda G protein-coupled receptor 5; UCP2, uncoupling protein 2.*

3.2 Gut microbiota-reproductive axis: Immune and hormonal regulatory networks

Through immune and hormonal networks, the gut microbiota mediates the pathological connection between obesity and reproductive dysfunction in both sexes. This process involves coordinated dysregulation of endotoxemia, inflammatory signaling, and steroid hormone metabolism [50]. A key mechanism is the direct influence of gut microbes on female reproductive function via estrogen enterohepatic circulation. Bacterial β-glucuronidase hydrolyzes hepatic-conjugated, inactive estrogen (e.g., estradiol-glucuronide), releasing bioactive free estrogen, which is subsequently reabsorbed into circulation. This process helps maintain systemic estrogen levels, thereby regulating physiological functions including menstrual cyclicity and bone metabolism [51]. The enzymatic activity depends on specific recognition and cleavage of β-glycosidic bonds. The liberated estrogen re-enters the bloodstream via passive diffusion or transporter-mediated uptake—a process modulated by gut microbiota composition, dietary patterns, and host genetics [52, 53]. Studies have indicated that gut microbiota dysbiosis, such as an increased abundance of Desulfobacterota, can upregulate β-glucuronidase activity, elevating free estrogen levels and potentially contributing to macrophage dysfunction and endometriosis progression [54]. Conversely, in pre-menopausal women, enrichment of beneficial microbes like *Akkermansia muciniphila* and *Parabacteroides johnsonii* enhances estrogen recycling, which may lower cardiometabolic risk after menopause [55]. These findings highlight the dual role of microbial β-glucuronidase in both disease pathogenesis and physiological homeostasis.

Furthermore, studies have reported altered gut microbiota in endometriosis patients, marked by reduced diversity, compositional imbalance, and increased pathobionts. Shifts such as an elevated F/B ratio or decreased *Lactobacillus* abundance may disrupt immune homeostasis and promote chronic inflammation, adversely affecting reproductive health [56]. Beyond direct hormonal regulation, the gut microbiota indirectly influences female reproduction via its metabolites. For example, pregnant women with pre-eclampsia show markedly reduced colonization of *Coprococcus* [57] , while patients with PCOS exhibit decreased abundance of *Lachnospira* and *Prevotella*, which involved in SCFA production and bile acid metabolism [58]. Transplantation of gut microbiota from PCOS patients into mice recapitulates key phenotypes including insulin resistance, altered bile acid metabolism, reduced interleukin-22 secretion, and reproductive abnormalities [59]. Agmatine, a metabolite derived from *Bacteroides vulgatus*, has been identified as a critical mediator in this process. It activates the FXR signaling pathway in intestinal epithelial cells and suppresses GLP-1 secretion via a bile acid-independent mechanism, contributing to insulin resistance and ovarian dysfunction [60]. Recent work also implicates gut fungi in PCOS pathogenesis: colonization with *Aspergillus tubingensis* promotes PCOS features by producing a secondary metabolite, AT-C1, which antagonizes AhR [61]. Collectively, these studies underscore the close relationship between gut microbes—including fungi—and their metabolites with female reproductive health. Dysbiosis or overgrowth of harmful microorganisms can initiate or worsen disease via direct and indirect pathways, ultimately compromising reproductive function.

Accumulating evidence positions gut microbiota dysbiosis as a pivotal link between obesity and female reproductive dysfunction, primarily through intertwined metabolic, inflammatory, and hormonal process. As a central hub interfacing metabolic and reproductive systems, the gut microbiota likely mediates obesity's detrimental effects via a triad of "metabolites–immune inflammation–hormone regulation." Several clinical trials have reinforced the close association between gut microbiota dysbiosis and obesity-related gestational diabetes mellitus (GDM). The gut microbiota of GDM patients exhibits characteristic alterations, including depletion of commensals such as *Prevotellaceae*, *Fusobacteriales*, and *Sutterella*, alongside enrichment of potential pathobionts like *Enterococcus*, *Erysipelotrichaceae* UCG-003, and *Ruminococcus obeum*. Fungal communities also shift, with dominance of *Mucor* in healthy pregnancy replaced by expanded *Candida* abundance in GDM, suggesting that bacterial-fungal interactions may contribute to dysglycemia [62, 63]. Functionally, the GDM microbiota displays impaired SCFA synthesis. Butyrate-producing bacteria such as *Coprococcus* and *Akkermansia* correlate positively with plasma acetate and valerate levels, and reduced SCFA output may exacerbate insulin resistance by dampening gut–brain axis signaling [62, 63]. It is worth noting that obesity, as an independent risk factor for GDM, further exacerbates microbiota dysbiosis. In overweight/obese pregnant women, the genera *Megasphaera* and *Odoribacter* are positively correlated with BMI, and the imbalance of the F/B ratio is significantly associated with abnormal blood lipids [63, 64]. It is worth noting that obesity serves as an independent risk factor for GDM, and further perturbs microbial ecology. In overweight/obese pregnant women, genera such as *Megasphaera* and *Odoribacter* exhibit positive correlations with BMI, and an imbalanced F/B ratio is significantly associated with dyslipidemia [62, 64].

In summary, specific microbial signatures have been identified across various female reproductive dysfunction, reinforcing the correlation between gut microbiota dysbiosis and disease pathogenesis. Targeted probiotics—such as strains of *Lactobacillus* and *Bifidobacterium*—hold promise for alleviating symptoms through microbiota modulation and may serve as novel standalone or adjunct therapies [65].

4. Dual-effect mechanism of probiotics targeting the gut microbiota to improve reproductive dysfunction

4.1 Mechanism of probiotics regulating obesity-related metabolic dysfunction through the microbiota

As live microorganisms that can bring health benefits to the host when appropriately ingested, probiotics can improve obesity-related metabolic dysfunction by reshaping the structure and function of the gut microbiota and have great potential in controlling and preventing obesity [66, 67]. One key mechanism involves the modulation of host lipid metabolism pathways. Specific probiotic strains regulate the expression of key enzymes involved in fatty acid oxidation and lipogenesis. For instance, Zhang et al. reported that *Lactobacillus rhamnosus* GG activates the AMPK pathway, thereby reducing fat deposition [68]. Similarly, *Latilactobacillus plantarum* LG42 was shown to downregulate the activity of lipogenic enzymes FAS and ACC, while enhancing fatty acid oxidase CPT activity and the expression of PPAR-γ and C/EBPα, collectively attenuating obesity progression [69]. Certain strains, including *Lactobacillus plantarum* and *Bifidobacterium bifidum,* not only inhibit the proliferation of harmful bacteria and alleviate dysbiosis-associated inflammation but also strengthen the intestinal mucosal barrier. These probiotics further modulate lipid synthesis genes and phosphoprotein profiles through signaling pathways such as AMPK/Nrf2, LPS-TLR4-NF-κB, AMPKα/PGC-1α, and SREBP-1/FAS/ACC, resulting in reduced hepatic lipid accumulation and oxidative stress [70].

Another study demonstrated that intervention with *Akkermansia muciniphila* in high-fat-diet-fed mice increased the lipid metabolism rate by 42.42% [71] and reduced body weight by 20.8% [72]. The outer membrane protein Amuc_1100, derived from *A. muciniphila*, enhances immune regulation via TLR2 activation, upregulates intestinal barrier proteins, limits endotoxin translocation [73], and suppresses cholesterol synthesis-related gene expression in the liver and ileum, thereby lowering hepatic and circulating cholesterol levels [74]. Beyond lipid modulation, Live biotherapeutics can attenuate systemic inflammation and improve metabolic health by suppressing pathogenic microorganisms or modulating microbiota-derived metabolites [75, 76]. For example, *Lactobacillus rhamnosus* HL-200 restores ethanolamine metabolism in the gut microbiota, counteracts obesity-induced ethanolamine accumulation, and repairs intestinal barrier function via the ARID3a/miR-101a/Zo1 axis, leading to reduced inflammation and improved glucose homeostasis[77]. The multi-strain probiotic preparation VSL#3 (containing *Lactobacillus strains, Bifidobacterium strains* and *Streptococcus salivarius subsp. thermophilus*) has been shown to mitigate high-fat-diet-induced weight gain, metabolic abnormalities—such as impaired glucose tolerance and insulin resistance—and adipose tissue inflammation by decreasing pro-inflammatory cytokines (TNF-α, IFN-γ, IL-6) and elevating anti-inflammatory mediators (IL-4, IL-10). These effects suggest that beneficial microbes alleviate

obesity-related metabolic dysregulation and chronic inflammation partly through modulating invariant natural killer T (iNKT) cell populations [78].

It is important to note that the efficacy of probiotics in counteracting obesity-associated metabolic disturbances and reshaping the gut microbiota is highly strain-specific. Although many strains share common benefits—such as reducing body fat and improving insulin sensitivity—their influence on gut microbial composition and function varies substantially in scope and intensity (Table 1). This specificity is reflected not only in shifts in the abundance of beneficial or conditional pathogenic bacteria but also in the formation of distinct intervention networks mediated through metabolite production and barrier reinforcement. A deeper understanding of how individual probiotic strains uniquely modulate host–microbiota crosstalk is essential for developing targeted and effective metabolic interventions.

Table 1 Effects of probiotic interventions on obesity and associated metabolic parameters in preclinical and clinical studies

Probiotic Strain	Study Model	Daily Dose (CFU)	Duration	Key Outcomes	Reference
Bacillus amyloliquefaciens SC06	Mice with HFD	~ 5×10^7	8 weeks	Decreased F/B ratio; reduced body weight gain and ameliorated hepatic steatosis.	[79]
Lactobacillus rhamnosus GG	Mice with HFD	1×10^7	10 weeks	Reduced F/B ratio; effective in obesity prevention.	[80]
Lacticaseibacillus plantarum K50	Adults with obesity	4×10^9	12 weeks	Increased abundance of *Lacticaseibacillus*; reduced *Actinobacteria*; lowered total cholesterol and triglyceride levels.	[81]
Lacticaseibacillus plantarum HAC01	Mice with HFD	1×10^8	12 weeks	Reduced mesenteric adipose; increased the lipid oxidative gene expressions.	[82]
Multi-strain mixture (*L. acidophilus, L. rhamnosus, L. paracasei, etc.*)	Patients with NAFLD	1×10^9	12 weeks	Enriched *Lacticaseibacillus* and *Bifidobacterium* species; reduced BMI and intrahepatic fat fraction	[83]
Lacticaseibacillus paracasei K56	Mice with HFD	1×10^9	10 weeks	Modulated gut microbiota (e.g., reduced *Verrucomicrobia*); decreased body weight and fat mass.	[84]
Lacticaseibacillus plantarum FRT10	Mice with HFD	1×10^{10}	8 weeks	Reduced fat mass and hepatic triacylglycerol content; lowered serum alanine aminotransferase levels; alleviated HFD-induced gut microbiota dysbiosis.	[85]
Bifidobacterium lactis LMG P-28149	Mice with HFD	1×10^9	7-16 weeks	Increased abundance of *Akkermansia muciniphila* and *Rikenellaceae*; remodeled adipose tissue immune cell populations; ameliorated adiposity, insulin resistance, and dyslipidemia.	[14]

4.2 Dual Pathway of Probiotics in Improving Female Reproductive Function

The beneficial effects of probiotics on female reproductive health are characterized by multi-dimensional and cross-system regulatory features, distinguishing this area of research. The core mechanisms can be innovatively summarized as a dual-pathway model: a direct pathway targeting the complex interplay between the reproductive tract and gut microbes, and an indirect pathway focused on ameliorating obesity-related metabolic disturbances. On one hand, probiotics directly inhibit pathogen proliferation and maintain local

immune homeostasis through colonization or modulation of the reproductive tract microbiota, thereby reducing risks of bacterial vaginosis and ascending infections [86]. On the other hand, the gut microbiota serves as a "remote regulatory hub," influencing ovarian function, endometrial receptivity, and hypothalamic–pituitary–ovarian (HPO) axis rhythm via circulating metabolites and immune signaling molecules, collectively forming a systemic network referred to as the "gut–reproductive axis" [87, 88]. In addition, obesity-associated insulin resistance (IR), chronic inflammation, and oxidative stress represent key drivers of reproductive impairment. By remodeling gut microbial structure and improving host metabolic status, probiotics can indirectly restore ovulatory function and enhance embryonic developmental potential [89, 90].

Accumulating evidence confirms the close association between the reproductive tract microbiota and female reproductive health. Lactic acid production contributes to endometrial receptivity and embryo implantation, underscoring the importance of *Lactobacillus* abundance in the reproductive tract for sustaining pregnancy [91]. A multicenter prospective observational study revealed that endometrial enrichment of *Lactobacillus* is positively associated with live birth rates in assisted reproduction, whereas pathogenic genera such as *Gardnerella*, *Klebsiella*, and *Streptococcus* are significantly increased in non-pregnant patients [92]. Oral or local administration of probiotics (e.g., *Lactobacillus* spp. and *Bifidobacterium* spp.) can suppress the growth of pathogens like *Gardnerella vaginalis* and modulate the local immune milieu, giving rise to improved pregnancy and live birth rates along with reduced miscarriage incidence [93]. Notably, the reproductive tract and gut microbes interact dynamically through immune homeostasis mechanisms. For instance, SCFAs derived from gut microbial metabolism can influence the vaginal immune environment via systemic circulation, while inflammatory mediators from the reproductive tract may in turn impair intestinal barrier integrity [94, 95]. This cross-niche crosstalk implies that the direct impact of probiotics on reproductive health depends on both reproductive tract colonization and gut microbiota regulation.

Consequently, the direct modulation of female reproductive function by probiotics via the gut–reproductive axis has gained increasing research attention. Probiotics have been shown to improve intestinal homeostasis, thereby suppressing the NF-κB pathway in ovarian tissue and attenuating inflammatory responses—a key mechanism in alleviating PCOS and enhancing overall health [96]. Metagenomic sequencing has revealed gut microbial imbalances in PCOS patients, marked by reduced beneficial bacteria such as *Faecalibacterium*, *Bifidobacterium*, and *Blautia*, along with increased abundance of potentially harmful taxa like *Parabacteroides* and *Clostridium*. Intervention with *Bifidobacterium animalis* subsp. *lactis* V9 in these patients demonstrated that successful intestinal colonization was associated with significant reductions in luteinizing hormone (LH) and the LH/FSH ratio, elevated sex hormone levels, and increased SCFA production. By contrast, five patients with poor colonization showed no marked improvements, underscoring the importance of colonization efficiency for probiotic efficacy [13]. Another study found that the probiotic *Escherichia coli* Nissle 1917 increased beneficial gut bacteria such as *Adlercreutzia* and *Allobaculum*, ameliorated glucose metabolic dysfunction, elevated anti-inflammatory

interleukin-22 (IL-22) levels, suppressed testosterone secretion and harmful metabolite expression, and reduced mitochondrial damage in granulosa cells, thereby alleviating PCOS phenotypes in mice [97]. Inactivated *Akkermansia muciniphila* has been shown to reduce gut pathobionts, enhance intestinal barrier function, and restore Treg/Th17 immune balance, leading to decreased placental inflammatory factors (TNF-α, IL-6) and lipid metabolites (cholesterol, triglycerides). These effects significantly lowered blood pressure and proteinuria in a preeclampsia (PE) mouse model, increased embryo counts and embryo/placental weights, and improved overall pregnancy outcomes [98]. Additionally, oral supplementation with *Lactobacillus crispatus* M247 increased clinical pregnancy and live birth rates in women undergoing ART. The clinical pregnancy rate was significantly higher in the treatment group (N=80) than in controls (N=80) (OR = 1.56), and the live birth rate rose from 7.5% to 12.5% (OR = 1.76) [99].

Beyond direct pathways, probiotics also indirectly support reproductive health by mitigating obesity and related metabolic dysregulation. Obesity-driven IR, chronic inflammation, and oxidative stress are pivotal contributors to reproductive dysfunction, and probiotics can counter these pathological processes through multiple routes. Several clinical studies have reported that *Lactobacillus* and *Bifidobacterium* strains reduce the incidence of gestational diabetes mellitus (GDM) in pregnant women by restoring microbial balance, boosting SCFA levels [100], lowering inflammatory markers and oxidative stress, and thereby improving glucose metabolism and insulin sensitivity [101]. Another investigation revealed that *Bifidobacterium longum* subsp. *longum* BL21 promotes the growth of beneficial gut bacteria, enhances glucose metabolism, and supports weight management. It also downregulates pro-inflammatory cytokines (IL-6, TNF-α), upregulates anti-inflammatory IL-10, and alleviates systemic inflammation. Moreover, BL21 elevates brain-derived neurotrophic factor (BDNF) to support neural balance and directly modulates sex hormones—such as increasing FSH and estradiol—to restore ovarian cyclicity. Together, these actions form an integrated gut–brain–ovary regulatory network that addresses metabolic, inflammatory, neural, and hormonal facets of PCOS [102].

However, a double-blind randomized controlled trial revealed that probiotic supplementation shortened the time to conception in overweight women (84.5 days in the intervention group vs. 117 days in the overweight control and 82.1 days in the non-overweight control), but unexpectedly prolonged time to conception in obese non-White women (132.7 days vs. 108.5 days in the obese control). Higher pre-pregnancy BMI and non-White ethnicity were generally associated with longer conception times [103]. These findings suggest that the reproductive benefits of probiotics in obese women may be population-specific and strain-dependent. Therefore, future studies should incorporate population stratification—by ethnicity, BMI, and other relevant factors—along with detailed functional analyses of probiotic strains to clarify their specific targets and metabolic networks. Integrating such data with individual gut microbiome profiles will enable the design of personalized probiotic strategies for precision management of reproductive health (Table 2).

Table 2 Efficacy of probiotic supplementation in improving female reproductive health outcomes

Probiotic Strain	Study	Daily	Duration	Primary Findings	Reference

	Population	Dose (CFU)			
Lactobacillus salivarius PS11610	Women undergoing ART	2×10^9	1-6 months	Inhibited pathogenic bacteria; improved clinical pregnancy and live birth rates; reduced miscarriage rate.	[104, 105]
Bifidobacterium lactis V9	Women with PCOS	1×10^{10}	10 weeks	Significantly decreased LH and LH/FSH ratio; improved sex hormone profiles and SCFA levels.	[13]
Escherichia coli Nissle 1917	PCOS mouse model	1×10^9	4 weeks	Enriched beneficial gut bacteria (*Adlercreutzia, Allobaculum*); elevated IL-22; inhibited testosterone secretion and mitigated mitochondrial damage in follicular cells.	[97]
Akkermansia muciniphila	Preeclampsia mouse model	2×10^8	5 days (GD14-18)	Reduced gut pathobionts; enhanced intestinal barrier; regulated Treg/Th17 balance; lowered placental inflammatory factors and lipids; improved fetal parameters.	[98]
Lactobacillus crispatus M247	Women undergoing ART	2×10^{10}	3 months	Significantly increased clinical pregnancy and live birth rates.	[99]
Bifidobacterium longum subsp. *longum* BL21	PCOS mouse model	1×10^9	8 weeks	Improved sex hormone levels (FSH, E2), glucose metabolism, and body weight; modulated inflammatory markers and BDNF.	[102]

The efficacy of probiotic interventions in ameliorating obesity-associated female reproductive conditions is modulated by numerous variables. Many clinical trials in this field are limited by relatively small sample sizes (typically 50–100 participants), which introduces considerable random error and limits statistical power. In contrast, studies enrolling larger cohorts (≥200 subjects) generally yield more robust and reproducible outcomes. Substantial heterogeneity among enrolled participants—including differences in obesity severity, specific reproductive endocrine diagnoses, age, and baseline gut microbiota profiles—further contributes to variability in probiotic-induced regulatory effects on reproductive hormonal indicators.

Additionally, the absence of standardized protocols for probiotic strain selection and dosage presents a major methodological challenge. Daily administered doses vary widely, typically ranging from 10^8 to 10^{10} CFU, and formulations may include single strains or multi-strain combinations. Different probiotic combinations exhibit distinct colonization dynamics and metabolic outputs, promoting divergent impacts on inflammatory markers and reproductive axis function. Intervention duration also significantly influences outcomes: short-term regimens (4–8 weeks) may only capture initial shifts in microbial composition, whereas longer interventions (12–24 weeks), while more likely to demonstrate efficacy, often encounter practical constraints such as participant dropout and reduced adherence.

To enhance the reliability and generalizability of future findings, it will be essential to establish unified protocols, standardize dosage regimens and treatment duration, and implement large-scale, multi-center trials designed to minimize heterogeneity (Figure 4).

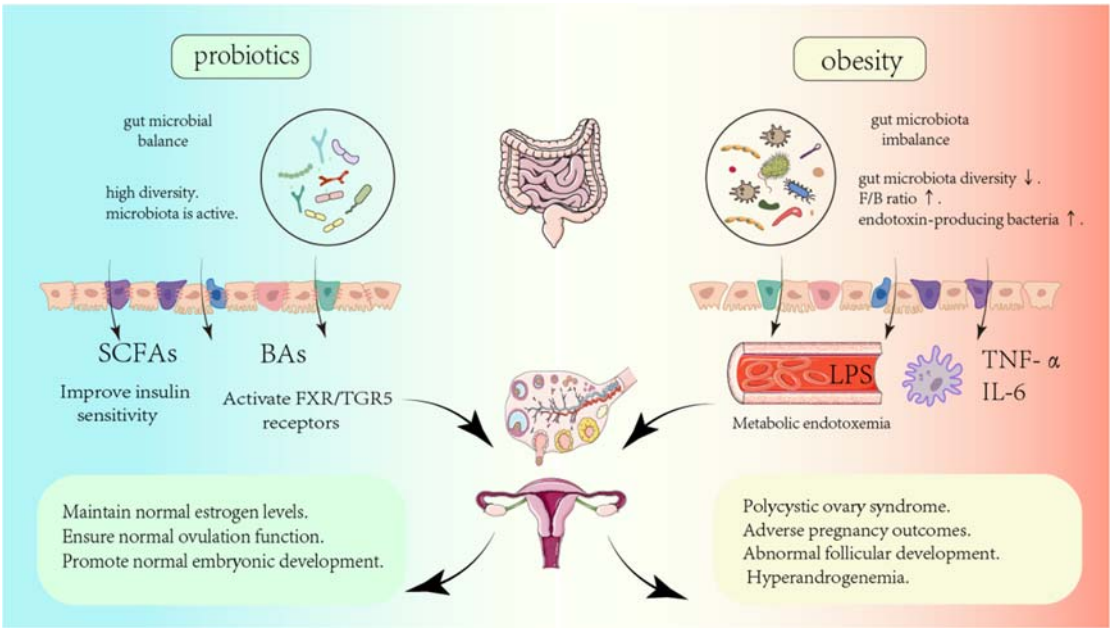

Figure 4. Comparative schematic of the gut microbiota in healthy and obese states and their distinct impacts on the female reproductive system. Under probiotic intervention (left panel), a balanced and diverse gut microbiota produces beneficial metabolites like SCFAs and secondary BAs. These metabolites improve insulin sensitivity, activate FXR/TGR5 receptors, and help maintain normal estrogen levels, ovulatory function, and embryonic development. In contrast, in the obese state (right panel), gut microbial diversity decreases, characterized by an increased F/B ratio and proliferation of endotoxin-producing bacteria. This triggers metabolic endotoxemia, elevated systemic inflammatory factors (e.g., TNF-α, IL-6), and hormonal imbalances. These alterations contribute to a range of reproductive disorders, including PCOS, adverse pregnancy outcomes, impaired follicular development, and hyperandrogenism.

5. Conclusion and Prospects

The pathological interplay between obesity and female reproductive dysfunction has evolved beyond traditional metabolic perspectives to encompass a multi-dimensional network integrating metabolic, immune, endocrine, and microbial components. This review systematically delineates the molecular cascades through which obesity impairs female reproductive function, focusing on insulin resistance IR, chronic inflammation, and hormonal dysregulation as central pathways. These mechanisms drive key clinical manifestations including ovulatory dysfunction, PCOS, gestational diabetes mellitus GDM, and impaired embryonic development. Emerging evidence has further established gut microbiota dysbiosis as a critical intermediary in the obesity-reproduction nexus. Through the "gut-reproductive axis," microbial communities regulate host metabolites such as SCFAs and bile acids, immune signaling molecules including inflammatory cytokines, and hormonal metabolism via estrogen enterohepatic recycling, collectively forming a self-reinforcing "gut-obesity-reproductive axis." Specifically, obesity-associated microbiota alterations—characterized by an imbalanced Firmicutes/Bacteroidetes ratio, diminished SCFA production, and endotoxemia—significantly aggravate reproductive impairment [106]. These alterations activate ovarian TLR4/NF-κB signaling, disrupt follicular fluid metabolic homeostasis, and compromise endometrial receptivity [107].

Probiotics represent a promising gut microbiota-targeted intervention with dual therapeutic potential against obesity-related reproductive conditions. Indirectly, they ameliorate metabolic disturbances through microbial restructuring, intestinal barrier enhancement, and systemic inflammation suppression. Directly, they improve reproductive outcomes by modulating reproductive tract microbiota, regulating sex hormone

secretion, and restoring oocyte mitochondrial function. Specific strains, including *Lactobacillus*, *Bifidobacterium*, and *Akkermansia muciniphila*, have demonstrated efficacy in reducing androgen levels in PCOS patients, improving assisted reproductive technology success rates, and lowering pregnancy complication risks [108]. These benefits are mediated through AMPK pathway activation, anti-inflammatory cytokine IL-10 elevation, and bile acid metabolic balance restoration [109].

Despite their therapeutic potential, probiotic applications carry non-negligible risks. Strain-specific effects present a major consideration, as mechanisms and efficacy vary substantially across different bacterial lineages. Inappropriate strain selection may not only yield suboptimal results but also provoke unforeseen adverse effects. Immunocompromised individuals face additional risks, as probiotics may potentially act as opportunistic pathogens causing systemic infections. Furthermore, inadequate investigation into long-term impacts on reproductive and systemic health creates significant uncertainty regarding extended probiotic use, complicating comprehensive risk assessment. Therefore, meticulous safety evaluation remains imperative when considering probiotics for reproductive disorders.

Current research faces several methodological challenges. The strain-specific mechanisms underlying probiotic actions require further elucidation through integrated multi-omics approaches—including metagenomics, metabolomics, and synthetic biology—to decipher functional gene-host interactions. Existing clinical trials are predominantly limited by small sample sizes and homogeneous populations, underscoring the need for large-scale, multi-center, stratified randomized controlled trials (e.g., by BMI and ethnicity) to establish time-response relationships, dose-effect curves, and long-term safety profiles. Simultaneously, personalized intervention strategies should incorporate host genetic background, baseline microbiota composition, and metabolic phenotypes, potentially leveraging artificial intelligence and machine learning for precision formulation design.

Future investigations should prioritize understanding cross-niche microbial interactions, particularly the dynamic crosstalk between gut and reproductive tract microbiota mediated by metabolites and immune factors. Advanced delivery systems such as engineered bacteria and microencapsulation technologies warrant exploration to enhance probiotic colonization efficiency and tissue targeting [110, 111]. As interdisciplinary technologies continue to advance, probiotics are poised to transition from fundamental research to clinical translation, emerging as valuable tools for preventing and treating obesity-related reproductive conditions while providing innovative strategies for female health management.

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Conflict of interest

The authors declare no competing interests.

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