THE MATERNAL MICROBIOME: IMPLICATIONS FOR FERTILITY, PREGNANCY, AND NEONATAL HEALTH

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Abstract

The maternal microbiome, encompassing microbial communities of the gut, vaginal tract, oral cavity, and placenta, experts profound effects on reproductive health, pregnancy outcomes, and early neonatal development. Recent advances in high-throughput sequencing and metabolomic profiling have illuminated the dynamic nature of maternal microbial ecosystems, revealing their pivotal role in fertility, immune modulation, and the programming of offspring health. Dysbiosis of maternal microbiota has been implicated in adverse obstetric outcomes, including infertility, preterm birth, preeclampsia, gestational diabetes, mellitus (GDM), and altered neonatal immune responses. This review synthesizes current understanding of maternal microbiome composition, functional pathways, and mechanisms linked to pregnancy physiology, emphasizing therapeutic interventions such as dietary modulation, probiotics, prebiotics, and microbiota-targeted therapies. By integrating recent evidence from 2023–2025, we highlight the translational potential of microbiome science in optimizing reproductive medicine and maternal-fetal health.

Introduction

The human microbiome, once considered a passive bystander, is now recognized as a critical determinant of systemic health and disease. In women of reproductive age, the maternal microbiome exhibits unique features shaped by hormonal fluctuations, metabolic demands,

and immune adaptations of pregnancy. Understanding the interplay between maternal microbial communities and reproductive physiology offers opportunities to predict and improve fertility, pregnancy maintenance, and neonatal outcomes.

The maternal microbiome encompasses several distinct yet interconnected microbial communities that play critical roles during pregnancy. The gut microbiome, being the largest microbial reservoir, significantly influences systemic metabolism, immune regulation, and the exchange of nutrients between mother and fetus. In healthy women, the vaginal microbiome is predominantly composed of *Lactobacillus* species, which help maintain an acidic environment essential for conception and pregnancy maintenance. The oral microbiome also contributes to maternal health by impacting systemic inflammatory pathways, with disruptions linked to pregnancy complications such as preeclampsia and preterm birth. Although the presence of a placental microbiome was previously debated, recent research supports the existence of a sparse but functionally important microbial population that may be involved in priming the fetal immune system.

During pregnancy, physiological adaptations—including insulin resistance, altered lipid metabolism, and immune tolerance—profoundly influence microbiome composition. Dysbiosis at any maternal site can perturb immune equilibrium, heightening the risk of obstetric complications. Mounting evidence from longitudinal cohort studies, gnotobiotic mouse models, and interventional trials underscores the causal role of microbiota in shaping pregnancy trajectories and offspring health.

This review integrates mechanistic insights and clinical evidence on the maternal microbiome's role in:

1. Fertility and implantation,
2. Maternal metabolic and immune adaptations,
3. Pregnancy complications (GDM, preeclampsia, and preterm birth),
4. Neonatal immune programming and long-term health, and
5. Therapeutic microbiome modulation.

By consolidating emerging findings, we aim to delineate opportunities for microbiome-informed diagnostics, risk prediction, and targeted interventions in reproductive medicine.

Composition of the Maternal Microbiome

The maternal microbiome comprises distinct microbial communities that play critical roles during pregnancy. The gut microbiome, primarily composed of Firmicutes and Bacteroidetes, undergoes significant shifts to support fetal development, although these changes may predispose to conditions such as gestational diabetes. Gut-derived microbial metabolites influence systemic inflammation and facilitate maternal-fetal nutrient exchange.

The vaginal microbiome is typically dominated by Lactobacillus species, which help maintain a low pH environment and protect against ascending infections. Disruption of this balance-characterized by reduced Lactobacilli and increased anaerobic bacteria-is associated with bacterial vaginosis, infertility, and an elevated risk of preterm birth. Emerging evidence suggests that the composition of the vaginal microbiota in early pregnancy may serve as a predictor of preterm labor.

Imbalances in the oral microbiome, particularly the overgrowth of pathogens such as *Porphyromonas gingivalis*, have been linked to systemic inflammation and adverse pregnancy outcomes, including preeclampsia and preterm delivery. These pathogens may translocate to the placenta, potentially impacting fetal health.

Although the existence of a placental microbiome remains debated, some studies report the presence of low-abundance microbial DNA-primarily of oral and vaginal origin-within placental tissues. Its role in shaping fetal immune development is under investigation, but contamination during sampling remains a concern, warranting further rigorous research.

Role in Fertility and Implantation

The maternal microbiome plays a crucial role in determining reproductive success, exerting significant influence even prior to conception. Among its various components, the gut micro biota has been shown to regulate systemic metabolic and immune functionsthat are essential for reproductive health. Through the modulation of hormonal balance, inflammatory signalin g pathways, and nutrient availability, gut microbes can directlyaffect ovarian follicular devel opment, oocyte quality, and endometrial receptivity. Alterations in gut microbial compositio n—often referred to as dysbiosis

can lead tosystemic inflammation and metabolic disturbances, both of which may impair ovu latoryfunction and reduce the likelihood of successful implantation.

Equally important is the role of the vaginal microbiome in supporting fertility.

A vaginalmicrobiota dominated by *Lactobacillus* species is considered optimal, as these ba cteriaproduce lactic acid and hydrogen peroxide, which help maintain an acidic vaginalenvir onment. This protective milieu inhibits the colonization of pathogenicmicroorganisms, thereb y reducing the risk of genital tract infections that can compromisesperm viability, disrupt cer vical mucus integrity, and interfere with fertilization. Incontrast, vaginal dysbiosis—characterized by decreased *Lactobacillus* abundance andan overgrowth of anaerobic bacter ia—has been associated with reduced fertility and poorreproductive outcomes.

Emerging evidence also points to the significance of the endometrial microbiome inimplantat ion. While previously assumed to be sterile, the endometrium has been shown toharbor its o wn unique microbial population.

A *Lactobacillus*-

dominated endometrialenvironment is positively associated with increased implantation and l ive birth rates, particularly in women undergoing in vitro fertilization (IVF). Conversely, a microbialprofile enriched with potentially pathogenic bacteria such as *Gardnerella vaginal is* and*Atopobium vaginae* has been correlated with chronic endometritis, impairedendom etrial receptivity, and recurrent implantation failure (RIF).

Moreover, microbial metabolites, particularly short-chain fatty acids (SCFAs) such asbutyrate, propionate, and acetate, play a vital role in modul ating the uterine immuneenvironment. These metabolites enhance immune tolerance at the m aternal-fetal interfaceby promoting the expansion of regulatory T cells (Tregs) and suppressing pro-inflammatory responses. Disruptions in SCFA production, commonly associated with gutor e ndometrial dysbiosis, may compromise immunological tolerance and increase the riskof impl antation failure, early pregnancy loss, and other gestational complications.

Taken together, these findings highlight the integral role of the maternal microbiome—encompassing the gut, vaginal, and endometrial microbial communities—in regulatingfertility and implantation. Therapeutic strategies aimed at restoring microbial bal ancethrough probiotics, prebiotics, or microbiota transplantation hold promise for improvingr eproductive outcomes, especially in women with unexplained infertility or thoseundergoing a ssisted reproductive technologies.

Impact on Pregnancy Outcomes

Preterm birth (PTB), defined as delivery before 37 weeks, remains a leading cause of neonatal complications globally. Vaginal microbiome dysbiosis—marked by reduced *Lactobacillus* and overgrowth of anaerobes like *Gardnerella vaginalis*, *Atopobium vaginae*, and *Ureaplasma* species—triggers inflammation that can cause cervical shortening and early labor. Recent multi-omics studies (2023–2025) have identified microbial patterns predictive of PTB as early as the first trimester. Preventive approaches under study include vaginal probiotics, targeted antimicrobials, and lifestyle changes to restore microbial balance. Gestational diabetes mellitus (GDM) arises partly due to pregnancy-related metabolic shifts influenced by gut microbiome alterations. Reduced microbial diversity, lower abundance of *Akkermansia muciniphila*, and decreased short-chain fatty acid (SCFA) producers contribute to insulin resistance. Microbial metabolites affect glucose regulation by modulating gut barrier function, incretin release, and inflammation. Strategies such as high-fiber diets, prebiotics, and next-generation probiotics are being tested for GDM prevention and treatment. Preeclampsia, characterized by hypertension and multi-organ effects, is associated with gut and oral microbiota imbalances. Gut microbiomes in preeclampsia show a higher Firmicutes/Bacteroidetes ratio and increased pro-inflammatory bacteria. Oral dysbiosis,

including *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, may promote systemic inflammation and endothelial damage. Placental microbial DNA signatures correlate with disease severity, suggesting potential for microbiome-based diagnostics. Probiotics that enhance SCFA production represent promising adjunctive therapies.

Other adverse outcomes linked to maternal dysbiosis include excessive gestational weight gain, intrauterine growth restriction (IUGR), and recurrent miscarriage, though the latter's causality remains under study. Mechanistically, maternal dysbiosis drives immune activation, increases intestinal permeability ("leaky gut"), disrupts metabolic signaling via SCFA and bile acid pathways, and may induce epigenetic changes in maternal and fetal tissues through microbial metabolites.

Maternal-Fetal Microbial Interactions and Neonatal Immune Programming

Recent evidence suggests that microbial components from the mother—including metabolites, antigens, and cell-free DNA—can cross the placenta and influence the developing fetal immune system. Although the presence of a placental microbiome remains debated, sterile sampling methods (2023–2025) have identified low levels of commensal microbes that may help establish fetal immune tolerance. Microbial metabolites, especially short-chain fatty acids like butyrate, have epigenetic effects on fetal immune cells, promoting regulatory T cell development and reducing inflammation.

The maternal immune system adapts to tolerate the fetus, with gut microbiota playing a central role by producing metabolites such as SCFAs, indole derivatives, and secondary bile acids. These compounds regulate dendritic cells, expand regulatory T cells, and modulate cytokine production, fostering an environment favorable to fetal tolerance. Dysbiosis can disrupt these processes, increasing risks for complications like preterm birth, preeclampsia, and intrauterine growth restriction.

At birth, microbial colonization begins, differing by delivery mode. Vaginally born infants acquire microbes resembling maternal vaginal and gut communities, while cesarean-born infants often show delayed and less diverse colonization, increasing susceptibility to allergies and metabolic disorders. Breastfeeding further shapes the neonatal microbiome by supplying human milk oligosaccharides and bioactive molecules that encourage growth of beneficial bacteria like *Bifidobacterium*. Maternal diet, probiotic use, and antibiotic exposure during pregnancy also significantly influence the infant's microbial landscape.

Early-life microbiota are critical for neonatal immune development and tolerance. Disruptions in this period are linked to higher risks of allergic, autoimmune, and metabolic diseases. Animal studies show that maternal supplementation with SCFA-promoting probiotics can reduce offspring susceptibility to conditions such as asthma and colitis, and human cohorts confirm associations between maternal microbiome patterns and childhood immune disorders.

To optimize maternal-fetal microbial interactions, strategies include: increasing dietary fiber and fermented foods to boost SCFA producers; targeted probiotic and synbiotic use (e.g., *Lactobacillus rhamnosus*, *Bifidobacterium breve*); careful antibiotic stewardship to preserve microbial diversity; and experimental approaches like vaginal microbiome transfer ("microbial seeding") for cesarean-born infants, which remains under investigation.

Therapeutic Perspectives: Microbiome-Targeted Interventions

Maternal diet is a key modulator of the microbiome. Diets rich in fiber, plant polyphenols, and omega-3 fatty acids promote short-chain fatty acid (SCFA)–producing bacteria, supporting maternal metabolic health and immunity. In contrast, high-fat and ultra-processed foods contribute to dysbiosis and inflammation, increasing risks of gestational diabetes and preeclampsia. Tailored nutritional counseling focused on microbiome health is gaining importance in prenatal care.

Probiotic supplementation during pregnancy shows promise in reducing gestational diabetes, bacterial vaginosis, and infant allergies. Strains like *Lactobacillus rhamnosus* GG and *Bifidobacterium breve* improve gut barrier function and immune tolerance. Prebiotics such as galactooligosaccharides and fructooligosaccharides selectively nourish beneficial microbes. Synbiotics—combinations of probiotics and prebiotics—may offer synergistic benefits but require further validation through large randomized trials.

Emerging microbiota-directed therapies include fecal microbiota transplantation for severe dysbiosis and engineered next-generation probiotics that deliver immunomodulatory compounds. Vaginal microbiota transplantation is being explored for recurrent bacterial vaginosis and infertility. Personalized interventions guided by metagenomic profiling represent the future of precision microbiome medicine in obstetrics.

Judicious antibiotic use during pregnancy is essential to preserve microbial diversity. Overuse of broad-spectrum antibiotics can disrupt maternal and neonatal microbiomes, potentially increasing risks for obesity, asthma, and autoimmune disorders in offspring. Current guidelines advocate targeted antimicrobial therapies that consider microbiome preservation.

Gaps, Controversies, and Future Directions

While substantial progress has been made in characterizing the maternal microbiome, key questions remain unresolved. One of the most debated topics is the existence of a true placental microbiome, current studies are limited by technical challenges, especially in separating real microbial signals from contamination in samples that contain very few microbes. In addition, there are few long-term studies that follow women from before pregnancy through to after birth. This makes it difficult to fully understand how changes in the microbiome affect both maternal health and newborn outcomes.

Another challenge is that every person's microbiome is different. This variation is influenced by factors like genetics, diet, ethnicity, and environment, making it hard to create one-size-fits-all treatments. It's also difficult to prove whether changes in the microbiome actually cause pregnancy problems, or if they are just linked to them. More advanced research methods are needed to understand these connections clearly.

To address these gaps, future research should focus on integrative multi-omics approaches that combine microbiome data with immune, metabolic, and transcriptomic profiling. Such strategies are essential to unravel complex host-microbiome interactions and identify predictive microbial signatures. There is also growing interest in personalized interventions, including the use of microbial biomarkers to stratify risk and guide early prevention of pregnancy-related disorders.

Therapeutic manipulation of the maternal microbiome through targeted use of prebiotics, probiotics, synbiotics, and next-generation biotherapeutics offers promising avenues for clinical application. Furthermore, long-term prospective studies are needed to assess how maternal microbial states and interventions affect not only pregnancy outcomes but also the long-term health of the offspring.

Finally, as microbiome-based therapies evolve, ethical considerations-particularly around interventions like microbial seeding post-cesarean or microbiome editing-must be addressed through robust clinical guidelines and transparent public discourse.

Conclusion

The maternal microbiome has emerged as a critical determinant of reproductive health, pregnancy outcomes, and neonatal immune development. This intricate ecosystem, comprising the gut, vaginal, oral, and possibly placental microbiota, exerts multifaceted effects on maternal metabolic regulation, immune tolerance, and fetal programming. Dysbiosis within these microbial niches is increasingly recognized not merely as a correlate, but as a potential causal contributor to a range of obstetric complications including infertility, gestational diabetes mellitus, preeclampsia, and preterm birth.

Recent advances in high-throughput sequencing, metabolomics, and multi-omics integration have elucidated novel mechanistic pathways by which maternal microbial communities influence both host physiology and offspring health trajectories. Maternal microbial metabolites, such as short-chain fatty acids, play pivotal roles in modulating systemic inflammation, maintaining epithelial integrity, and inducing fetal immune tolerance through epigenetic mechanisms.

The translational implications of this expanding field are profound. Microbiome targeted interventions ranging from dietary modulation and probiotic supplementation to personalized microbiota directed therapeutics hold promise for optimizing maternal-fetal health and

preventing pregnancy-related disorders. However, substantial knowledge gaps remain, particularly in establishing causality, defining microbiome reference states, and developing clinically validated biomarkers.

To fully harness the therapeutic potential of the maternal microbiome, future research must prioritize longitudinal cohort studies, controlled interventional trials, and the ethical integration of precision microbiome medicine into obstetric care. A paradigm shift toward microbiome informed reproductive medicine is both timely and necessary, offering an unprecedented opportunity to improve health outcomes across generations.

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