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Gestational Diabetes and the Maternal Microbiome:

The Role of Probiotics in Metabolic and Immune Modulation

Editor-in-Chief: Dr. Deivis O. Guimarães
Gon1 Biotech
Av .N.S Navegantes, 955/719 Vitoria/ES
frontiersofbioscience@gon1.com.br

DRA. RACIRE SAMPAIO SILVA
DR. DEIVIS O. GUIMARÃES

Gestational diabetes mellitus is one of the most common metabolic complications of pregnancy, affecting approximately 14% of pregnancies worldwide and presenting significant implications for both maternal and fetal health (WANG et al., 2022). Although advances in early diagnosis and glycemic control have improved outcomes, treatment remains largely focused on dietary interventions and insulin therapy. While these strategies are effective in lowering blood glucose levels, they do not fully address the complex inflammatory and metabolic disruptions associated with the condition (STOREY et al., 2025).

In recent decades, the gut microbiota has transitioned from being viewed as a passive commensal ecosystem to a promising therapeutic target in chronic diseases such as diabetes. This conceptual shift has opened the door to more nuanced, biologically integrated interventions. Among these, probiotics stand out as living microorganisms that, when administered in adequate amounts, confer health benefits to the host. In the context of type 2 diabetes, studies have demonstrated their ability to improve fasting glycemia and lipid profiles by modulating the intestinal microbiota and reducing inflammatory mediators (BOCK et al., 2021).

However, the clinical application of probiotics during pregnancy remains underexplored, mainly due to ethical constraints and methodological variability. Pregnancy itself is a state of physiological inflammation, progressive insulin resistance, and dynamic microbial remodeling. In this scenario, microbiota modulation emerges as a potentially safe strategy, with low toxicity and the ability to induce epigenetic effects with long-term benefits for both mother and fetus (LIU et al., 2024).

This review aims to synthesize the most recent evidence regarding the use of probiotics in women with gestational diabetes mellitus, exploring the underlying physiological mechanisms, available clinical data, and the therapeutic and preventive implications of this evolving intervention.

Gestational Diabetes Mellitus

Gestational diabetes mellitus is recognized as a transient metabolic condition that develops during pregnancy, most commonly diagnosed between the second and third trimesters. Although it often resolves postpartum, its metabolic consequences can extend for many years, affecting both mother and child. Clinically, it is defined by glucose intolerance resulting from a combination of gestational insulin resistance and an inadequate compensatory response by pancreatic beta cells (GRECO et al., 2024).

During pregnancy, the maternal body undergoes complex physiological adaptations to support fetal development. One of the most prominent is the progressive increase in peripheral insulin resistance, driven by placental hormones such as progesterone, human placental lactogen, and cortisol. In healthy pregnancies, this resistance is offset by an

TABLE 1 - Summary of probiotic effects in women with gestational diabetes mellitus

Study	Probiotic Strains	Fasting Glucose Reduction (%)	Inflammatory Marker Reduction (%)
Li et al. (2024)	*L. acidophilus* *L. casei* *B. bifidum*	12	15
Liu et al. (2021)	*L. acidophilus* *B. lactis*	8	10
Yang et al. (2020)	*L. rhamnosus* GR-1 *L. reuteri*RC-14	5 (indirect effect)	7
Seif El Dahan et al. (2022)	Multistrain (meta-analysis)	10 (combined average)	13 (combined average)

Source: Adapted from Li et al. (2024), Liu et al. (2021), Yang et al. (2020), Seif El Dahan et al. (2022).

expansion of beta cell mass and enhanced insulin secretion. When this adaptive response fails, hyperglycemia ensues, resulting in gestational diabetes (STOREY et al., 2025).

The clinical consequences of GDM are significant. In the short term, mothers face increased risks of preeclampsia, cesarean delivery, and metabolic disturbances in the postpartum period. For the fetus, risks include macrosomia, neonatal hypoglycemia, respiratory distress at birth, and greater susceptibility to obesity and type 2 diabetes later in life. These outcomes are closely linked to intrauterine metabolic programming and, more recently, to changes in the maternal microbiota (LIU et al., 2024).

Recent studies have shown that women with GDM exhibit reduced microbial diversity and lower abundance of anti-inflammatory species in the gut microbiota. These alterations may not only reflect the metabolic state but also actively contribute to its persistence, creating a feedback loop of inflammation, immune dysfunction, and insulin resistance (WANG et al., 2023).

Therefore, gestational diabetes mellitus must be understood as a multifactorial condition that extends beyond hyperglycemia. It represents a clinical and metabolic window in which targeted interventions such as microbiota modulation through probiotics may act preventively and therapeutically, influencing not only short-term outcomes but also long-term risks of chronic disease.

Mechanisms of Action of Probiotics in GDM

The growing interest in probiotic use for gestational diabetes is supported by well-established physiological mechanisms. These microorganisms do not act in isolation but instead interact with multiple host systems, exerting simultaneous effects on intestinal permeability, energy metabolism, systemic inflammation, and hormonal signaling. This multifaceted potential is particularly relevant in a condition as complex and dynamic as GDM.

One of the most studied mechanisms is the modulation of the intestinal barrier. In metabolic and inflammatory states such as GDM, increased epithelial permeability allows lipopolysaccharides (LPS) from gut bacteria to translocate into the systemic circulation. This metabolic endotoxemia activates inflammatory cascades involving cytokines like TNF-alpha and IL-6, further exacerbating insulin resistance. Specific probiotic strains, such as *Lactobacillus acidophilus* and *Bifidobacterium bifidum*, have been shown to reinforce epithelial tight junctions, restore intestinal integrity, and reduce circulating inflammation (SEIF EL DAHAN et al., 2022).

Another important mechanism involves the production of short-chain fatty acids, including acetate, propionate, and butyrate. These metabolites are generated through the fermentation of dietary fibers by commensal bacteria and exert multiple metabolic effects, such as improving insulin sensitivity, regulating lipid metabolism, and modulating hormonal signaling. Butyrate, in particular, serves as a key energy source for

Next Edition

Bridging Theory and Practice

DEIVIS O.G.

In our next issue, we will present an in-depth article on **S-adenosyl-L-methionine (SAMe)**, an essential endogenous metabolite that plays a pivotal role in numerous biochemical reactions within the human body. SAMe is a key methyl donor, involved in neurotransmitter synthesis, epigenetic regulation, and the maintenance of cellular homeostasis. Extensively studied for its relevance to neurological, hepatic, and joint health, SAMe has recently attracted attention for its therapeutic potential in inflammatory conditions, degenerative disorders, and mitochondrial dysfunction. The article will explore the major metabolic pathways in which SAMe is involved, discuss the latest clinical evidence regarding its effects on mood regulation, liver protection, and joint integrity, and examine the molecular mechanisms that underpin its biological activity. We will also address technological advances aimed at improving its stability and bioavailability, as well as perspectives for future applications in preventive and personalized medicine. well as perspectives for future applications in preventive and personalized medicine.By tracing SAMe's journey from theory to practice, we will highlight how decades of biochemical research are now translating into tangible clinical applications. Through case studies, translational research findings, and real-world therapeutic experiences, readers will gain a clear understanding of how this molecule is moving from the laboratory bench to patient care. This exploration will not only showcase its proven benefits but also reveal the challenges, innovations, and regulatory considerations shaping SAMe's path into mainstream medical use.

colonocytes, promotes anti-inflammatory responses, and improves glucose homeostasis (TOSHIMITSU; IRIE, 2025).

In addition, probiotics modulate the maternal immune system, which during pregnancy maintains a carefully regulated balance to allow fetal tolerance without compromising immune defense. Certain strains promote the release of anti-inflammatory cytokines like IL-10 and TGF-beta while reducing pro-inflammatory mediators, helping to restore immune balance in the context of chronic metabolic inflammation (BOCK et al., 2021).

A fourth mechanism, still in early stages of research, involves the modulation of gut-derived hormones such as GLP-1. This incretin hormone enhances insulin secretion, delays gastric emptying, and influences appetite regulation. Some studies have observed increased GLP-1 expression and secretion following probiotic supplementation, suggesting another pathway by which probiotics may improve glycemic control (LI et al., 2024).

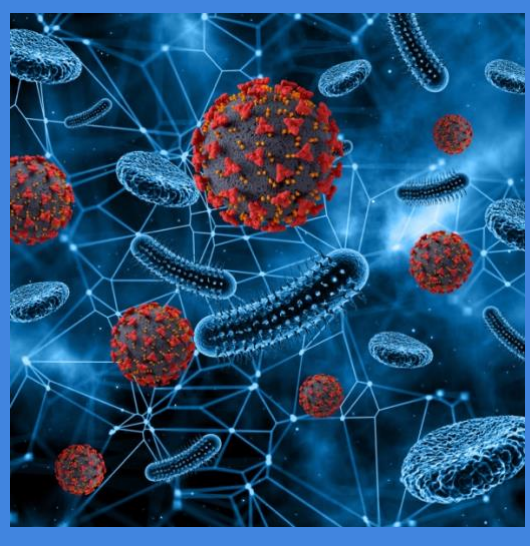
Together, these mechanisms highlight how probiotics, especially when used in combination and for sustained periods, offer an integrated model of intervention. They align with maternal physiology, support metabolic equilibrium, and minimize adverse effects. Unlike pharmacologic agents that often act on isolated targets, probiotics interact with the intestinal ecosystem in a coordinated manner, representing a therapeutic model consistent with the principles of translational and ecological medicine.

Clinical Evidence in Pregnant Women with GDM

Although the biological plausibility for probiotic use in GDM is strong, clinical evidence remains varied. The current literature includes trials with different probiotic strains, treatment durations, gestational timings, and outcome measures. Nevertheless, there is growing consensus on the safety of probiotic use during pregnancy and its potential metabolic and immunological benefits.

By modulating the maternal microbiome, probiotics may transform gestational diabetes management from a solely glycemic-focused intervention into a comprehensive strategy for long-term maternal and offspring health.

The management of gestational diabetes has traditionally focused on achieving glycemic targets to reduce immediate obstetric risks. While this approach remains essential, it often overlooks the broader biological disruptions that accompany the condition, including chronic low-grade inflammation, immune dysregulation, and alterations in the maternal microbiome. Probiotics offer a unique opportunity to address these interconnected pathways simultaneously. By restoring microbial balance, enhancing intestinal barrier integrity, and promoting the production of anti-inflammatory metabolites, probiotics may help shift the paradigm of gestational diabetes care. This shift moves beyond short-term glycemic control toward a more comprehensive strategy aimed at improving long-term health outcomes for both mother and child.



Li et al. (2024) conducted one of the most comprehensive trials to date, evaluating the effects of a combination of *Lactobacillus acidophilus*, *Lacticaseibacillus casei*, and *Bifidobacterium bifidum* in women diagnosed with GDM. Their results showed an average reduction of 12% in fasting glucose and a 15% decrease in C-reactive protein levels, indicating improvements in both glycemic control and systemic inflammation.

Probiotics emerge as safe, multi-targeted allies in redefining gestational diabetes care.

The available clinical trials show encouraging outcomes, particularly with multistrain formulations. The observed reductions in fasting glucose, systemic inflammation, and oxidative stress, although moderate, are clinically meaningful when considering the long-term metabolic consequences of GDM (LI et al., 2024; SEIF EL DAHAN et al., 2022).

Nevertheless, current studies exhibit methodological limitations. Sample sizes are often small, randomization procedures are inconsistent, and the duration of probiotic administration is usually short. Furthermore, many trials prioritize laboratory biomarkers over clinically meaningful outcomes such as neonatal health, insulin therapy necessity, or delivery complications.

Liu et al. (2021) investigated a simpler formulation, combining *L. acidophilus* and *B. lactis*, and found reductions of up to 8% in fasting glucose and 10% in inflammatory markers. Although more modest, these findings confirm the safety and gradual effectiveness of probiotic supplementation.

Yang et al. (2020) assessed *L. rhamnosus* GR-1 and *L. reuteri* RC-14, focusing on the vaginal microbiota and systemic cytokine profiles. While the study was not specific to GDM, increased IL-10 and decreased IL-6 levels were observed, supporting the immunomodulatory effects of probiotics with potential metabolic implications.

A broader synthesis by Seif El Dahan et al. (2022) reviewed multiple probiotic interventions during pregnancy. Their conclusions emphasized that multistrain formulations consistently outperformed single-strain approaches in terms of metabolic, inflammatory, and oxidative markers.

These results are summarized in Table 1 in the page 2.

These findings suggest a clear trend: multistrain formulations, especially those containing *Lactobacillus* and *Bifidobacterium* species, tend to yield more consistent benefits in both glycemic and inflammatory outcomes. Importantly, none of the reviewed studies reported adverse effects, reinforcing the favorable safety profile of probiotics during pregnancy.

Despite these encouraging results, most trials still rely on small sample sizes and short follow-up periods and rarely assess obstetric outcomes such as insulin use, birth weight, or mode of delivery. Therefore, further studies are necessary to validate these findings in broader clinical contexts.

Discussion and Future Perspectives

The use of probiotics in the management of gestational diabetes represents an emerging clinical strategy, combining strong biological rationale with a low-risk, preventive approach that is increasingly aligned with contemporary healthcare practices. Unlike conventional therapies that focus solely on glycemic control, probiotics influence multiple systems simultaneously, including the intestinal barrier, inflammatory signaling, microbial metabolism, and hormonal pathways.

One of the most promising aspects of probiotic interventions is their excellent safety profile. No serious adverse events have been reported across trials using well-characterized strains. This is particularly relevant in obstetrics, where therapeutic thresholds for safety are understandably conservative.

Future directions include multicenter randomized controlled trials with standardized protocols, longer durations, and comprehensive obstetric endpoints. The integration of omics technologies—such as metagenomics, microbial transcriptomics, and metabolomics—will likely enable more precise patient stratification and the development of personalized probiotic formulations tailored to the maternal microbiome.

Additionally, regulatory frameworks must evolve to ensure the quality, viability, and consistency of probiotic products throughout the supply chain. This includes guaranteeing that clinical-grade strains remain viable until ingestion and are delivered at effective dosages.

In conclusion, probiotics should not be viewed as replacements for traditional therapies, but rather as biologically intelligent tools that can expand the scope of prenatal care. They represent a shift toward working with, rather than against, the maternal physiology, supporting a more integrated, safe, and sustainable approach to maternal-fetal health.

Conclusion

Gestational diabetes mellitus remains a critical challenge in modern obstetrics, not only because of its immediate impact on maternal and neonatal health but also due to its long-lasting metabolic repercussions for both mother and child. While conventional interventions such as dietary control and insulin therapy remain essential, they often fall short in addressing the multifactorial nature of the disorder.

In this context, probiotics emerge as a biologically coherent and clinically promising adjunct. Their ability to modulate intestinal permeability, influence short-chain fatty acid production, regulate

immune responses, and potentially alter incretin secretion offers a wide-ranging set of mechanisms that align well with the complex pathophysiology of GDM. The available clinical evidence, although still developing, suggests that multistrain probiotic formulations—particularly those combining *Lactobacillus* and *Bifidobacterium* species—can modestly improve glycemic control and reduce inflammatory markers in pregnant women diagnosed with GDM, without compromising safety.

However, this therapeutic avenue is still in its early stages. The heterogeneity of strains, dosages, durations, and endpoints among published trials highlights the need for methodological refinement and scientific rigor. Future research should aim for larger, better-controlled, and more longitudinal studies capable of evaluating not only biochemical markers but also obstetric outcomes and long-term effects on offspring health.

More than a therapeutic tool, probiotics represent a conceptual shift. They reflect a move toward interventions that are aligned with the physiology of pregnancy, respectful of microbial ecology, and minimally invasive. In a medical field often shaped by the urgency of risk mitigation, this approach offers a quieter, yet potentially more profound form of care. It is a model that treats the microbiome as an ally, not as an afterthought.

The path ahead will require collaboration among microbiologists, obstetricians, endocrinologists, and nutrition scientists to build a robust evidence base. Yet the opportunity is clear. By harnessing the intelligence of the microbial world, we may be able to rewrite the narrative of gestational diabetes. It may cease to be viewed solely as a condition to be controlled and instead be seen as a window for preventive, personalized, and ecologically attuned health care.

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