



The Positive Role of Probiotics in Controlling and Treating Gestational Diabetes in Pregnancy

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| ARTICLE INFO | ABSTRACT |
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| <i>Article type:</i> Review Paper | Introduction: Diabetes, including gestational diabetes mellitus (GDM), has a high global prevalence and remains a significant public health concern. The pathophysiology of GDM involves carbohydrate intolerance and can have substantial effects on pregnancy outcomes. Probiotics—naturally occurring microorganisms in the human gut—have been suggested to confer health benefits. Inflammatory processes play a central role in the development of GDM, and probiotics may influence immune system function and modulation. This study aims to explore the potential role of probiotics as a therapeutic intervention for GDM through a comprehensive review of the literature published between 2010 and 2024. Key search terms included: "probiotics," "symbiosis," "Bifidobacterium," "Lactobacillus," "gestational diabetes," "infantile consequences," and "metabolic profile." Only studies involving human subjects were included in this review. |
| <i>Article History:</i> Received: 19 May 2025 Accepted: 13 Jul 2025 | Methods: A comprehensive review of literature from 2010 to 2024 was conducted to clarify the role of probiotics as a treatment for GDM. Key search terms included "probiotics," "symbiosis," "bifidobacterium," "Lactobacillus," "Gestational diabetes," "Infantile consequences," and "Metabolic profile." This research includes human articles. |
| <i>Keywords:</i> Gestational diabetes Probiotics Insulin resistance | Results: Although the evidence is limited, probiotics have a positive effect on blood glucose levels and reduce insulin resistance, making them potentially effective in treating GDM. Conducting more studies on different types of probiotics and in larger patient populations can provide further insights into this issue. |

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Introduction

After cancer and cardiovascular diseases, diabetes is recognized as the third major "silent killer" globally (1). According to the International Diabetes Federation (IDF), over 425 million people were diagnosed with diabetes in 2017, and the World Health Organization (WHO) projects that this number will increase to 629 million by 2045 (2). Diabetes is categorized into three types: type 1 diabetes, type 2 diabetes (T2DM), and gestational diabetes mellitus (GDM) (1,3,4). Due to the rising global prevalence of hyperglycemia and obesity among women of reproductive age, the incidence of GDM is also increasing, making it one of the most common metabolic disorders worldwide (5). Maternal diabetes during pregnancy is associated with numerous complications, including miscarriage, preterm birth, and even neonatal mortality (2,4,6). GDM affects approximately 14% of pregnancies, and its occurrence is influenced by

both environmental and genetic factors, such as race, ethnicity, maternal age, body mass index (BMI), and population screening methods (7). Obesity is a well-established risk factor for GDM, primarily due to its strong association with insulin resistance and chronic inflammation. Excess adipose tissue promotes the release of pro-inflammatory cytokines, which impair glucose metabolism. Additionally, a family history of diabetes contributes to genetic susceptibility, further increasing insulin resistance and systemic inflammation (8). Maternal inflammation naturally increases during pregnancy, but is markedly higher in women with GDM. This leads to elevated blood glucose levels and increased concentrations of cytokines and other inflammatory markers. Inflammation plays a crucial role in the pathogenesis of GDM, and effective management of inflammatory responses can improve both maternal and neonatal outcomes (9). The close

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relationship between the gut microbiota and immune system modulation has been well-documented. Consequently, targeting the gut microbiota has emerged as a promising therapeutic strategy for immune-mediated disorders. Previous studies have demonstrated that specific probiotic strains play an essential role in regulating host immunity and reducing inflammation. For instance, *Bifidobacterium bifidum* promotes the differentiation of regulatory T cells (Tregs) and enhances their immunosuppressive activity in the intestinal tract. Furthermore, multi-strain probiotic formulations have shown significant immunomodulatory effects, with benefits observed in various inflammatory, autoimmune, and allergic conditions, including atopic dermatitis, rheumatoid arthritis, myasthenia gravis, and multiple sclerosis (10).

Materials and Methods

This comprehensive narrative review covers literature published between 2010 and 2024. The primary research strategy involved an extensive online search using databases such as Google Scholar and PubMed. Key search terms included: “probiotics,” “symbiosis,” “*Bifidobacterium*,” “*Lactobacillus*,” “gestational diabetes,” “infantile consequences,” and “metabolic profile.”

The review process encompassed the identification of relevant research questions, the retrieval of pertinent studies, the critical evaluation of the evidence, and the synthesis of the findings. The focus was limited to human studies. Articles were selected based on their relevance to the review’s objectives, and not all publications within the specified time frame were included.

The inclusion criteria were that the document contained at least two of the designated search terms in either the title or the abstract, had a substantial amount of discussion regarding keywords, and addressed at least two search subject terms, regardless of whether they were clearly articulated.

The exclusion criteria included delete articles published before 2010, deletion of meta-analyses or systematic reviews published more than a decade before the search period (i.e., before 2009), articles that focus solely on one unit or a search term that does not meet the above entry criteria, and articles that refer to one or more

search terms primarily related to alternative forms of drug resistance or other bacterial species (e.g., methicillin-resistant *Staphylococcus aureus*).

Results and Discussion

After the evaluation and investigation, the articles are presented and reported in the following format:

Gestational Diabetes Mellitus

Glucose Regulation During Healthy Pregnancy

Although insulin sensitivity initially increases during early pregnancy, promoting the conversion of glucose into fat reserves to support gestation, its progression is accompanied by rising levels of maternal and placental hormones. These include estrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone, all of which contribute to the development of insulin resistance. As gestational age advances, maternal blood glucose levels increase and are efficiently transferred across the placenta to support fetal growth and development. This metabolic shift is associated with enhanced mobilization of maternal fat stores, resulting in elevated circulating levels of glucose and free fatty acids (FFAs).

Risk Factors for Gestational Diabetes

Maternal obesity and overweight before conception and up to the 20th week of pregnancy—particularly among women aged 30 to 34 years—as well as advanced maternal age, a family history of type 2 diabetes mellitus (T2DM), and hypothyroidism, have all been strongly associated with an increased risk of developing gestational diabetes mellitus (GDM). Similarly, the prevalence of obesity, hypertension (HTN), diabetes, and thyroid disorders is significantly higher in women with polycystic ovary syndrome (PCOS) compared to unaffected individuals. Notably, the incidence of GDM in women with PCOS is reported to be approximately twice as high (2).

Development of gestational diabetes mellitus (GDM). Notably, the prevalence of GDM among individuals with the highest CRP concentrations is approximately three times greater than among those with the lowest levels (2). Multiple factors contribute to the onset and progression of GDM, particularly the role of the placenta and its secreted peptides and hormones, which influence maternal insulin resistance. Placental growth factor (PIGF) and pregnancy-associated

plasma protein-A (PAPP-A) play a crucial role in modulating insulin sensitivity and endothelial function. PAPP-A primarily acts by regulating circulating insulin-like growth factor-binding protein 4 (IGFBP-4), whereas PlGF plays an essential role in placental vascular development and maturation. Although some studies have reported conflicting findings, the majority indicate that low serum levels of PAPP-A and elevated levels of PlGF are significantly associated with an increased risk of GDM (7).

The relationship between age at menarche (AAM) and the risk of gestational diabetes mellitus (GDM) remains inconclusive, with existing studies yielding conflicting results. However, a recent study utilizing Mendelian randomization (MR) analysis systematically investigated the potential causal link between AAM and GDM in humans. The findings revealed that genetic variants associated with an earlier onset of AAM were independently linked to an increased risk of developing GDM (11).

The Mechanisms of Action of Probiotics

The term "probiotic" is derived from the Greek word "probiotikos, meaning "for life." Probiotics are defined as live, non-pathogenic microorganisms that, when administered in adequate amounts (typically $\geq 10^6$ CFU/g), contribute to the maintenance and restoration of the intestinal microbiota. They are naturally present in various biological environments and are commonly incorporated into dietary supplements and functional foods. Probiotics enhance the microbial balance in the gut and exert beneficial effects on host metabolism. Their unique characteristics—such as resistance to acidic pH, bile salts, and pancreatic enzymes, along with their capacity to adhere to and colonize intestinal epithelial cells—allow them to survive the gastrointestinal environment and promote digestive function. Moreover, probiotics can synergistically enhance the efficacy of antibiotics against pathogenic strains by modulating the intestinal ecosystem and supporting the functional activity of other commensal microorganisms.

Various studies have investigated the efficacy of different probiotic types, including lactic acid bacteria (LAB), Bifidobacterium species, and specific strains such as Bifidobacterium infantis, B. longum, B. lactis, Escherichia coli, Saccharomyces cerevisiae, S. boulardii, and S. lactis. These strains have been widely recognized

for their potential health benefits and probiotic effectiveness (13).

In the field of nutritional science, lactic acid bacteria (LAB) play a pivotal role. These organisms are gram-positive, catalase-negative bacteria that produce lactic acid as the main byproduct of carbohydrate fermentation. Among them, the genus *Lactobacillus* is the largest, comprising over 237 known species. Other notable genera within the LAB group include *Streptococcus*, *Enterococcus*, *Lactococcus*, and *Leuconostoc* (13). Recent studies have led to the identification and characterization of novel species, such as *Lactobacillus metriopectera* (14, 15) and *Lactobacillus timonensis* (14). *Lactobacillus* remains one of the most widely used probiotic genera in both clinical and commercial applications (16). A growing body of evidence suggests that the beneficial effects of these bacteria may be attributed to their cellular components or the metabolites they produce through interactions with host cells (17–22).

In addition to their well-documented benefits, there is growing evidence of potential side effects associated with probiotics (23, 24). This has led to increased scientific attention on the interactions between probiotic species and the host, as well as a deeper investigation into their underlying mechanisms of action.

The Immunomodulatory Effects of Probiotics

There is growing evidence supporting the beneficial effects of probiotics in modulating immune responses and exhibiting anti-tumor properties. They aid in the detection and elimination of carcinogenic metabolites and contribute to the production of short-chain fatty acids (SCFAs), which influence cellular proliferation and apoptosis by acting as signaling molecules within the immune system (25). Through modulation of the gut microbiota and its associated inflammatory networks, probiotics generate antimicrobial compounds with cytotoxic properties that may trigger immune-mediated responses against malignant cells (26). Additionally, they play a crucial role in regulating the balance of pro-inflammatory and anti-inflammatory cytokines, which may contribute to cancer prevention. Some strains have been shown to activate phagocytes, facilitating the early elimination of tumor cells (25). Probiotics also help prevent chronic inflammation by promoting anti-inflammatory cytokines such as interleukin (IL)-4, IL-10, IL-11, and IL-13, while

suppressing pro-inflammatory cytokines like IL-1, IL-6, and tumor necrosis factor-alpha (TNF- α) (27, 28). In the context of metabolic disorders, numerous studies have demonstrated that probiotics significantly reduce weight gain and body mass index (BMI). They regulate glucose and lipid metabolism by increasing anti-inflammatory adipokines and reducing pro-inflammatory ones, thereby enhancing insulin sensitivity and decreasing systemic inflammation (29).

By modulating the intestinal microbiota, probiotics can influence both immune system

function and carbohydrate and lipid metabolism. They are also believed to reduce inflammation and oxidative stress, which may help lower the risk of gestational diabetes (GD) in pregnant women (30). However, several studies investigating the effects of probiotics on fat metabolism have reported no significant differences between probiotic supplementation and placebo groups (31–34).

The beneficial roles of probiotics are briefly outlined in Figure 1 (13).

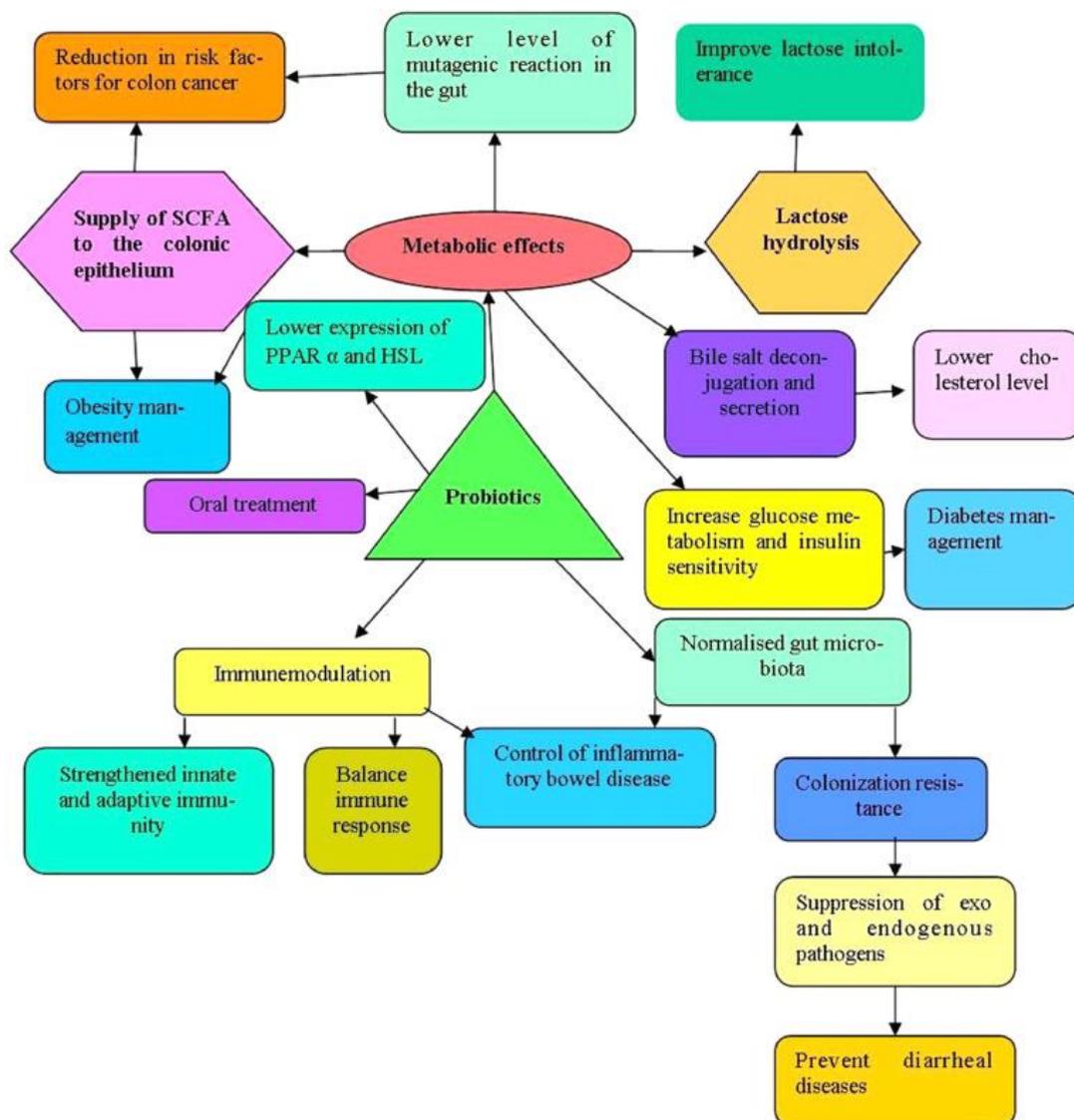


Figure 1. Different health beneficial effects of probiotic

The Clinical Evidence of Probiotic Effects in Diabetes

Several studies have explored the effects of probiotics on carbohydrate metabolism. Some findings suggest that probiotic supplementation can decrease glucose utilization as an energy source, enhance intestinal fat metabolism, and increase glutathione (GSH) levels, a key antioxidant. Probiotics have also been associated with reductions in inflammatory biomarkers such as C-reactive protein (CRP) and high-sensitivity CRP (hs-CRP), as well as markers of oxidative stress. Furthermore, they may improve cellular insulin sensitivity and help mitigate insulin resistance in pregnant women with gestational diabetes (GD) (35, 36).

Inflammatory conditions tend to intensify during pregnancy and can influence the composition and balance of the gut microbiota. Probiotic supplementation may stimulate beneficial microbial activity, potentially improving underlying metabolic disturbances. In pregnant women with gestational diabetes (GD), a form of microbial imbalance—commonly referred to as gut microbiome dysbiosis—is often characterized by a reduction in *Bifidobacterium* species. This dysbiosis has been identified as a contributing factor to maternal overweight and obesity, although it does not appear to be associated with maternal blood pressure levels (37–39).

Probiotics are generally considered safe and well tolerated during pregnancy (40). However, selecting the most effective probiotic strain and determining the optimal dosing requires further investigation. A commonly recommended daily dose for *Bifidobacteria* and *Lactobacilli* species is approximately 10^7 CFU/mL, which has been associated with improvements in metabolic parameters (41, 31).

The SPRING trial, conducted on obese and overweight pregnant women, evaluated the impact of *Lactobacillus rhamnosus* and *Bifidobacterium animalis* subsp. *Lactis* administered from the second trimester. The findings showed no preventive effect on the development of gestational diabetes mellitus (GDM) by the 28th week of pregnancy (37, 42, 43). Similarly, the trial by Taylor et al. reported no significant differences in fasting plasma glucose (FPG) levels ($p = 0.18$) or low-density lipoprotein (LDL) cholesterol levels ($p = 0.67$) between the probiotic and placebo groups (44).

Additionally, no significant differences in gestational weight gain were observed between the intervention and control groups (45).

Several studies have failed to demonstrate a significant benefit of probiotic supplementation in preventing gestational diabetes mellitus (GDM) (46). A systematic review and meta-analysis of 17 randomized controlled trials (RCTs) also concluded that probiotics were not effective in reducing the overall incidence of GDM. However, a slight reduction in fasting plasma glucose levels was observed between groups, although it was not considered clinically meaningful. Notably, a significant decrease in maternal insulin requirements was reported in the probiotic group (47). Another clinical trial reported a beneficial effect of specific probiotic strains on reducing the incidence of preterm birth, though no effect was observed on GDM outcomes (40). In contrast, some studies not only failed to show benefits in preventing GDM but also suggested an increased risk of preeclampsia associated with probiotic use during pregnancy (46, 47). Given the inconsistencies in these findings, caution is advised when recommending probiotics during pregnancy. Further investigation into the underlying pathophysiological mechanisms is warranted.

Some clinical trials have reported potential benefits of probiotic supplementation on neonatal outcomes and maternal metabolic parameters during pregnancy (42). For instance, Taylor et al. observed a significant improvement in insulin resistance among pregnant women receiving probiotics ($p = 0.01$) (44). Similarly, a meta-analysis by Zheng et al. demonstrated that the use of probiotics during pregnancy can significantly enhance glucose metabolism in women with diabetes (41). Notably, a substantial increase in plasma insulin levels was reported following the consumption of *Bifidobacteria* and *Lactobacillus* strains for approximately one month during the second half of pregnancy in women with gestational diabetes mellitus (GDM) ($p = 0.001$) (48). However, no significant difference in gestational weight gain was observed between the probiotic and placebo groups (45).

To evaluate the impact of probiotics on neonatal outcomes, Okesene-Gafa et al. reviewed data from nine randomized controlled trials and reported a significant reduction in hyperbilirubinemia among 695 infants born to

mothers with gestational diabetes, compared to placebo (relative risk [RR]: 0.18; 95% confidence interval [CI]: 0.05–0.66) (45, 48, 49).

Furthermore, a large-scale review involving 33,378 patients across 27 studies demonstrated that probiotic supplementation for a minimum duration of 7 weeks, at doses ranging from 0.5×10^9 to 823×10^9 colony-forming units (CFU), significantly decreased fasting blood glucose, insulin levels, homeostatic model assessment for insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), and homeostatic model assessment of β -cell function (HOMA-B) (50). However, no significant changes were observed in 1-hour and 2-hour oral glucose tolerance test (OGTT) results, glycated hemoglobin (HbA1c), or C-peptide levels. These findings have been further supported by additional studies (51).

A meta-analysis involving 896 participants across 13 studies evaluated the effects of *Lactobacillus* and *Bifidobacterium* species over a 4- to 8-week period in the management of gestational diabetes mellitus (GDM) and lipid markers (52). The findings indicated that both probiotics and synbiotics significantly reduced insulin resistance, as measured by the homeostatic model assessment of insulin resistance (HOMA-IR) and fasting serum insulin (FSI), along with a notable decrease in triglyceride (TG) levels (52, 53).

Experimental and clinical studies further support the role of probiotics in modulating the secretion of pro-inflammatory mediators and in regulating both local and systemic inflammation. These effects are primarily mediated through the normalization of intestinal permeability and the modulation of gut microbiota composition. Such immunoregulatory activity contributes to the enhancement of host immune responses and may play a preventive or therapeutic role in gestational diabetes (44, 45, 49).

Conclusion

In conclusion, probiotics appear to have the potential to modulate blood glucose levels and improve insulin regulation within a specific range in both healthy women and those with gestational diabetes. However, the precise mechanisms underlying these effects in both normal and pathological pregnancies remain unclear. Considering the heterogeneity of study designs, the variability in probiotic bacterial

strains, and the unique physiological context of pregnancy, a rigorously designed clinical trial is warranted to validate the findings reported in the current literature. Furthermore, environmental and genetic factors may influence the interplay between gut microbiota and inflammatory as well as biochemical markers, thereby affecting immune system modulation and function. Such a trial would be instrumental in clarifying the efficacy of probiotics and in determining the optimal dosage, bacterial strains, and duration of administration required to achieve beneficial outcomes. Given its prevalence and associated complications during pregnancy, diabetes represents a critical area of focus for such interventions.

Declarations

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Conflicts of Interest

The authors have declared no conflicts of interest.

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Authors' Contributions

E.H., and N.Y.; methodology, E.H and N.Z.H.; writing. All authors have read and agreed to the published version of the manuscript.

AI

During the preparation of this manuscript, the authors didn't use Ai services. The authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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CORRECTED PROOF