


MINI REVIEW

# Modulation of gut microbiota by diet and probiotics: potential approaches to prevent gestational diabetes mellitus

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## Abstract

Gestational diabetes mellitus (GDM) is a rising global health problem that affects approximately 6% of pregnant women. Lifestyle interventions, particularly diet, and exercise are the first-line treatment, followed by pharmacotherapy, but with associated side effects to both mother and offspring. Modulation of gut microbiota may help prevent or manage GDM. Some gut bacterial groups associated with GDM are also associated with inflammatory biomarkers and gut dysbiosis. Available literature reports that low-glycaemic index diet reduces maternal fasting and 2-hour postprandial glucose and maintains a beneficial gut bacterial composition. Pre- and probiotics can aid GDM therapy by modulating gut microbiota to eubiotic status and improving glucose metabolism. Probiotics as adjuvant GDM therapy should consider bacterial strains, dosage, and treatment duration. Limitations in their use require further studies to develop specific probiotic-based GDM supplement therapy that impacts glycaemic control and inflammatory status by reducing fasting plasma glucose, insulin resistance, and improving lipid profiles of pregnant women.

**Keywords:** gut microbiota; pregnancy; probiotics; diet; gestational diabetes mellitus

## Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance that results in hyperglycaemia with first recognition during pregnancy (Eades et al., 2017; Hasain et al., 2020), is an increasing public health concern with a rising prevalence of 5.4% in European and 7.6% in North American pregnant women (Casagrande et al., 2018). GDM impacts maternal-foetal health causing both short- and long-term adverse effects, including higher risk of preeclampsia and caesarean delivery for mothers; and macrosomia, preterm birth, respiratory distress, and shoulder dystocia for foetuses (HAPO Study Cooperative Research Group et al., 2008; Schneider et al., 2011; Wendland et al., 2012; Kc et al., 2015; Billionnet et al., 2017). More than half of pregnant women who develop GDM have at least one risk factor: >25 years old, body mass index (BMI) > 30 kg/m<sup>2</sup>, history of impaired glucose tolerance, previous pregnancies with GDM or macrosomia, multiple pregnancies, family history of type 2 diabetes, among others (Lefkovits et al., 2019). GDM diagnosis is made in the first trimester if a fasting glucose test returns a plasma glucose value ≥92 and <126 mg/dL or if returning a normal value, through an oral glucose tolerance test (OGTT) made at 24–28 weeks of gestation if a fasting plasma glucose value ≥92 mg/dL or ≥180 mg/dL at one hour or

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≥153 mg/dL at 2 hours (Wendland et al., 2012). Appropriate management of hyperglycaemia combined with lifestyle interventions, diet, and exercise prevents maternal obesity and GDM (Koivusalo et al., 2016; Wang et al., 2017). Other approaches are also available when diet and exercise alone are insufficient to control blood glucose levels, including pharmacological (insulin and/or oral hypoglycaemic agents, such as metformin) and non-pharmacological therapies (probiotics; Simmons, 2015). Pharmacotherapy has benefits for glucose control, especially insulin since it is unable to cross the placental barrier. However, this approach may result in side effects, including hypertensive disorders, when using insulin (Brown et al., 2017) and diarrhoea, abdominal pain, and headache, when using metformin (Dodd et al., 2018). Probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (Food and Agricultural Organization [FAO] of the United Nations and World Health Organization [WHO], 2001) and thus may be part of a non-pharmacological therapy. Gut microbiota, the group of living microorganisms colonising the gastrointestinal tract, is linked to human metabolism regulation. Alterations in gut microbiota composition are associated with metabolic diseases such as obesity, type 2 diabetes, and metabolic syndrome (Pascale et al., 2018) and can play an essential role in modulating insulin resistance (IR) and inflammatory response in GDM (Kuang et al., 2017). Diet and probiotics can affect gut microbiota composition (Wen and Duffy, 2017; Ponzio et al., 2019,b) and therefore can be a potential associative therapy for GDM if applied simultaneously.

The aim of this literature review was to compare the results of studies reporting the efficacy of both approaches (probiotics and diet) to prevent and manage GDM during pregnancy and to clarify if they could be potential therapeutic adjuvants for GDM treatment.

## Current status of knowledge

### *The role of human gut microbiota in homeostasis*

The human gastrointestinal tract is colonised by a collection of approximately 100 trillion microorganisms (Lozupone et al., 2012), whose composition is determined by host genetics, diet, immune responses, and the environment (Lynch and Pedersen, 2016). The development of our gut microbiota begins immediately at birth, being initially undifferentiated and progressively shaped by three major factors – type of delivery, breastfeeding, and weaning (Nicholson et al., 2012). In adult life, the gut microbiota has similar patterns between individuals at higher phylogenetic levels, being mainly composed of five bacteria phyla – *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia* (Tremaroli and Bäckhed, 2012). *Firmicutes* and *Bacteroidetes* are the most prevalent, representing more than 90% of the overall intestinal microbiota (Shen et al., 2013). At a genus level, some of the most frequently found bacteria are *Bifidobacterium*, *Lactobacillus*, *Bacteroides*, *Clostridium*, *Escherichia*, *Streptococcus*, and *Ruminococcus* (Conlon and Bird, 2015). At a species level, the variability is much higher, with healthy individuals having highly diverse gut microbiota (Flint et al., 2015). This complex micro-ecosystem holds a symbiotic relationship between each other (the microbes) and the host, who provides them a balanced environment to live while microbes provide the host with several benefits through a variety of functions such as modulating the intestinal barrier (Natividad and Verdu, 2013), producing bioactive compounds like short-chain fatty acids (SCFA; Topping and Clifton, 2001), maintaining host immune system (Gensollen et al., 2016), and protecting the host against ingested pathogens (Bäumler and Sperandio, 2016). Alterations in the intestinal microbiota and its metabolic pathways, termed dysbiosis (major changes in the resident microbial community with impairments for the host; Clemente et al., 2012), may contribute to the development of several chronic diseases, such as inflammatory bowel disease, multiple sclerosis, arthritis, and allergic inflammation (Kamada et al., 2013). Hence, it is important to maintain the balance of our gut microbiota composition to ensure homeostasis. Gut microbial fermentation of non-digestible foods (dietary fibres and resistant starches) maintains bowel health (Canfora et al., 2015) and leads to the production of SCFA, mainly butyrate, acetate, and propionate, via diverse biochemical pathways (Topping and Clifton, 2001). These metabolites can be used as energy sources by colonic epithelial cells or absorbed into the bloodstream (den

Besten et al., 2013). In the colon lumen, acetate, and propionate, mainly produced by *Bacteroidetes* (LeBlanc et al., 2017), release peptide YY (PPY) and glucagon-like peptide (GLP-1), which influence satiety and bowel transit; whereas butyrate, mainly produced by Firmicutes (LeBlanc et al., 2017), inhibits histone deacetylases (HDACs) and a specific G protein-coupled receptor (GPR109A), conferring anti-inflammatory effects (Koh et al., 2016), apart from modulating the expression of tight junction protein and mucins (Canfora et al., 2015). Additionally, SCFA also plays an important role in blood glucose level regulation and glucose homeostasis by inhibiting glycolysis and stimulating lipogenesis or gluconeogenesis, along with managing excessive production of cholesterol and conferring anti-carcinogenic action (Pascale et al., 2018). Further studies are needed to understand the impact of the different compounds produced by gut microbiome in the metabolism of both mother and offspring, and elucidate which microorganisms are responsible for these changes.

### **Modification of gut microbiota during pregnancy**

Pregnancy imposes a great number of physiological adaptations. Currently, there is no specific definition of healthy gut microbiota; however, it is known that its composition is highly diverse in healthy individuals (Meijnikman et al., 2018). Studies that explored the gut microbiota composition of healthy pregnant women found some important changes associated with an increase in maternal body weight by fat deposition and new dietary habits that culminate in a progressive increase in the food intake, essential for the foetus growth (di Simone et al., 2020). Physiological changes are also part of a normal pregnancy, with maternal tissues becoming increasingly resistant to insulin in approximately 50–60% of women with normal glucose tolerance or with GDM (Kampmann et al., 2019). In addition to weight gain and adiposity, pregnant women have significantly higher leptin, insulin and IR, cholesterol, and glycated haemoglobin levels as compared with nonpregnant women (Collado et al., 2008). In the pregnancy first trimester, the gut microbiota is expected to be similar to that of a healthy nonpregnant woman, classified into different enterotypes, considering three different groups of bacteria: one enterotype characterised by the presence of *Bacteroides*; another enterotype by higher proportion of *Prevotella*; and a third enterotype dominated by *Ruminococcus* (di Simone et al., 2020). Between the first and the third trimester, gut microbiota changes substantially decreasing its diversity, with increased proportions of *Proteobacteria*, commonly associated with inflammation, while the number of butyrate-producing bacteria with anti-inflammatory effects decreases (Koren et al., 2012).

Studies comparing the intestinal microbiota between healthy-weight pregnant women and overweight and/or obese pregnant women were also considered. Gomez-Arango et al. (2016) indicate that the ratio between phyla *Firmicutes* and *Bacteroidetes* was approximately 3:1 when analysing stool samples of both overweight and obese pregnant women, showing a slightly higher abundance of *Firmicutes* in obese women. These results were linked with the higher expression of enzymes engaged in the digestion of polysaccharide, highlighting that more energy can be obtained from the same diet (Cani, 2013). Some correlations between specific taxa and pregnancy variables were observed. *Lachnospiraceae* and *Ruminococcaceae* families (both from *Firmicutes* phyla) were strongly correlated with leptin and positively associated with BMI. *Bacteroidaceae* relates with ghrelin that, in turn, was negatively associated with BMI, and positively correlated with *Rikenellaceae* (both from *Bacteroidetes* phyla). *Collinsella* positively correlated with insulin levels and triglycerides while *Coprococcus* (butyrate producer) correlated with gastric-inhibitory polypeptide (GIP), an incretin hormone (Gomez-Arango et al., 2016). When gestational weight gain (GWG) is excessive, pregnant women have an increased risk of developing GDM, obesity, metabolic syndrome (Carreno et al., 2012; Gilmore et al., 2015) and delivering a baby larger-for-gestational age (Carreno et al., 2012; Ferraro et al., 2012; Kim et al., 2014). In this situation, gut microbiota is associated with lower  $\alpha$ -diversity (DiGiulio et al., 2015), and the presence of *Eisenbergiella*, *Lactobacillus* (Crusell et al., 2018), *Blautia*, *Ruminococcus*, and *Feacalibacterium* (Stanislawski et al., 2017) genus and *Escherichia coli* (Santacruz et al., 2010) species. On the other hand, *Bifidobacterium* and *Akkermansia muciniphila* (Collado et al., 2008;

Santacruz et al., 2010), along with *Christensenella* and *Alistipes* (Crusell et al., 2018), are associated with the opposite trend. Additionally, overweight and obese pregnant women were reported to have higher levels of *Bacteroides* (Collado et al., 2008), *Staphylococcus* (Collado et al., 2008; Santacruz et al., 2010) as well as Enterobacteriaceae and *E. coli* (Santacruz et al., 2010).

### **Gut microbiota modifications during GDM pregnancy**

Gut microbiota is involved in human metabolism regulation but can also contribute to the pathogenesis of many diseases, including GDM (Chwalba and Otto-Buczowska, 2017; Ponzo et al., 2019a,b). During gestation, adjustments in the women's glucose metabolism occur to ensure proper glucose levels to warrant foetal growth and development combined with appropriate maternal nutrition (Angueira et al., 2015). In early gestation, fasting blood glucose (FBG) levels decrease, possibly due to dilution effects (caused by an increased plasma volume), increased glucose uptake by the placenta (Lain and Catalano, 2007; Angueira et al., 2015), and inadequate hepatic glucose production (Lain and Catalano, 2007). These levels remain constant in the second trimester and increase during the last trimester (Angueira et al., 2015). In a regular pregnancy's last trimester, maternal insulin sensitivity declines, which is considered to be advantageous to support foetal development with increased energy requirements at this stage (Koren et al., 2012). In a severe GDM pregnancy, insulin decreases an additional 40% (relatively to a healthy gestation), leading to glucose intolerance (Lain and Catalano, 2007). To balance these alterations, and due to a decreased capacity of insulin to suppress lipolysis, an increase in free fatty acids, hepatic gluconeogenesis, and severe IR occurs (Taddei et al., 2018).

In recent years, more information on the correlation between GDM and gut microbiota has become available, demonstrating a distinct microbiota profile associated with this pathology (Kuang et al., 2017; Mokkalá et al., 2017; Crusell et al., 2018; Ferrocino et al., 2018; Hasan et al., 2018; Cortez et al., 2019; Liu et al., 2015; Ye et al., 2019; Ma et al., 2020; Zheng et al., 2020). At a genus level, increased abundance of *Klebsiella* (Kuang et al., 2017), *Collinsella* (Collado et al., 2008; Santacruz et al., 2010; Carreno et al., 2012; Koren et al., 2012; Jost et al., 2014; Kim et al., 2014; Priyadarshini et al., 2014; DiGiulio et al., 2015; Gomez-Arango et al., 2016; Stanislawski et al., 2017; Aatsinki et al., 2018; Crusell et al., 2018; Ferrocino et al., 2018; Meijnikman et al., 2018; Smid et al., 2018; Crusell et al., 2018), *Rothia* (Angueira et al., 2015; Chwalba and Otto-Buczowska, 2017; Mokkalá et al., 2017; Crusell et al., 2018; Taddei et al., 2018; Liu et al., 2015; Ponzo et al., 2019a,b; Zheng et al., 2020), *Eubacterium* (Kuang et al., 2017), *Ruminococcus* (Cortez et al., 2019), *Blautia* (Crusell et al., 2018; Ye et al., 2019; Zheng et al., 2020), *Prevotella* (Cortez et al., 2019; Zheng et al., 2020), *Parabacteroides* (Kuang et al., 2017; Dong et al., 2020), *Eisenbergiella* and *Tyzzerella* (Ma et al., 2020), and a reduced richness in *Akkermansia* (Cortez et al., 2019), *Marvinbryantia*, *Acetivibrio*, *Anaerospobacter* (Jost et al., 2014), and *Roseburia* (Kuang et al., 2017; Cortez et al., 2019) were described in patients with GDM compared with normoglycemic women (Figure 1). Mokkalá et al. (2017) reported changes in the gut microbiota before GDM diagnosis, indicating that higher abundance of Ruminococcaceae in the intestine, a family of bacteria important for starch digestion in the large intestine and production of SCFAs (Oriá et al., 2020), may be associated with an increased probability to develop GDM (Mokkalá et al., 2017).

There is evidence suggesting associations between some bacterial taxa and GDM indicators. *Desulfovibrio*, reported as a GDM biomarker (Crusell et al., 2018), is also a known lipopolysaccharide (LPS) producer, which is one of the strongest inducers of inflammation (Cani et al., 2012), associated with IR (Kim et al., 2018) and leading to intestinal barrier damage (Sanchez-Alcoholado et al., 2017; Zhang et al., 2018a). *Collinsella* has been related to higher scores in the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) scale and insulin levels (Ferrocino et al., 2018). *Blautia* was associated with glucose intolerance (Egshatyan et al., 2016) and unfavourable metabolic profile in high BMI patients (Crusell et al., 2018; Ye et al., 2019). *Prevotella* was positively associated with increased LPS and gut inflammation mediated by pro-inflammatory cytokines (Alves et al., 2019).

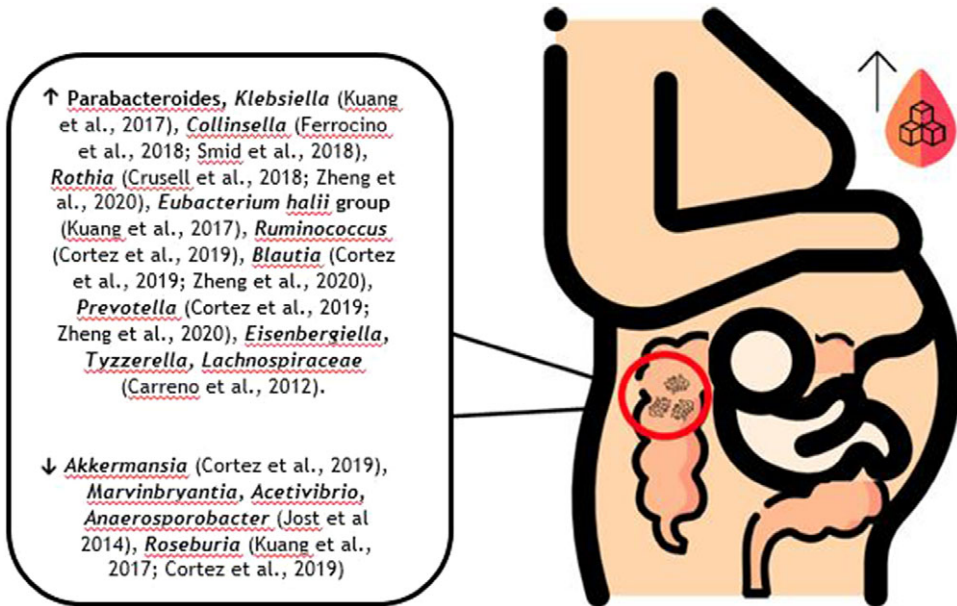


Figure 1. Possible composition of the gut microbiota in pregnant women with GDM according to the available literature.

Although such associations have been established, subjacent mechanisms concerning host and microbiota interactions remain unidentified (Angueira et al., 2015). Also, there are some controversial results since *Megasphaera* and *Eggerthella* were reported to be enriched in normoglycaemic controls in some studies (Stanislawski et al., 2017; Wen and Duffy, 2017) while in others both genera were described to be enriched in the GDM group (Zheng et al., 2020). Additionally, at a phylum level, *Actinobacteria* was found simultaneously to be increased (Crusell et al., 2018) and decreased in GDM cohorts (DiGiulio et al., 2015; Cortez et al., 2019).

In an attempt to outline available information in a more visual format, Figure 1 presents the possible composition of a pregnant woman with GDM gut microbiota, mainly at the genus level, separating those currently described to be increased from those currently described as being decreased in these patients.

Finally, GDM mother's offspring gut microbiota have differences in  $\alpha$ -richness compared with neonates of mothers without GDM, with a higher abundance of *Actinobacteria*, associated with higher levels of fasting glucose, and reduction in *Bacteroides* abundance. At a genus level, an increase of opportunistic pathogens, such as *Escherichia* and *Parabacteroides*, and a decrease in probiotic *Lactobacillus* were observed in GDM mother's offspring (Su et al., 2018; Ponzio et al., 2019b). Therefore, the influence of the mother's gut microbiota composition, blood glucose, BMI, and dietary intake on the gut microbiota of their offspring needs to be further investigated.

### Interactions between diet and gut microbiota during pregnancy

The microbial community living in the gut highly depends on the host's diet, one of the most significant contributors to the modulation of intestinal microbiota and human health (Hasan and Yang, 2019). Among nutrients, the effects of complex carbohydrates (CHO) are the best studied, having an important impact on microbiota composition (Gentile and Weir, 2018). It has been reported that diets rich in CHO can modify the gut microbial composition in only a few days or weeks, because in the large intestine there is an intensive fermentative activity of resistant starch and fibres, creating a set of metabolites produced by bacteria – the human metabolome – that can be detected in the host faeces, urine, and blood that can pass the intestinal barrier (Flint et al., 2015). Dietary fibre is the energy



source for commensal SCFA-producing bacteria and its fermentation has the potential to decrease postprandial blood glucose, insulin responses and, decrease cholesterol absorption. Dietary patterns marked by low-fibre intake inhibit the growth of SCFA-producing bacteria and enable the development of other bacterial strains that use glycoproteins as energy, leading to harmful effects on the gut barrier (Gomez-Arango et al., 2017). A different study also showed that, in early pregnancy, diets associated with higher ingestion of fibres, like vegetarian diets, resulted in a diminished abundance of *Collinsella* (lactate producing bacteria, instead of SCFA, associated with IR), as well as an increased richness of *Roseburia* (a butyrate producing bacteria) when compared with the gut microbiota of early pregnant women with omnivore diets (Barret et al., 2018). Additionally, *Prevotella* was found to be enriched in maternal microbiota related to diets with higher CHO intake, whereas *Ruminococcus* was more enriched in the cohorts ingesting vegetal protein and fat diets (García-Mantrana et al., 2020). Furthermore, in overweight and obese pregnancies higher fibre intake increased intestinal microbiota richness, while greater fat intake (saturated fatty acids, monounsaturated fatty acids, and *n*-6 polyunsaturated fatty acids) decreased its richness (Röytiö et al., 2017).

Current literature also reports the association between pro-inflammatory bacteria and dietary patterns. *Proteobacteria* were associated with a diet abundant in vitamin D, retinol, and mono-unsaturated fat in normal-weight pregnant women, whereas vitamin E was associated with the opposite trend (Mandal et al., 2016). One study implemented routine dietary counselling according to International Federation of Gynecology and Obstetrics (FIGO) guidelines (Hod et al., 2015) to a cohort of 41 overweight pregnant women with GDM, where participants completed a 3-day food record and it was found that only one-third accomplished the recommendations, with two-third consuming a diet rich in fat and low in fibre (Ferrocino et al., 2018). Adherent participants, whose diet was poor in saturated and total fats, showed a decreased abundance of *Bacteroides* in their gut microbiota composition, which is associated with high-fat animal-based diets (David et al., 2014). In conclusion, food and its constituents are crucial in regulating host health and disease since they can modulate the environment in which gut microbes live, as well as their diversity and metabolism.

### Medical nutrition therapy in GDM

Most GDM women are diagnosed between 24 and 28 weeks of pregnancy, when there is already an increased maternal IR that tends to be higher each week (Farabi and Hernandez, 2019). Medical nutrition therapy (MNT), defined as an individualised nutritional plan developed between the woman and the dietitian (American Diabetes Association Professional Practice Committee, 2022), can be an effective first-line therapy to treat GDM. It should be a food plan that provides adequate calories for both mother and foetus, based on nutrition assessment and the control of the amount and distribution of CHO in the diet, in order to achieve adequate nourishment and normoglycaemia without ketosis and also to improve glycaemic control (Reader, 2007; Moreno-Castilla et al., 2013). For a successful treatment, individual and personalised dietary counselling and prescription should be assumed by a registered dietitian (or universal equivalent) for all pregnant women diagnosed with GDM (Duarte-Gardea et al., 2018).

The major focus of MNT is to lower postprandial plasma glucose levels, either by adjusting CHO distribution or by altering the glycaemic load (GL; Hernandez et al., 2013). The first steps of diet manipulation were taken during the 1950s and 60s, focusing on CHO restriction, with approximately 40% of total daily calories (Hernandez, 2016), considering the principle that it could help lower postprandial glucose and prevent foetal hyperinsulinemia (Mulla, 2016). Currently, it is recommended by the Institute of Medicine (United States of America – USA) a minimum of 175 g CHO/day for pregnant women, equivalent to 35% of a 2000 calories diet, with an extra 45 g compared with non-pregnant women, since an average of 33g glucose/day are required to support foetal brain development and functioning (Trumbo et al., 2002), and also 71 g of protein and 28 g of fibre. Low-CHO diets remain the conventional diet therapy for GDM in some countries. Hence, more studies are needed to

construct solid evidence about CHO restriction diets (Trumbo et al., 2002; Moreno-Castilla et al., 2016; Mulla, 2016). Moderation seems to be key, since proportions greater than 55% CHO are associated with increased postprandial plasma glucose (Filardi et al., 2019).

Considering CHO, part is categorised as complex, since their structure is resistant to digestion or even completely undigested, resulting in a slower rise in blood glucose, low-GI (Mustad et al., 2020). Worldwide, 10 clinical practice guidelines (in a total of 16 analysed) on CHO considerations for GDM recommend a low-GI diet (foods under 55 on the GI scale; Tsirou et al., 2019), as it can reduce maternal FBG and 2-hour postprandial glucose, compared with high-GI diet. Viana et al. (2014) systematically reviewed various dietary patterns and concluded that a low-GI diet was the only one confirmed as beneficial for GDM women. Moreover, this diet may also have beneficial effects on the offspring by significantly reducing FBG, postprandial glucose levels, insulin use, and risk of macrosomia (Zhang et al., 2018b; Xu and Ye, 2020). Different types of CHO have diverse impacts on gut microbiota composition. Mardinoglu et al. (2018) conducted a short-term intervention study on 10 obese individuals with non-alcoholic fat disease, in order to understand the gut microbial composition, by applying a restricted-CHO diet with increased protein for 14 days. The results show a reduction of CHO-degrading bacteria *Ruminococcus*, *Eubacterium*, *Clostridium*, and *Bifidobacterium*, and levels of SCFA, along with an increased richness in *Lactococcus*, *Eggerthella*, and *Streptococcus* (Mardinoglu et al., 2018). Another study examined the effects of a CHO-restricted diet on the gut bacteria in mice, showing a significant increase in *Clostridium* (bacteria that promote inflammation) and *Suterella* (associated with increased LPS and gut inflammation; He et al., 2020).

Regarding fibre intake, a study about the effects of high fibre with low-GI on gut microbiota in type 2 diabetes patients reported a decreased richness in *E. coli* and *Enterococcus* (opportunistic pathogens) and a significant increase in *Bifidobacterium* and *Lactobacillus* (beneficial bacteria) compared with the control group (Singh et al., 2017). *Bifidobacterium* is solidly associated with SCFA production – produced by the fermentation of microbiota-accessible carbohydrates (MACs) – decreased gut LPS levels and improved intestinal mucosal barrier. *Lactobacillus* is associated with anti-inflammatory and anti-carcinogenic effects, and also SCFA production (Singh et al., 2017). Additionally, the richness of *Lactobacillus* and *Bifidobacterium* are associated with the intake of prebiotic fibres (Moszak et al., 2020). These are indigestible fermented fibres that promote bacterial growth in the intestine with health benefits for the host, such as fructooligosaccharides (FOS), galactooligosaccharides (GOS), and inulin (Wilson and Whelan, 2017). The majority of GDM guidelines recommend an augmented quantity of fibre, with some indicating approximately 28 g/day of fibres intake (Tsirou et al., 2019).

DASH diet is another dietary pattern that has been studied for patients with GDM. Characterised by low-GI, low-energy density with high quantities of fibre and decreased levels of sodium, it was originally designed for patients with hypertension, but favourable effects were reported for metabolic syndrome and type 2 diabetes (Asemi et al., 2013a,b). The American Academy of Nutrition and Dietetics (USA) also considers this dietary pattern to be effective in improving both mother and foetal outcomes in GDM, including glucose tolerance, IR, glycosylated haemoglobin, insulin requirements, lipid profile and incidence of macrosomia (Duarte-Gardea et al., 2018), HOMA-IR results and medication needs (Yamamoto et al., 2018), systolic blood pressure and lipid profiles – these last two reported on a 4-week DASH diet in patients with GDM (Asemi et al., 2013a,b). DASH shares numerous similarities with the Mediterranean diet, except for the intake of olive oil. Fruits, vegetables, and grains are the major food sources in the DASH pattern diet, containing different fibre types (Jama et al., 2019), which may predict its positive role in GDM nutrition, as discussed above. Although there is a lack of studies directly targeting the influence of a DASH diet on GDM women's gut microbiota, it is already demonstrated that high adherence to DASH promotes the increased richness of SCFA-producing bacteria, such as *Roseburia*, whereas no adherence leads to higher urinary trimethylamine N-oxide (TMAO) levels, a microbial metabolite possibly associated with cardiovascular and neurological disorders (Filippis et al.,

2016). Further studies are required to better clarify the DASH diet role in gut microbiota modulation for GDM management.

### Probiotics in GDM

Even though the adherence of the probiotics to the intestinal mucosal cells is challenging, which influences its effect (O'Sullivan et al., 1992; Kullen et al., 1997), regular use of probiotics is reported to beneficially modulate intestinal microbiota composition metabolic activities (Taylor et al., 2017). Thus, maternal gut microbiota modulation with probiotic intervention is emerging as a safe approach capable of improving intestinal commensal bacteria and also providing beneficial effects for both mother and foetus health (Swartwout and Luo, 2018; Hasain et al., 2021). Currently, probiotic agents are mainly produced by gram-positive bacteria such as lactic acid bacteria, namely *Bifidobacterium* and *Lactobacillus*. Its use, particularly *L. casei*, *L. helvetica*, *L. acidophilus*, and *L. rhamnosus* are associated with an improvement of some GDM biomarkers (Pereira et al., 2018). Several other promising data suggest that probiotics may positively contribute to beneficial effects on glucose metabolism or even prevent GDM, either by probiotic-fortified foods or capsules (Dolatkhah et al., 2015; Lindsay et al., 2015; Ahmadi et al., 2016; Jafarnejad et al., 2016; Karamali et al., 2016; Wickens et al., 2017; Badehnoosh et al., 2018; Kijmanawat et al., 2019).

Seven studies assess the effect of probiotics on metabolic health in pregnant women with GDM (Table 1). Only one randomised control trial (RCT) demonstrated no impact on the metabolic health of GDM pregnant women, with the consumption of one single strain probiotic capsule, *L. salivarius*, in a dose of  $1 \times 10^9$  CFU/day during 6 weeks. A double-blind, placebo-controlled study performed with 60 GDM pregnant women demonstrated that probiotic intervention with 3 strains, *L. acidophilus*, *L. casei* and *B. bifidum*, in a dose of  $6 \times 10^9$  CFU/day during 6 weeks resulted in a significant decrease of FBG, insulin, HOMA-IR and HOMA for  $\beta$  cell function (HOMA- $\beta$ ) levels in the probiotic group compared with the placebo group. There were also positive results in the probiotic group concerning lipid metabolism, with considerable reductions in serum triglycerides and very low density lipoprotein (VLDL) cholesterol. Similar results were reported when administering a symbiotic supplement (probiotics plus inulin) with the same probiotic strains and doses used in Karamali et al. (2016) to GDM pregnant women, supplemented with 800 mg of inulin (a prebiotic fibre) during a 6-week-treatment, resulting in decreased insulin levels, and HOMA-IR and HOMA- $\beta$  results, along with similar lipid outcomes when compared with placebo (Ahmadi et al., 2016). Another RCT involving 70 pregnant women diagnosed with GDM showed that daily consumption of a probiotic capsule containing eight different strains, *S. thermophilus*, *B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei* and *L. delbrueckii*, in a dose of  $15 \times 10^9$  CFU during 8 weeks, had significant differences in insulin levels and HOMA-IR; however, no changes were observed in FBG and HbA1c in the probiotic group compared with the placebo group (Jafarnejad et al., 2016). Data from a double-blind, placebo-controlled, and randomised study revealed that an 8-week treatment of probiotics in a  $4 \times 10^9$  CFU/day dose with four probiotic strains, *L. acidophilus*, *Bifidobacterium* sp., *S. thermophilus*, and *L. bulgaricus*, showed reductions in FBG, HOMA-IR and GWG (Dolatkhah et al., 2015). Moreover, a 4-week randomised double-blind and placebo-controlled study performed with a two-strain probiotic capsule containing *L. acidophilus* and *B. bifidus* in a  $2 \times 10^9$  CFU dose in 57 GDM pregnant women, demonstrated significant improvements in glucose metabolism in the probiotic group compared with the placebo, comprising fasting plasma insulin, FBG, and HOMA-IR (Kijmanawat et al., 2019). Two other RCTs conducted with the same number of participants ( $n = 60$ , 30 in the probiotic group, 30 in placebo group) and the same three strains of probiotics, *L. acidophilus*, *L. casei* and *L. bifidum*, and doses ( $6 \times 10^9$  CFU/day) but with different treatment duration and type of participants, 6 weeks with GDM pregnant women (Badehnoosh et al., 2018) and 12 weeks with healthy pregnant women (Ahmadi et al., 2016), have both exhibited positive results in the probiotic group. In GDM pregnant women probiotic treatment significantly reduced FBG and other inflammatory biomarkers, total glutathione, high



**Table 1.** Studies of probiotics in GDM diagnosed women during gestation.

References	Dietary intervention/assessment	Intervention/control	Duration (weeks)	Probiotic strains	Dosage (CFU)	Outcomes
Lindsay et al. (2015)	Low glycaemic index (3-day food record)	Probiotic/ placebo (48/52)	6	<i>L. salivarius</i>	$1 \times 10^9$	↔ Fasting plasma glucose ↔ HOMA-IR ↔ C-peptide ↓ Total cholesterol ↓ LDL cholesterol ↔ Triglycerides ↔ Gestational weight gain
Dolatkhah et al. (2015)	Usual dietary habits (24-h recall questionnaire of 3 days)	Probiotic/ placebo (29/27)	8	<i>L. acidophilus</i> , <i>Bifidobacterium</i> , <i>S. thermophilus</i> , <i>L. bulgaricus</i>	$4 \times 10^9$ ( $1 \times 10^9$ each strain)	↓ Fasting plasma glucose ↓ HOMA-IR ↓ Gestational weight gain
Karamali et al. (2016)	Usual dietary habits (3-day food record)	Probiotic/ placebo (30/30)	6	<i>L. acidophilus</i> , <i>L. casei</i> , <i>B. bifidum</i>	$6 \times 10^9$ ( $2 \times 10^9$ each strain)	↓ Fasting plasma glucose ↓ HOMA-IR ↓ HOMA-β ↓ Serum insulin levels ↑ QUICKI ↓ VLDL cholesterol ↓ Triglycerides
Jafarnejad et al. (2016)	Usual dietary habits (24-h recall questionnaire of 3 days)	Probiotic/ placebo (37/35)	8	<i>B. longum</i> , <i>B. infantis</i> , <i>L. acidophilus</i> , <i>L. plantarum</i> , <i>L. paracasei</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i>	$15 \times 10^9$	↔ Fasting plasma glucose ↓ HOMA-IR ↓ Serum insulin levels ↓ IL-6 ↓ TNF-α ↓ hs-CRP ↔ HbA1c
Ahmadi et al. (2016)	Usual dietary habits (3-day food record)	Synbiotic/ placebo (35/35)	6	<i>L. acidophilus</i> , <i>L. casei</i> , <i>B. bifidum</i>	$4 \times 10^9$ ( $2 \times 10^9$ each strain)	↔ Fasting plasma glucose ↓ Serum insulin levels ↓ HOMA-IR ↓ HOMA-β ↑ QUICKI ↓ Triglycerides ↓ VLDL cholesterol

Table 1. Continued

References	Dietary intervention/ assessment	Intervention/ control	Duration (weeks)	Probiotic strains	Dosage (CFU)	Outcomes
Badehnoosh et al. (2018)	Usual dietary habits (3-day food record)	Probiotic/ placebo (30/30)	6	<i>L. acidophilus</i> , <i>L. casei</i> , <i>B. bifidum</i>	$6 \times 10^9$ ( $2 \times 10^9$ each strain)	↓ Fasting plasma glucose ↓ hs-CRP ↓ Plasma MDA concentrations ↑TAC levels ↔ Gestational weight gain
Kijmanawat et al. (2019)	No specific diet-controlled GDM (3-day food record)	Probiotic/ placebo (28/29)	4	<i>L. acidophilus</i> , <i>B. bifidum</i>	$2 \times 10^9$ ( $1 \times 10^9$ each strain)	↓ Fasting plasma glucose ↓ Fasting plasma insulin ↓ HOMA-IR ↔ Gestational weight gain

↔ No significant differences between probiotic and control groups; ↓significantly lower in the probiotic group compared with the control; ↑significantly higher in the probiotic group compared with the control. HbA1c, glycosylated haemoglobin; HOMA-IR, homeostatic model of assessment of insulin resistance; HOMA-β, homeostatic model assessment for B-cell function; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; MDA, malondialdehyde; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity; TNF-α, tumour necrosis factor alpha; VLDL, very low density lipoprotein.

sensitivity C-reactive protein, malondialdehyde, and nitric oxide (Badehnoosh et al., 2018), whereas in healthy pregnant women substantially diminished insulin levels, HOMA-IR and HOMA- $\beta$  (Ahmadi et al., 2016). Hasain et al. (2021) conducted a meta-analysis of studies using multispecies probiotics, including *Lactobacillus* and *Bifidobacterium*, similarly to the previous studies presented. Authors reported significant reduction in different glycemic control biomarkers as FPG, fasting serum insulin, and HOMA-IR in women with GDM when taking a probiotic supplementation in a dose between  $10^6$  to  $10^9$  CFU. However no significant impact was observed when comparing the data for total cholesterol levels, which does not concur with other studies presented in this review. Further studies can help clarify this discrepancy.

Current literature reveals that probiotic therapy may be an important non-pharmacological approach in terms of improving glycaemic control in pregnant women diagnosed with GDM. Probiotic mechanisms of action for treating diabetes mellitus are diverse and depend on different aspects (Khursheed et al., 2019). Anti-diabetic effects emerge when the administration of probiotics is accomplished, homeostasis is recovered, along with diminished LPS levels, supporting the synthesis of different SCFA (butyrate, acetate, and propionate) on the intestine. This leads to an increased release of incretin hormones (like GLP-1), stimulating insulin secretion and delaying gastric emptying, which affects blood glucose levels and reduces intestinal permeability, by improving tight junction proteins, thus diminishing inflammation, oxidative stress, glucose intolerance, and IR (Sanchez-Alcoholado et al., 2017; Khursheed et al., 2019).

However, additional studies are needed to clarify the underlying mechanisms of action through which probiotic therapy improve glycaemic control in GDM pregnant women and determine variables such as what strains, dosage and duration of probiotic treatment confer the highest benefits during gestation. Hsu et al. (2018) reported the influence of maternal therapy with *Lactobacillus casei* probiotic and inulin prebiotic for hypertension treatment in rat's offspring, showing a protective effect when a high fructose diet is administered during pregnancy and lactation. However, the mechanism behind the effect on the offspring is still not clear, as it may be due to a direct consequence of the probiotic passage through the milk or the placenta or the modification of the mother's metabolism. Other studies evaluated the use of probiotics to manage offspring overweight. The meta-analysis developed by Wang et al. (2020) reveals the decrease of the newborn birth weight when women with GDM are treated with probiotics. On the other hand, the intake of probiotic by obese pregnant women has the opposite effect, increasing the newborn birth weight.

Discrepancies between studies are also present. Badehnoosh et al. (2018) and Karamali et al. (2018) observed a positive effect of 6 weeks probiotic therapy with *L. acidophilus*, *L. casei*, and *B. bifidum* on offspring birth weight from women with GDM, while Kijmanawat et al. (2019) observed that supplementation with only *L. acidophilus* and *B. bifidum* during 4 weeks do not produce any effect on the infant weight. The success of the probiotic intake seems to be dependent on the type of probiotic strains used, being cocktails with higher diversity of microorganism more beneficial. The duration of treatment also appears to influence the effect of the treatment, with Wang et al. (2020) analysis indicating the need of at least 6 weeks to see effects.

Although proven safe and without adverse effects both for mother and offspring (Didari et al., 2014), additional studies need to elucidate the modification not only in the mother's metabolism and gut microbiome but also in the offspring. All of this should be taken in consideration when recommending probiotic treatment to pregnant women diagnosed with GDM.

## Conclusion

Gut microbiota suffers alterations during healthy and pathological gestations like GDM. Modulating its composition through diet and probiotics can be a valid non-pharmacological preventive approach to reduce adverse GDM outcomes in both mother and offspring. Dietary management without probiotics, particularly with a low-GI approach, the currently most recommended diet for patients with GDM,

showed benefits in reducing maternal FBG and 2-hour postprandial glucose, apart from being associated with beneficial gut bacteria, such as *Bifidobacterium* and *Lactobacillus*. As reviewed, probiotic supplements may ameliorate glycaemic control and inflammatory status of GDM pregnant women, demonstrating the ability to reduce fasting plasma glucose, IR, and improved lipid profiles. However, further high-quality studies are needed to verify the effectiveness of dietary interventions with probiotics as well as the definition of the bacterial strains, doses, and duration of treatment that have the best clinical significance for GDM pregnant women. Achieving this will securely increase the use of probiotic supplementation in GDM diets to better contribute to healthier GDM pregnancies and post-partum outcomes for both mother and offspring.

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**Significance statement.** With the increase of gestational diabetes mellitus (GDM) and the universal difficulties in the pharmacological management of diseases during pregnancy, the role of diet interventions with probiotics supplementation is incrementally becoming more important. Current literature contributes relevant information on the best approach to manage GDM through medical nutrition therapy, particularly regarding carbohydrates, lipids, and fibre intake, combined with probiotics supplementation. That is the theme that this manuscript reviews highlights, including future approaches to propel this field of work.

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