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Nutritional Supplementation for the Prevention and/or Treatment of Gestational Diabetes Mellitus

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Abstract

Purpose of Review Gestational diabetes mellitus (GDM) is a common pregnancy complication that has short- and long-term health implications for both the mother and child. While lifestyle modifications, insulin therapy, and oral agents such as metformin are effective, they can be difficult to adhere to, and there remain concerns over long-term effects of oral agents on the infant. Further, GDM has no proven preventive strategies, which could be more effective than treatment postdiagnosis. Nutritional supplements are an appealing, potentially safer, and better tolerated alternative to pharmaceuticals to treat and/or prevent GDM. Here, we review the existing evidence for nutritional supplementation for treatment and prevention of GDM.

Recent Findings There is limited evidence that myo-inositol, vitamins D and B6, magnesium, selenium, zinc, fatty acids, and probiotics might be beneficial for the prevention or treatment of GDM. There are very few studies for each nutrient, and the existing studies tend to have few participants. Where multiple studies of a nutrient exist, often those studies were conducted within the same country, limiting the generalizability of the findings, or alternatively there was no consensus across findings.

Summary There is limited evidence that nutritional supplementation of myo-inositol, vitamins D and B6, magnesium, selenium, zinc, fatty acids, and probiotics could improve glycemic control or prevent GDM. Our understanding is constrained by the small number of studies, small sample sizes in most studies, and by lack of consistency across findings. Further large, high-quality, randomized controlled trials are required to determine the efficacy of nutritional supplements to treat or prevent GDM.

Keywords Gestational diabetes · Nutrition · Supplementation · Diet · Pregnancy

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Introduction

In recent years, the global prevalence of obesity and its frequency in women of reproductive age has rapidly increased, with no apparent end to the trend in sight [1]. The growing burden of obesity and its relationship with type 2 diabetes mellitus (T2DM) have prompted a surge in diabetes-related research, which has demonstrated that hyperglycemia during pregnancy is related to adverse pregnancy outcomes [2]. Gestational diabetes mellitus (GDM) refers to the subset of patients in which hyperglycemia is first diagnosed during the second or third trimester and excludes those women with overt diabetes that existed prior to pregnancy [3]. Current estimates suggest that GDM affects around 14% of pregnancies worldwide, although this figure may reach 25% of pregnancies in some populations, and the rate is climbing in parallel with the increasing prevalence of obesity and T2DM [4]. Exact estimates of the number of pregnancies affected are difficult to ascertain due to the wide variety of diagnostic criteria used

across study populations and the lack of adequate screening in some populations [5]. GDM is of great concern due to the lifelong consequences it can pose for both the mother and the baby. Women who experience GDM are more likely to develop T2DM and cardiovascular disease (CVD) in later life, as well as GDM in subsequent pregnancies [6]. Babies born to mothers with GDM are more likely to be born large for gestational age (LGA), experience respiratory distress or stillbirth, and are themselves predisposed to later obesity and T2DM [7]. Being overweight or obese is a significant risk factor for GDM, and this gives rise to a vicious intergenerational cycle of obesity and diabetes. In order to halt this cycle, effective interventions for GDM are required [8].

Unfortunately, there are no widely accepted preventive strategies for GDM, and current treatment approaches are not ideal. Management usually includes diet and lifestyle changes, followed by insulin supplementation, which, while usually effective, requires frequent self-injection and blood glucose monitoring. Further, insulin therapy is associated with increased gestational weight gain and increases risk of hypoglycemia [9, 10]. Oral diabetes agents, such as metformin and glyburide, have shown short-term promise [11, 12], but long-term effects on the mother and fetus remain poorly understood, and for this reason, the American Diabetes Association does not currently recommend their use in GDM [13]. Further, by the time GDM is diagnosed—typically between 24 and 28-week gestation—the most effective window to prevent long-term harm may have passed. GDM prevention may therefore be a more effective strategy than treatment alone. For these reasons, there is scope to develop new effective, safe, and easy-to-administer interventions to prevent GDM in pregnant women, or women planning a pregnancy. In recent years, the relationship between GDM and diet has prompted investigators to examine nutritional supplementation as a potential prevention and treatment strategy for GDM. Nutritional supplements are an exciting avenue because they are typically well-tolerated, safe, and easy to administer—including during pregnancy. This review will discuss the available evidence for nutritional supplements as treatments and/or preventive strategies for GDM.

The Association Between Nutrition and Risk of Developing GDM

A substantial body of evidence suggests an association between diet and GDM. Excess calorie consumption is the strongest determinant of overweight and obesity, and the risk of GDM is known to increase progressively with maternal body mass index (BMI) and degree of body fat (adiposity) [14]. A meta-analysis of the relationship between maternal obesity and GDM reported the risk of GDM as approximately two, four, and eight times greater in overweight, obese, and severely obese women, respectively [15]. Excessive gestational weight gain—especially in early pregnancy (up to 18-week gestation)—is also considered a risk factor for GDM, regardless of pre-pregnancy BMI [10].

Independently of BMI, a number of dietary patterns have been identified that confer increased or decreased risk of GDM. Overall, the evidence suggests that excess saturated and trans fats, simple sugars, and red and processed meat consumption are risk factors for GDM [16, 17]. These dietary patterns are associated with dysregulation of insulin signaling, inflammation, and/or endothelial dysfunction—all pathogenic factors in GDM [18, 19]. Interestingly, high protein intake (~ 16–20% of energy) is also emerging as a risk factor for GDM [20, 21]. It is uncertain why this relationship exists, although the role of amino acids as substrates for hepatic glucose production [22], and in hepatic lipotoxicity [23], may be contributing factors. Conversely, diets high in fruits, vegetables, and fish are associated with a reduced risk for GDM—likely due to their high fiber, micronutrient, and anti-inflammatory *n*-3 polyunsaturated fat content [24–27].

A number of micronutrients have also been associated with GDM. Decreased gestational plasma concentrations of vitamin C [28], vitamin D [29], vitamin E [30], vitamin B1 [31], vitamin B12 [32], selenium, and zinc [33] have been associated with GDM, although results across studies are conflicting. Vitamin D deficiency is arguably the micronutrient insufficiency most consistently associated with GDM. However, confounding variables, including ethnicity, sun exposure, and seasonality, can be difficult to control for, and as such, the independent relationship between vitamin D status and GDM remains uncertain [34]. High intake of heme iron and increased plasma ferritin have consistently been associated with increased risk of GDM and T2DM [35–38]. However, two randomized controlled trials of iron supplementation found no association with GDM, suggesting that some other factors, such as red meat consumption, may be responsible [39, 40].

Interactions and relationships between micronutrients may be as, or more, important than the contribution of individual micronutrients to the development of GDM. For example, supplementation with folic acid—part of the B vitamin complex—has been consistently linked with increased risk of GDM, despite it being recommended in pregnancy to prevent fetal neural tube defects [41]. This observation is almost always coupled with vitamin B12 deficiency, suggesting that the *combination* of high folate concentration and B12 deficiency contributes to insulin resistance [42, 43]. A recent prospective cohort study of 3607 Australian women over 12 years found no relationships between inadequate intake of individual micronutrients and risk of developing GDM, but that women in the highest quartile of micronutrient adequacy overall had a 39% reduced risk of developing GDM [44]. This

suggests that total nutrition, rather than individual micronutrient sufficiency, is most protective against GDM.

Nutritional Supplements to Treat GDM

Due to the many concerns surrounding the safety and effectiveness of currently available treatments, and the lack of preventative strategies, there is a growing interest for novel GDM therapies and preventative approaches. Nutritional supplements are an exciting avenue for this. The fact that nutrition plays a major role in the risk of GDM suggests that nutritional supplements could be a safe, affordable, and effective strategy for combating GDM. The available evidence for the use of nutritional supplements for the treatment of GDM are discussed below and summarized in Table 1.

Inositol for Treatment of GDM

Inositol is a simple carbohydrate that naturally occurs in a variety of foods, including fruits, nuts, and cereals. Nine stereoisomers of inositol exist, of which myo-inositol (MI) is the most common. Originally believed to be an essential vitamin (vitamin B8), MI was subsequently discovered to be sufficiently produced within the body from D-glucose. MI forms the structural basis of a number of signaling and secondary messengers in eukaryotic cells. These include phosphatidylinositol (PI) and its various phosphates, as well as the phosphatidyl phosphate lipids (PIP2/PIP3), which feature downstream of the insulin receptor in the insulin signaling pathway [67]. By this mechanism, MI can improve insulin sensitivity. Insulin resistance in T2DM, polycystic ovary syndrome (PCOS), and GDM is associated with excess excretion of inositol in urine [68–70]. There is also an association between dysregulation of the inositol pathway in pregnancy and folate-resistant neural tube defects, which represent approximately 30% of all neural tube defects [71].

A small number of studies have examined the effects of MI supplementation utilizing experimental animal models of GDM. However, the majority have focused on preventing neural tube defects and diabetes-induced fetal malformations. For example, Khandelwal et al. (1998) divided pregnant Sprague Dawley rats into three groups: no intervention, streptozotocin (STZ injected at day 6 of pregnancy: a method for inducing GDM by irreversibly destroying the β cells of the pancreas), and STZ + 0.5 mg/mL/day MI. Not only did MI partially protect STZ rats against fetal neural tube defects, it also significantly reduced maternal fasting glucose concentrations [45]. One recent study treated two mouse models—a model of obesity before and during pregnancy and a model of metabolic syndrome before and during pregnancy—with two inositol isomers: MI and D-chiro-inositol (at 7.2/0.18 mg/mL, respectively). Obesity was induced with 4-week feeding of a high fat diet (HFD) prior to pregnancy, while metabolic syndrome was induced by a combination of 4-week HFD prior to pregnancy and genetic KO of endothelial nitric oxide synthase ($eNOS^{-/-}$). As eNOS promotes vasodilation, $eNOS^{-/-}$ primarily causes hypertension, but it also results in glucose intolerance. This study reported that inositol supplementation reduced gestational weight gain in the obese model and improved glucose tolerance, blood pressure, and hyperleptinemia in the metabolic syndrome model [46]. Outside of pregnancy, MI has been associated with decreased fat deposition, but no improvement in glycemia or insulin resistance, in HFD-induced rodent models of type 2 diabetes [72].

Only one RCT has examined the effectiveness of MI as a treatment for GDM. This trial randomized 84 women with GDM onto 8 weeks of treatment with either 4 g MI plus 400 μg folic acid or 400 μg of folic acid alone. Three women in the MI group and nine in the control group were excluded because they required insulin treatment, resulting in a final number of 69 participants. In this trial, MI was associated with significantly decreased fasting glucose (− 0.9 vs. − 0.3 mmol/L; $p < 0.05$), insulin (− 12.2 vs. − 7.9 μIU/mL, $p < 0.05$), HOMA-IR (a measure of insulin resistance; − 3.4 vs. − 2.1; $p < 0.05$), and increased adiponectin (+ 3.3 vs. − 0.9 μg/mL; $p < 0.05$), but no difference in gestational weight gain, after 8 weeks of treatment. A weakness of this trial was that it was not blinded and only involved Caucasian women [47].

Vitamin Supplementation for Treatment of GDM

The critical importance of micronutrient balance in healthy pregnancy is illustrated by the drastic consequences of folic acid (vitamin B9) deficiency. Low concentrations of folic acid during pregnancy are believed to be the cause of over half of all neural tube defects [73]. A recent study similarly uncovered a causal relationship between vitamin B3 deficiency and congenital malformations [74]. There is now evidence that culturing bovine embryos in B vitamins epigenetically alters the expression of metabolic and developmental genes [75]. This suggests that supplementation of beneficial micronutrients around the time of conception can have powerful, potentially long-lasting developmental effects. These observations, combined with the evidence that certain dietary deficiencies are associated with GDM, suggest that vitamin supplementation could help to prevent or treat GDM. However, very few studies on the effects of vitamin supplementation on GDM have been conducted.

Vitamin D is the most studied vitamin supplement in GDM. Not only is it the deficiency most frequently associated with GDM, but there is evidence that vitamin D directly stimulates insulin release from β cells [76]. Asemi et al. conducted a randomized double-blind placebo-controlled study of

Table 1 Summary of studies of nutritional supplements to treat gestational diabetes mellitus (GDM)

	Type of study	Dose	Treatment duration	Participants	Primary outcome	Relevant effects of supplement of interest	Citations
Inositol	Animal (rat)	0.5 mg/mL/day	Day 0–12 gestation	Control ($n = 14$) STZ at GD6 ($n = 24$) STZ + inositol ($n = 27$)	Fetal neural tube defects	Significantly reduced in maternal fasting blood glucose	Khandelwal, 1998 [45]
	Animal (mice)	7.2 mg/mL MI 0.18 mg/mL D-chiro-inositol	Entirety of pregnancy	Obese mice/placebo ($n = 6$) Obese mice/inositol ($n = 8$) Metabolic syndrome/placebo ($n = 8$) Metabolic syndrome/inositol ($n = 9$)	Blood pressure, glucose tolerance, serum metabolic markers, maternal, fetal, placental weights	Significantly reduced gestational weight gain in obese model Improved glucose tolerance, blood pressure, and hyperleptinemia in metabolic syndrome model	Ferrari, 2016 [46]
	Human open-label RCT	4 g/day MI	Daily from diagnosis for 8 weeks	Italy Folic acid alone ($n = 45$) Folic acid + MI ($n = 24$)	HOMA-IR	Significantly reduced fasting glucose, insulin, HOMA-IR, increased adiponectin	Corrado, 2011 [47]
Vitamin D	Human RCT (double-blind, placebo-controlled)	50,000 IU	Twice during pregnancy (upon GDM diagnosis and 21 days later)	Iran Placebo ($n = 27$) Vitamin D ($n = 27$)	Fasting blood measures	Significantly reduced fasting plasma glucose, insulin, HOMA-IR, plasma LDL cholesterol	Asemi, 2013 [48]
	Human RCT (double-blind, placebo-controlled)	200 IU (low dose) 2000 IU (medium dose) 4000 IU (high dose)	Daily from diagnosis to delivery	China Placebo ($n = 20$) low ($n = 38$) medium ($n = 38$) high ($n = 37$)	Fasting blood measures	Significantly reduced insulin, HOMA-IR, total cholesterol in medium and high group compared with placebo.	Zhang, 2016 [49]
Vitamin B6	Human single-arm intervention	100 mg/day	Daily from diagnosis for 14 days	Netherlands $n = 14$	Oral glucose tolerance	Significantly improved oral glucose tolerance (only 2 patients still had impaired glucose tolerance to justify a GDM diagnosis)	Bennink, 1975 [50]
	Human single-arm intervention	100 mg/day	Daily from diagnosis for 14 days	USA $n = 13$	Oral glucose tolerance	Significantly improved oral glucose tolerance, no change in plasma insulin	Spellacy, 1977 [51]
	Human single-arm intervention	100 mg/day	Daily from diagnosis for 14 days	USA $n = 4$	Oral glucose tolerance	No beneficial effects on glucose tolerance	Perkins, 1977 [52]
Magnesium	Human RCT (double-blind, placebo-controlled)	250 mg/day	Daily from diagnosis for 6 weeks	Iran Placebo ($n = 35$) Magnesium oxide ($n = 35$)	Fasting blood measures	Significantly reduced fasting plasma glucose, serum insulin, HOMA-IR, triglycerides, reduced newborn hyperbilirubinemia and hospitalization	Asemi, 2015a [53]

Table 1 (continued)

	Type of study	Dose	Treatment duration	Participants	Primary outcome	Relevant effects of supplement of interest	Citations
Selenium	Human RCT (double-blind, placebo-controlled)	200 μg/day	Daily from diagnosis for 6 weeks	Iran Placebo ($n = 35$) Selenium ($n = 35$)	Fasting blood measures	Significantly decreased fasting glucose, insulin, C-reactive protein, biomarkers of oxidative stress	Asemi, 2015b [54]
	Human RCT	60 μg	Daily from first antenatal visit until delivery	China Placebo ($n = 107$) Selenium ($n = 104$)	Hypertensive conditions in pregnancy	No effect on adiponectin—fasting insulin not measured	Mao, 2016 [55]
Zinc	Human RCT (double-blind, placebo-controlled)	233 mg	Daily from diagnosis for 6 weeks	Iran Placebo ($n = 25$) Zinc ($n = 25$)	Biomarkers of inflammation, oxidative stress, and pregnancy outcomes	Significantly reduced C-reactive protein, increased total antioxidant capacity, no effect on pregnancy outcomes	Karamali, 2016 [56]
	Human RCT (double-blind, placebo-controlled)	30 mg	Daily from diagnosis for 8 weeks	Iran Placebo ($n = 22$) Zinc ($n = 22$)	Fasting blood measures	No effects on fasting blood sugar, insulin, or HOMA-IR	Roshanravan, 2015 [57]
Fiber	Human three-arm intervention study	3 groups: < 20 g 40–60 g 70–80 g	Daily from diagnosis until delivery	USA < 20 g 40–60 g 70–80 g	Fasting and postprandial blood glucose	No effects on mean blood glucose or postprandial glucose	Reece, 1993 [58]
Fatty acids	Animal (rat)	47.2 mg/g n-6, n-3, and 40.2 mg/g monounsaturated fatty acids, integrated into diet	15 days before mating and throughout pregnancy	France Control ($n = 5$) STZ ($n = 8$) Fatty acids ($n = 5$) STZ + fatty acids ($n = 7$)	Total antioxidant status	Significantly improved hyperlipidemia and restored antioxidant status	Yessoufou, 2006 [59]
	Human RCT (double-blind, placebo-controlled)	1000 mg omega-3 fatty acids	Daily from diagnosis for 6 weeks	Iran Placebo ($n = 27$) Omega-3 ($n = 27$)	Inflammatory, oxidative stress markers, and pregnancy outcomes	Significantly improved C-reactive protein, malondialdehyde, newborn hyperbilirubinemia, newborn hospitalization	Jamilian, 2016 [60]
	Human RCT (double-blind, placebo-controlled)	1000 mg omega-3 fatty acids	Twice daily for 6 weeks	Iran Placebo ($n = 35$) Vitamin D only ($n = 35$) Omega-3 only ($n = 35$) Vitamin D + omega 3 ($n = 35$)	Fasting blood measures	Significantly improved fasting glucose, insulin, HOMA-IR, triglycerides, VLDL in combination group compared with all other groups.	Jamilian, 2017 [61]
	Human RCT (double-blind, placebo-controlled)	1000 mg omega-3 fatty acids	Daily from diagnosis for 6 weeks	Iran Placebo ($n = 28$) Omega-3 ($n = 28$)	Fasting blood measures	Significantly improved insulin and HOMA-IR, no effect on glucose, HOMA-B, QUICKI, lipid profile.	Samimi, 2015 [62]

Table 1 (continued)

	Type of study	Dose	Treatment duration	Participants	Primary outcome	Relevant effects of supplement of interest	Citations
Probiotics	Human RCT (double-blind, placebo-controlled)	*Lactobacillus acidophilus* LA-5, *Bifidobacterium* BB-12, *Streptococcus thermophilus* STY-31, and *Lactobacillus delbrueckii bulgaricus* LBY-27 (4×10^9 CFU/g)	Daily from diagnosis for 8 weeks	Iran Placebo ($n = 27$) Probiotic ($n = 29$)	Gestational weight change	Significantly reduced gestational weight gain, fasting blood sugar, HOMA-IR	Dolatkhah, 2015 [63]
	Human RCT (double-blind, placebo-controlled)	*Lactobacillus acidophilus* (2×10^9 CFU/g), *L. casei* (2×10^9 CFU/g), and *Bifidobacterium bifidum* (2×10^9 CFU/g)	Daily from diagnosis for 6 weeks	Iran Placebo ($n = 30$) Probiotic ($n = 30$)	Lipid profile	Significantly improved fasting blood glucose, insulin, HOMA-IR, VLDL-cholesterol and triglycerides	Karamali, 2016 [64]
	Human RCT (double-blind, placebo-controlled)	*Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, and *Lactobacillus delbrueckii* subsp. *Bulgaricus* (112.5×10^9 CFU)	Daily from diagnosis for 8 weeks	Iran Placebo ($n = 41$) Probiotic ($n = 41$)	Inflammatory markers	Significantly improved triglyceride, IL-6, TNFα, c-reactive protein. No differences in fasting blood glucose, HBA1c, HOMA-IR (except when comparing change), or insulin.	Jafarnejad, 2016 [65]
	Human RCT (double-blind, placebo-controlled)	*Lactobacillus salivarius* UCC118 (10^9 CFU)	Daily from diagnosis for 4–6 weeks	Ireland Placebo ($n = 75$) Probiotic ($n = 74$)	Fasting blood glucose	No impact on glycemic control, attenuation of normal pregnancy-induced rise in total and LDL cholesterol	Lindsay, 2015 [66]

GDM gestational diabetes, *STZ* streptozotocin, *RCT* randomized controlled trial, *MI* myo-insotiol, *IU* international units, *CFU* colony-forming units

women with GDM who did not require insulin therapy. Half ($n = 27$) received 50,000 IU vitamin D twice during pregnancy (upon GDM diagnosis and 21 days later), while the remaining women received a placebo. Six-week vitamin D supplementation was associated with a significant decrease in fasting glucose (-17.1 ± 14.8 vs. -0.9 ± 16.6 mg/dL; $p < 0.001$), insulin (-3.08 ± 6.62 vs. $+1.34 \pm 6.51$ μIU/mL; $p = 0.01$), HOMA-IR (-1.28 ± 1.41 vs. $+0.34 \pm 1.79$; $p < 0.001$), and plasma LDL cholesterol (-10.8 ± 22.4 vs. $+10.4 \pm 28.0$ mg/dL; $p = 0.003$) [48]. Another, more recent trial randomized women diagnosed with GDM to a placebo, or either 200 IU, 2000 IU, or 4000 IU vitamin D daily. Insulin, HOMA-IR, and total cholesterol were all significantly reduced in the highest-dose group (4000 IU) [49]. The most recent meta-analysis on the topic, which included six studies encompassing 187 subjects and 184 controls, concluded that vitamin D supplementation improves insulin resistance scores (e.g., HOMA-IR: standardized mean difference (SMD) −0.66; 95% confidence interval (CI), −1.14 to −0.18) and LDL-cholesterol concentrations (SMD −0.33; 95% CI, −0.58 to −0.07), but does not affect fasting glycemia or total triglyceride or cholesterol concentrations [77]. The implications of these results for the mother and baby remain unclear.

Vitamin B6 has also been investigated as a treatment for GDM, although only in a few small studies that date back to the 1970s. In a study of 14 women with GDM in the Netherlands, over 90% were found to be deficient in vitamin B6. All patients were treated with 100 mg/day vitamin B6, and after 14 consecutive days, the deficiency disappeared and glucose tolerance improved (−4.8 mmol/L in mean total of all glucose values across glucose tolerance test; $p < 0.01$) [50]. The study was repeated in the USA, and the same effects were reported [51]. However, another attempt to replicate these findings reported no effect of vitamin B6 on gestational glucose intolerance and suggested that the benefits seen in the previous studies were due to confounding lifestyle changes [52]. Vitamin B6 has not been further investigated in GDM. Furthermore, despite the aforementioned relationship between GDM and vitamin deficiencies, there appear to be no other published studies of vitamin supplementation in GDM, either in animal models or humans.

Minerals for Treatment of GDM

Very few minerals have been tested as potential treatments for GDM. Magnesium—an essential mineral required for nerve transmission, body temperature regulation, and protein and nucleic acid synthesis—supplemented at 250 mg/day for 6 weeks among women with GDM ($n = 35$ subjects and $n = 35$ controls) was demonstrated to exert beneficial effects on fasting plasma glucose (-9.7 ± 10.1 vs. $+1.8 \pm 8.1$ mg/dL, $p < 0.001$), serum insulin (-2.1 ± 6.5 vs. $+5.7 \pm 10.7$ μIU/mL, $p = 0.001$), HOMA-IR (-0.5 ± 1.3 vs. $+1.4 \pm 2.3$, $p < 0.001$), triglycerides ($+2.1 \pm 63.0$ vs. $+38.9 \pm 37.5$ mg/dL, $p = 0.005$), newborn hyperbilirubinemia (8.8% vs. 29.4%, $p = 0.03$), and newborn hospitalization (5.9% vs. 26.5%, $p = 0.02$) in a 2015 double-blind placebo-controlled RCT [53]. These effects may be mediated by the ability of magnesium to indirectly stimulate insulin secretion (through acetyl-CoA and calcium-dependent channels [78]), suppress postprandial hyperlipidemia [79], and possess anti-inflammatory properties [80].

Selenium has also been investigated as a potential treatment for GDM. A double-blind placebo-controlled RCT of women with GDM randomly assigned to receive either 200 μg selenium or a placebo for 6 weeks following GDM diagnosis resulted in decreased fasting glucose (-10.5 ± 11.9 versus $+4.5 \pm 12.9$ mg/dL; $p < 0.001$), insulin (-1.98 ± 11.25 versus $+5.26 \pm 9.33$ μIU/mL; $p = 0.005$), C-reactive protein (-791.8 ± 2271.8 versus $+500.5 \pm 2563.3$ ng/mL; $p = 0.02$), and biomarkers of oxidative stress [54]. More modest supplementation (60 μg) had no effect on insulin resistance in pregnant women [55].

At least two double-blinded, placebo-controlled RCTs in Iran have also investigated effects of zinc supplementation on inflammation, oxidative stress, and pregnancy outcomes in GDM. GDM patients who were randomly allocated to receive 233 mg zinc gluconate (containing 30 mg zinc) for 6 weeks had reduced serum high-sensitivity C-reactive protein (hs-CRP) and increased plasma total antioxidant capacity compared with placebo, but there was no effect of the supplement on pregnancy outcomes [56]. Another Iranian clinical trial found no influence of a lower dose oral zinc supplement (30 mg/day zinc gluconate) on fasting glucose, insulin, or HOMA-IR [57].

Fiber for Treatment of GDM

There has been one study of fiber supplementation in GDM, which was published in 1993 [58]. Non-insulin-requiring GDM patients were provided with a high fiber drink in addition to a high fiber diet, and three groups were compared: < 20 g, 40–60 g, and 70–80 g fiber per day. However, no differences were observed in mean blood glucose or postprandial glucose, suggesting that fiber supplementation does not improve GDM. However, additional studies would be beneficial, given the aforementioned evidence that high fiber diets are protective against GDM.

Fatty Acids for Treatment of GDM

Due to the inverse association between oily fish consumption and GDM, there has been some investigation into whether omega-3 fatty acid supplementation can improve GDM. In rats injected with mild doses of STZ during pregnancy, omega-3 fatty acids reduce hyperlipidemia and fetal macrosomia

[59, 81, 82]. A double-blind, placebo-controlled RCT of women with GDM randomly assigned to either 1000 mg omega-3 fatty acid supplements or placebo for 6 weeks found beneficial effects on maternal serum hs-CRP (−245.1 ± 1570.5 vs. +913.9 ± 2329.4 ng/mL, $p = 0.03$), malondialdehyde (−0.4 ± 1.3 vs. +0.6 ± 2.3, $p = 0.04$), incidence of newborn's hyperbilirubemia (7.7% vs. 33.3%, $p = 0.02$), and newborn hospitalization (7.7% vs. 33.3%, $p = 0.02$) [60]. Another study examined vitamin D (50,000 IU) and omega-3 fatty acid (1000 mg) supplementation taken twice daily both together and separately on glucose metabolism and lipid concentrations in GDM patients [61]. After 6 weeks of intervention, the combination of vitamin D and omega-3 fatty acids compared with vitamin D, omega-3 fatty acids, and placebo had decreased fasting plasma glucose (−7.3 ± 7.8, −6.9 ± 6.6, −4.0 ± 2.5, and +1.0 ± 11.4 mg/dL, respectively, $p < 0.001$), serum insulin (−1.9 ± 1.9, −1.3 ± 6.3, −0.4 ± 6.3, and +2.6 ± 6.5 μIU/mL, respectively, $p = 0.005$), HOMA-IR (−0.7 ± 0.6, −0.5 ± 1.4, −0.2 ± 1.5, and +0.6 ± 1.5, respectively, $p < 0.001$), serum triglycerides (−8.2 ± 41.0, +7.6 ± 31.5, +3.6 ± 29.9, and +20.1 ± 29.6 mg/dL, respectively, $p = 0.006$) compared with both control and the individual groups (vitamin D or omega-3 alone). In contrast, another study of women with GDM randomly assigned to either 1000 mg omega-3 fatty acids or placebo saw only beneficial effects on insulin resistance and no effects on plasma glucose or lipid profiles [62]. The available evidence is limited by the small number of studies, number of participants per study, and high variability within study populations, and further investigation is warranted. However, one of the emerging concerns with omega-3 fatty acids is that oxidization may result in high rates of neonatal morbidity and mortality in rats and that many commercially available options are inadvertently oxidized [83, 84]. Therefore, the use of omega-3 supplements during pregnancy remains contentious.

Probiotics for Treatment of GDM

Modifying the gut microbiome has become a popular new area of research in many medical disciplines, including type 1 and type 2 diabetes [85, 86]. Probiotic supplementation involves ingesting capsules of "live microorganisms that confer a health benefit on the host" [87]. Although it is uncertain exactly how probiotics might exert beneficial effects on glucose metabolism, there are several proposed mechanisms. Short-chain fatty acids (SCFAs) are a by-product of bacterial fermentation of fiber in the gut. SCFAs can be used as an energy source for intestinal cells and may impact the expression of appetite regulation hormones, such as leptin, ghrelin, and glucagon-like peptide-1 (GLP-1) [88]. GLP-1 both slows intestinal transit time and increases insulin sensitivity [89]. SCFAs may also decrease gut permeability by upregulating expression of tight junction proteins such as zonula occludens-1 (ZO-1) in the gut lining [88]. While few trials have yet been published examining the impact of probiotic supplementation on GDM, there have been some promising initial results.

The majority of RCTs examining the treatment effects of probiotic supplementation in women with GDM have been conducted in Iran, with each utilizing a different formulation of microbes and examining slightly different outcomes in addition to glycemia (gestational weight change [63], lipid profile [64], and inflammation [65]). In two of these trials [63, 64], fasting glycemia (−15.3 ± 1.8 vs. −7.3 ± 3.0 mg/dL, $p < 0.05$; −9.2 ± 9.2 mg/dL vs. +1.1 ± 12.2 mg/dL, $p < 0.001$), and insulin resistance (HOMA-IR; −0.40 ± 0.13 vs. 0.01 ± 0.12, $p < 0.05$; −0.4 ± 0.9 vs. +1.1 ± 2.5, $p < 0.01$) were significantly reduced in the probiotic group. Whereas in the third [65], fasting glycemia and HOMA-IR were not significantly changed by probiotic treatment, but the difference in change in HOMA-IR between the probiotic and placebo group was significant (3.7 ± 1.5, $p < 0.05$). Further, probiotics reduced gestational weight gain [63], serum VLDL-cholesterol and triglyceride concentrations [64], and serum triglyceride, IL-6, TNFα, and hs-CRP concentrations [65]. A recent study which randomized women with GDM to probiotics (*Bifidobacterium bifidum* and *Lactobacillus acidophilus*, 10^9 colony-forming units (CFU) per day) or placebo for four consecutive weeks also reported significant improvement in glucose metabolism in the probiotic group, including fasting glucose, insulin, and HOMA-IR [90]. However, an RCT in Ireland that assigned 149 women with GDM to either probiotic (*Lactobacillus salivarius*, 10^9 CFU per day) or placebo found no significant differences between the groups with the exception of total cholesterol [66]. So far, there is no evidence to suggest that probiotic intervention affects pregnancy outcomes, such as cesarean delivery, pre-eclampsia, or macrosomia [91]. Furthermore, a systematic review of the evidence involving women with GDM found no effect of probiotic supplementation on fasting blood glucose (mean difference −0.13; 95% CI −0.32, 0.06, $p = 0.18$) or LDL-cholesterol (−0.16; 95% CI −0.45, 0.13, $p = 0.067$) [88]. However, HOMA-IR was significantly reduced (−0.69; 95% CI −1.24, −0.14, $p = 0.01$), which appeared to be associated mainly with the genus *Bifidobacterium* [88]. The analysis concluded that larger, longer duration trials, across different strains of probiotics, needed to be performed.

Nutritional Supplements to Prevent GDM

While treatment is important, prevention of GDM is more desirable. The available evidence for the use of nutritional supplements for prevention of GDM are discussed below and summarized in Table 2.

Table 2 Summary of studies of nutritional supplements to prevent gestational diabetes mellitus (GDM)

	Type of study	Dose	Treatment duration	Participants	Primary outcome	Relevant effects of supplement of interest	Citations
Inositol	Human open-label RCT	4 g/day MI	End of first trimester until delivery	Italy Pregnant outpatients with a parent with type 2 diabetes Folic acid alone ($n = 110$) Folic acid + MI ($n = 110$)	Incidence of GDM	GDM rate significantly reduced, significantly reduced fetal macrosomia/mean fetal weight.	D'Anna [92]
	Human retrospective observational	4 g/day MI	Before and throughout pregnancy	Italy Women taking MI for PCOS who did not stop taking it when pregnant ($n = 54$) compared with women taking metformin for PCOS who did stop taking it upon pregnancy ($n = 44$)	Incidence of GDM	GDM rate significantly reduced	D'Anna [93]
	Human RCT (double-blind, placebo-controlled)	4 g/day MI	From diagnosis of first trimester hyperglycemia (≥ 5.1 mmol/L and ≤ 7.0 mmol/L) to delivery	Italy Folic acid alone ($n = 39$) MI + folic acid ($n = 36$)	Incidence of GDM	GDM significantly reduced, less insulin therapy required, later delivery, smaller babies with fewer episodes of neonatal hypoglycemia	Matarrelli [94]
	Human open-label RCT	4 g/day MI	Daily from first trimester to delivery	Italy Overweight Folic acid alone ($n = 110$) MI + folic acid ($n = 110$)	Incidence of GDM	GDM rate significantly reduced	Santamaria [95]
	Human open-label RCT	4 g/day MI	Daily from first trimester to delivery	Italy Obese Folic acid alone ($n = 101$) MI + folic acid ($n = 101$)	Incidence of GDM	GDM rate significantly reduced	D'Anna [96]
	Human open-label RCT	1100 mg MI 27.6 mg D-chiro-inositol	Daily from first trimester to delivery	Ireland Family history of type 2 diabetes Folic acid alone ($n = 120$) Insoitols + folic acid ($n = 120$)	Incidence of GDM	Non-significant increase in GDM rate, significantly increased neonatal hypoglycemia	Farren [97]
Vitamin D	Human RCT (double-blind, placebo-controlled)	5000 IU	Daily from first antenatal visit until week 26 pregnancy	Placebo ($n = 44$) Vitamin D ($n = 46$)	Incidence of GDM	GDM rate significantly reduced	Shahgheibi [98]
	Human RCT (double-blind, placebo-controlled)	2 groups: 5000 IU 400 IU	Daily from < 20-week gestation until delivery	Australia Women with vitamin D deficiency Low-dose vitamin D ($n = 90$)	Oral glucose tolerance test results	No effect on oral glucose tolerance	Yap [99]

Table 2 (continued)

	Type of study	Dose	Treatment duration	Participants	Primary outcome	Relevant effects of supplement of interest	Citations
				High-dose vitamin D ($n = 90$)			
	Human RCT	Dependent on vitamin D status: Sufficient vitamin D = 1 × dose of 60,000 IU at 20 weeks Insufficient vitamin D = 2 × doses of 120,000 at 20 and 24 weeks Deficient vitamin D = 4 × 120,000 at 20, 24, 28, 32 weeks	20 weeks to delivery	India Pregnant women with vitamin D deficiency No supplementation ($n = 60$) Vitamin D ($n = 120$)	Incidence of pregnancy complications	No effect on incidence of GDM	Sablok [100]
Magnesium	Human RCT	300 mg/day	Daily from 12 to 14 weeks gestation until delivery	Iran Pregnant women with no Mg deficiency ($n = 60$) Pregnant women with Mg deficiency given multimineral tablet ($n = 60$). Pregnant women with Mg deficiency given magnesium ($n = 60$)	Incidence of pregnancy complications	Significantly reduced incidence of GDM	Zarean [101]
Probiotics	Human RCT (double-blind, placebo-controlled)	*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12 (10^{10} CFU/day)	Daily from first trimester until end of exclusive breastfeeding	Finland Control + placebo ($n = 85$) Diet intervention + placebo ($n = 86$) Diet intervention + probiotics ($n = 85$)	Pregnancy outcomes and fetal growth	Significantly reduced incidence of GDM, no differences in fetal growth.	Luoto [102]
	Human RCT (double-blind, placebo-controlled)	*Lactobacillus rhamnosus HN001* (6×10^9 CFU/day)	14–16 weeks gestation until 6 months post birth	New Zealand Pregnant women with history of atopic disease Placebo ($n = 211$) Probiotic ($n = 212$)	Incidence of GDM	Significantly reduced incidence of GDM	Wickens [103]

GDM gestational diabetes, *STZ* streptozotocin, *RCT* randomized controlled trial, *MI* myo-insotiol, *IU* international units, *CFU* colony-forming units

Inositol for Prevention of GDM

Several studies have investigated the preventative effects of MI in women at risk of GDM. A 2013 RCT compared a daily dose of 4 g MI plus 400 μg folic acid ($n = 110$) with 400 μg folic acid alone ($n = 100$), taken from 12 to 13-week gestation until the end of pregnancy in non-obese pregnant women with a family history of T2DM. Incidence of GDM was 6% in the MI group compared with 15.3% in the control group. This was coupled with a significant decrease in mean fetal weight at delivery [92]. One retrospective observational study reported that the risk of GDM was more than halved (17.4% (8/46) vs. 54% (20/37)) if women taking MI to treat PCOS did not stop taking it during pregnancy, compared with those who took metformin for PCOS and stopped upon falling pregnant [93]. A double-blind trial of 75 pregnant women with first trimester hyperglycemia (≥ 5.1 mmol/L and ≤ 7.0 mmol/L) reported reduced incidence of GDM (6% (2/35) vs. 71% (27/38); RR 0.127; 95% CI 0.032–0.502; $p = 0.001$). In those women who did develop GDM, MI was associated with reduced need for insulin therapy (3% (1/35) vs. 21% (8/38); RR 0.136; 95% CI 0.018–1.031, $p = 0.05$), smaller babies (42.8 ± 20.4 vs. 56.6 ± 25.9th percentile; $p = 0.001$), and fewer episodes of neonatal hypoglycemia (0% vs. 26%; RR = 0.052, 95% CI 0.003–0.849; $p = 0.038$) [94]. MI has also been effective at preventing GDM in overweight and obese women. Daily supplementation of 4 g MI plus 400 μg folic acid from the first trimester until delivery significantly reduced incidence of GDM in overweight (11.6% vs. 27.4%) and obese (14% vs. 33.6%) women in two open-label RCTs [95, 96]. However, it should be noted that all of the aforementioned studies were undertaken by the same research group across a relatively homogeneous population. A recent open-label RCT in Ireland found no protective effect of combined MI and D-chiro-inositol. In this trial, 240 women with a family history of T2DM (120 per group) received either 1100 mg myo-inositol, 27.6 mg D-chiro-inositol and 400 μg folic acid, or 400 μg of folic acid only starting from their first antenatal visit. The authors reported a non-significant increase in GDM in the intervention group (23% vs. 18%), and this was associated with a significantly increased rate of neonatal hypoglycemia [97]. However, it is uncertain whether the observed neonatal hypoglycemia was a result of the intervention or of the increased rate of GDM in the intervention group. Furthermore, the dose of MI in this study was significantly lower than in other reported trials (1100 mg vs. 4000 mg), which may have been responsible for the lack of observed effects.

A recent systematic review and meta-analysis of the effects of MI in the prevention of GDM concluded that there is evidence for a benefit, but that the current studies are too small and homogenous and are not powered sufficiently to detect differences in perinatal outcomes [104]. The promise of early evidence suggests that larger studies, in a variety of populations, are required.

Vitamins for Prevention of GDM

Some studies have investigated the efficacy of vitamin D supplementation to prevent GDM. A randomized controlled trial of women with vitamin D deficiency (plasma 25-hydroxyvitamin D concentration < 32 ng/mL), supplemented with either a high dose (5000 IU) or low dose (400 IU) of vitamin D daily (90 per group beginning at < 20-week gestation), saw little effect of a higher dose on glycemia. However, they noted the dose was well tolerated and beneficial for preventing neonatal vitamin D deficiency [99]. A later randomized placebo-controlled trial gave a weekly dose of 5000 IU vitamin D to women at risk of GDM (history of GDM, birth macrosomia, BMI > 25) and noted a significant reduction in incidence of GDM (11.4% vs. 34.8%) [98]. Sablok et al. measured vitamin D concentrations during early pregnancy and administered vitamin D depending on the woman's level of deficiency (where sufficient vitamin D was defined as > 50 nmol/L, insufficient 25–50 nmol/L, and deficient < 25 nmol/L): women in sufficient category received 1 × 60,000 IU at 20 weeks, insufficient category received 2 × 120,000 IU at 20 and 24 weeks, and deficient category received 4 × 120,000 IU at 20, 24, 28, and 32 weeks [100]. They reported several maternal and neonatal outcomes, including GDM. The number of cases of GDM in both the control and intervention groups was very low (1.8% vs. 0.9%), and the difference was not statistically significant. A recent systemic review graded the quality of the evidence that vitamin D supplementation prevents GDM to be very low and suggested that further large RCTs are required [105]. No other vitamins have been examined with regard to GDM prevention.

Minerals for Prevention of GDM

Only one study has examined the effect of mineral supplementation to prevent GDM. In this RCT, women were split into two groups depending on their serum magnesium levels (insufficient < 1.9 mg/dL). The sufficient group (group A) received a standard multimineral tablet containing 100 mg magnesium per day. The insufficient group was further split into two groups, where one received the 100 mg multimineral tablet (group B) and the other received the same tablet plus an additional 200 mg/magnesium supplement (group C) for a total of 300 mg/day during pregnancy (starting at 12–14-week gestation and continuing until delivery). Group C (8.3% (5/60)) had significantly fewer cases of GDM than group B (21.7% (13/60)) and the same number of cases as group A

(8.3% (5/60)). In other words, 300 mg/day magnesium supplementation in magnesium-insufficient pregnant women reduced risk of GDM to the same extent as magnesium-sufficient pregnant women [101]. To our knowledge, no other studies of minerals to prevent GDM have been conducted.

Fiber for Prevention of GDM

No studies yet exist examining the ability of fiber to prevent GDM. Again, high-quality RCTs of fiber supplementation would be beneficial, given the available evidence that high-fiber diets are associated with reduced risk of GDM.

Fatty Acids for Prevention of GDM

A meta-analysis encompassing 328 from two RCTs of omega-3 fish oil in healthy pregnant women found no beneficial effect on risk of GDM (RR = 0.73; 95% CI 0.22, 2.37) [106].

Probiotics for Prevention of GDM

A small number of RCTs have examined the ability of probiotic supplementation to prevent GDM. The Finnish "Probiotics and Pregnancy Outcome Study" randomized women with no diagnosis of any chronic disease in their first trimester to both dietary intervention and probiotic supplementation (*Lactobacillus rhamnosus* and *Bifidobacterium lactis*, 10^{10} CFU per day), dietary intervention only, or placebo. The rate of GDM was significantly lower in the probiotic group—13%—compared with 36% in the diet-only group and 34% in the control group. No differences in fetal growth were observed, and no adverse effects were noted [102]. A double-blind, randomized, placebo-controlled probiotic intervention trial in women with a history of asthma, hayfever, or eczema (primary outcome of the study) in New Zealand was recently published [103]. The authors randomized women to receive either a probiotic (*Lactobacillus rhamnosus,* 6×10^9 CFU per day) or placebo, at 14–16-week gestation until 6 months after birth, and similarly noted that GDM prevalence was significantly lower in the intervention group (2.1% vs. 6.5%). While promising, further trials need to be conducted to determine whether probiotic supplementation should be widely used in early pregnancy to prevent GDM.

Conclusion

While current therapies such as lifestyle intervention, insulin therapy, and oral anti-diabetics can be effective at managing glycemia and reducing fetal growth, they can be difficult to adhere to, and questions remain about drugs safety and benefits in the short and long term. Furthermore, many of these therapies such as insulin cannot be used for prevention, which may be a more successful approach than treatment alone. Nutritional supplements, on the other hand, can be safely used for prevention and are typically easy to administer. While there is some promise in MI, vitamin, mineral, fiber, fatty acid, and probiotic supplementation, there is a need for large, high-quality, RCTs in a variety of populations, in order to strengthen the evidence and ensure the safety of both the mother and child.

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Compliance with Ethical Standards

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