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

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Abstract

Gestational diabetes mellitus (GDM) is defined as hyperglycemia that is diagnosed during pregnancy and is not clearly overt diabetes that existed prior to pregnancy. GDM prevalence has increased in recent decades in parallel with the obesity and type 2 diabetes (T2DM) epidemics, and has major health implications for both the mother and the child – impacting the health of the population as a whole. While a number of treatment and prevention options have been developed, they are not without side-effects, and there remain concerns over long-term effects on the infant. As GDM is associated with diet, dietary supplements are an appealing, potentially safer and better tolerated alternative to pharmaceuticals to prevent and/or treat GDM. This review discusses the available evidence for the efficacy of current treatments and emerging dietary supplements (including inositols, vitamins, minerals, and probiotics) for the prevention and treatment of GDM.

Keywords: gestational diabetes, supplementation, diet, pregnancy

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) has 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 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/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 far from ideal. Management usually includes diet and lifestyle changes, followed by insulin supplementation – which is only of limited effectiveness due to the insulin resistance that is often present [9]. Insulin is also associated with increased gestational weight gain – itself a risk factor for GDM [10] – requires frequent self-injection and blood glucose monitoring, and increases risk of hypoglycemia [11]. Some emerging drugs, including metformin and glyburide, are promising, but long-term effects on the mother and fetus remain poorly understood [12,13]. Furthermore, by the time GDM is diagnosed – typically between 24 and 28 weeks' gestation – the

most effective window for intervention 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 dietary supplementation as a potential prevention and treatment strategy for GDM. Dietary supplements are an exciting avenue because they are typically well-tolerated, safe, and easy-to-administer – including during pregnancy. This review will first summarize the pathophysiology, risk factors, and current non-dietary treatment options for GDM, before discussing the available evidence for dietary supplements as treatments and/or preventive strategies for GDM.

Pathophysiology of GDM

During the course of normal pregnancy, a surge of local and placental hormones (including oestrogen, progesterone, cortisol, leptin, placental growth hormone and placental lactogen) contribute toward a state of mild insulin resistance [14]. As a result, blood glucose is slightly elevated, and glucose is transported across the placenta to the developing fetus. This mild insulin resistance also promotes endogenous glucose production and breakdown of adipose tissue, resulting in a further increase in plasma glucose and free fatty acid (FFA) concentrations [15]. In order to maintain glucose homeostasis, the pancreas of a normal pregnant woman responds to these changes through compensatory mechanisms, which include hypertrophy and hyperplasia of the β cells, as well as increased insulin secretion [16]. Maternal insulin sensitivity returns to pre-pregnancy levels within a few days of delivery, exemplifying the importance of placental hormones to this process [17].

When the normal metabolic adaptations to pregnancy do not adequately occur, this can result in GDM. While the exact mechanisms are poorly understood, the majority of cases (~80%) manifest as a result of β cell dysfunction on a background of chronic insulin resistance, to which the normal insulin resistance of pregnancy is partially additive [18]. In other words, the pancreatic β cells of affected individuals do not adequately expand in size and number to meet the demands of pregnancy, and this is exacerbated by systemic insulin resistance acquired before pregnancy and worsened with the normal insulin resistance of pregnancy. GDM can therefore be the result of failures within the β cells themselves, in mediators of insulin signaling, or both. Predisposition to these defects may be the result of genetics and/or epigenetics, as race/ethnicity (particularly Aboriginal Australian, Middle Eastern, and Pacific Island populations) and a family history of any form of diabetes are risk factors for GDM [19]. In addition, diet and nutrition are important modifying factors, as described below.

The role of diet in 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) [20]. 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 [21]. Excessive gestational weight gain is also considered a risk factor for GDM, regardless of pre-pregnancy BMI [10].

Even 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 [22,23]. These dietary patterns are associated with a dysregulation in of insulin signaling, inflammation, and/or endothelial dysfunction – all pathogenic factors in GDM [24,25]. Interestingly, high protein intake (~16-20% of energy) is also emerging as a risk factor for GDM [26,27]. It is uncertain why this relationship exists, although the role of amino acids as substrates for hepatic glucose production [28], and in hepatic lipotoxicity [29], 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 [30–33].

A number of micronutrients have also been associated with GDM. Decreased gestational plasma concentrations of vitamin C [34], vitamin D [35], vitamin E [36], vitamin B1 [37], vitamin B12 [38], selenium, and zinc [39] 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 [40]. High intake of heme iron and increased plasma ferritin have consistently been associated with increased risk of GDM and T2DM [41–44]. However, two randomized-controlled trials of iron supplementation found no association with GDM, suggesting that some other factor, such as red meat consumption, is responsible [45,46]

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 [47]. 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 [48].

Current non-dietary treatments for GDM

Lifestyle intervention

The first line of treatment for GDM is usually lifestyle intervention – encompassing diet and exercise – combined with self-monitoring of blood glucose [49]. Recommendations generally include a varied diet – sufficient in complex carbohydrates, polyunsaturated fats, and fiber, and low in saturated fats, sugars, and processed foods – accompanied by 30 minutes of medium-intensity exercise per day. Currently it is not recommended that women strenuously exercise during pregnancy, due to concerns that this could contribute to fetal growth restriction in some women [50]. Despite lifestyle intervention being the most commonly prescribed treatment or prevention strategy for GDM, there is limited evidence for its effectiveness. Interventions vary widely across trials, and are often confounded by alternative pharmacological treatments, making it difficult to determine how beneficial lifestyle interventions truly are [51].

Insulin

After lifestyle intervention, the next-line of treatment is typically subcutaneous insulin injection for those women with poorly controlled glucose concentrations [49]. When combined with lifestyle intervention, insulin is effective at managing GDM [52,53]. However, one of the major disadvantages of insulin treatment is that it typically requires self-injection as the use of insulin pumps in the setting of GDM has not been well studied. This requires education from health professionals, strict adherence and planning, and can add anxiety to the sometimes already stressful

time of pregnancy. Insulin therapy is also associated with hypoglycemia and excess gestational weight gain [54]. As detailed above, excess gestational weight gain is itself a risk factor for GDM, and has implications for long-term maternal and child health. Further, insulin is an expensive therapy, and requires refrigeration for safe storage. This limits its availability in many low-income countries with hot climates [55]. Therefore, while insulin is effective, there is a requirement for alternative treatments that are as safe and effective as insulin but easier to adhere to and with fewer side-effects. Moreover, insulin cannot be used as a preventative measure, as the risk of inducing hypoglycemia is too high. Therefore, even if insulin is the most effective treatment for poorly controlled GDM, there is a need for preventative strategies.

Oral anti-diabetic agents

Oral anti-diabetic pharmacologic treatments are less widely used than insulin, but are becoming more common, due to their lower costs, ease of administration, and the emerging evidence of their benefit [56]. Two oral anti-diabetic agents have been tested in pregnancy: glyburide and metformin [57]. Glyburide is a sulphonylurea that enhances insulin secretion. Metformin is a biguanide that improves both fasting and postprandial hyperglycemia through a number of mechanisms, including decreased hepatic gluconeogenesis, delayed glucose absorption in the gastrointestinal tract, increased post-receptor insulin signaling, and improved glucose uptake [58]. Both glyburide and metformin are known to cross the placenta [59,60]. Therefore, medical professionals have been cautious about prescribing their use during pregnancy [61]. The results of a number of randomized control trials (RCTs) generally suggest that glyburide and metformin are at least as effective as insulin in controlling maternal glycemia and improving fetal outcomes [62–65]. However, glyburide has been associated with maternal weight gain, preeclampsia, neonatal jaundice and neonatal hypoglycemia [55,66]. In contrast, metformin has not been associated with

any perinatal complications [67]. Furthermore, combined treatment of insulin and metformin has been shown to result in less gestational weight gain than insulin alone [68]. However, long-term effects of gestational metformin on the children are unknown, and many clinicians remain cautious [55]. On follow-up of the Metformin in Gestational Diabetes (MiG) trial, 2-year-old offspring of mothers treated with metformin (rather than insulin) had no difference in total fat mass or percentage body fat, but larger subscapular and biceps skinfolds and mid-upper arm circumference [69]. The implications of these findings are unclear, but they do suggest that offspring body composition is affected by metformin treatment in pregnancy. Both glyburide and metformin are also associated with side effects including nausea, vomiting, abdominal pain, heartburn, and diarrhea [55]. Further, accumulation of metformin is associated with maternal lactic acidosis, although this is extremely rare (0.03 cases per 1000 patients) [70]. A recent development of note is that metformin use is strongly associated with vitamin B12 deficiency [71,72]. This is a concern because, as previously mentioned, vitamin B12 deficiency is a risk factor for GDM. Intrauterine exposure to maternal vitamin B12 deficiency is also a risk factor for later insulin resistance [48]. Glyburide and metformin may therefore be effective at regulating blood glucose and preventing macrosomia, but there remain concerns for the long-term safety of both the mother and child.

Dietary supplements to prevent and 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 requirement for novel GDM therapies. Dietary supplements are an exciting avenue for this. The fact that nutrition plays a major role in the risk of GDM suggests that dietary supplements could be a safe, affordable, and effective strategy for combating GDM. The available evidence for the use of dietary supplements for the prevention and treatment of GDM are discussed below.

180 *Inositol*

181 Inositol is a simple carbohydrate that naturally occurs in a variety of foods, including fruits, nuts,
182 and cereals. Nine stereoisomers of inositol exist, of which myo-inositol (MI) is the most common.
183 Originally believed to be an essential vitamin (vitamin B8), MI was subsequently discovered to be
184 sufficiently produced within the body from D-glucose. MI forms the structural basis of a number
185 of signaling and secondary messengers in eukaryotic cells. These include phosphatidylinositol (PI)
186 and its various phosphates, as well as the phosphatidyl phosphate lipids (PIP2/PIP3), which feature
187 downstream of the insulin receptor in the insulin signaling pathway [73]. By this mechanism, MI
188 can improve insulin sensitivity. Insulin resistance in T2DM, polycystic ovary syndrome (PCOS)
189 and GDM is associated with excess excretion of inositol in urine [74–76]. There is also an
190 association between dysregulation of the inositol pathway in pregnancy and folate-resistant neural
191 tube defects, which represent approximately 30% of all neural tube defects [77].

192 A small number of studies have examined the effects of MI supplementation utilising experimental
193 animal models of GDM. However, the majority have focused on preventing neural tube defects
194 and diabetes-induced fetal malformations. For example, Khandelwal et al. (1998) divided Sprague
195 Dawley rats into three groups: no intervention, streptozotocin (STZ: a method for inducing GDM
196 by irreversibly destroying the β cells of the pancreas), and STZ + 0.5 mg/mL/day MI. Not only
197 did MI partially protect STZ rats against fetal neural tube defects, it also significantly reduced
198 maternal fasting glucose concentrations [78]. One recent study treated two mouse models – a
199 model of obesity in pregnancy, and a model of metabolic syndrome in pregnancy – with two
200 inositol isomers: MI and D-chiro-inositol. Obesity was induced with 4 weeks feeding of a high fat
201 diet (HFD), while metabolic syndrome was induced by a combination of 4 weeks HFD, and genetic
202 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 [79]. Outside of pregnancy, MI has been associated with decreased fat deposition, but no improvement in glycaemia or insulin resistance, in HFD-induced rodent models of type 2 diabetes [80].

Only one RCT has examined the effectiveness of MI as a treatment for GDM. This trial randomized 69 women with GDM onto either 4g MI plus 400µg folic acid, or 400µg of folic acid alone. In this trial, MI was associated with decreased fasting glucose, insulin, HOMA-IR (a measure of insulin resistance) and increased adiponectin, but no difference in gestational weight gain. A weakness of this trial was that it was not blinded and only involved Caucasian women [81].

Several studies have investigated the preventative effects of MI in women at risk of GDM. 110 women with a family history of T2DM were given 4g MI plus 400 µg folic acid daily, while 100 women were given just 400 µg folic acid daily. 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 [82]. One trial reported that the risk of GDM was halved if women taking MI to treat PCOS did not stop taking it during pregnancy, compared with those who stopped taking MI upon falling pregnant [83]. A further double-blind trial of 75 pregnant women with first trimester hyperglycemia reported reduced incidence of GDM. In those women who did develop GDM, MI was associated with reduced need for insulin therapy, smaller babies, and fewer episodes of neonatal hypoglycemia [84]. Unlike metformin, MI has also been effective at preventing GDM in overweight and obese women. Supplementation of 4g MI plus 400 µg folic acid daily significantly reduced incidence of GDM in overweight (11.6% vs 27.4%) [85] and obese (14% vs

33.6%) women [86]. 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 study in Ireland found no protective effect of combined MI and D-chiro-inositol. In this study, 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. 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 [87]. 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 systematic review 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 [88]. The promise of early evidence suggests larger studies, in a variety of populations, are required.

Vitamin supplementation

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 [89]. A recent study similarly uncovered a causal relationship between vitamin B3 deficiency and congenital malformations [90]. Interestingly, there is now evidence that culturing bovine embryos in B vitamins epigenetically alters the expression of metabolic and developmental genes [91]. 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 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 [92]. Asemi et al. (2013) conducted a randomized double-blind placebo-controlled study of women with GDM. Half received received 50,000 IU vitamin D twice during pregnancy (upon GDM diagnosis and 21 days later), while the remaining women received a placebo. Vitamin D supplementation was associated with a significant decrease in fasting glucose, insulin, and HOMA-IR. Plasma LDL-cholesterol was also decreased [93]. Another, more recent trial randomized women diagnosed with GDM to a placebo, or either 200IU, 2000IU or 4000 IU vitamin D daily. Insulin, HOMA-IR and total cholesterol were all significantly reduced in the highest-dose group (4000 IU) [35]. The most recent meta-analysis on the topic, which included 6 studies and a total of 371 women, concluded that vitamin D supplementation improves insulin resistance scores and LDL-cholesterol concentrations, but does not affect fasting glycaemia or total triglyceride or cholesterol concentrations [94]. The implications of these results for the mother and baby remain unclear.

Some studies have investigated the efficacy of vitamin D supplementation to prevent GDM. A randomized controlled trial of women with vitamin D deficiency, supplemented with either a high dose (5000 IU) or low dose (400 IU) of vitamin D daily (90 per group beginning at < 20 weeks gestation), saw no effect on glycaemia. However, they noted the dose was well tolerated and

beneficial for preventing neonatal vitamin D deficiency [95]. 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%) [96]. Sablok et al. measured vitamin D concentrations during early pregnancy and administered vitamin D depending on the woman's level of deficiency [97]. 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 studies be performed [98].

Vitamin B6 has also been investigated as a treatment for GDM, although only in a few small studies that date back to the 1970s. Of women with GDM in the Netherlands tested for vitamin B6 deficiency, over 90% were found to be deficient. After 14 consecutive days of 100 mg/day vitamin B6 supplementation, the deficiency disappeared and glucose tolerance improved considerably [99]. The study was repeated in the USA, and the same effects were reported [100]. 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 [101]. 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.

292 *Minerals*

293 Very few minerals have been tested as potential treatments or preventive measures for GDM.
294 Magnesium – an essential mineral required for nerve transmission, body temperature regulation,
295 and protein and nucleic acid synthesis – supplemented at 300 mg/day during pregnancy has been
296 associated with reduced risk of GDM in one study [102]. Further, magnesium supplementation
297 among women with GDM has been demonstrated to exert beneficial effects on metabolic status
298 (fasting plasma glucose, serum insulin, HOMA-IR, triglycerides) and pregnancy outcomes
299 (reduced newborn hyperbilirubinemia and hospitalization) [103]. These effects may be mediated
300 by the ability of magnesium to indirectly stimulate insulin secretion (through acetyl-CoA and
301 calcium-dependent channels [104]), suppress postprandial hyperlipidemia [105], and possess anti-
302 inflammatory properties [106].

303 Selenium has also been investigated as a potential treatment for GDM. A double-blind placebo
304 controlled RCT of women with GDM randomly assigned to receive either 200 µg selenium or a
305 placebo for six weeks following GDM diagnosis resulted in decreased fasting glucose, insulin, C-
306 reactive protein, and biomarkers of oxidative stress [107]. More modest supplementation (60 µg)
307 had no effect on insulin resistance in pregnant women [108].

308 At least two double-blinded, placebo-controlled RCTs in Iran have also investigated effects of zinc
309 supplementation on inflammation, oxidative stress, and pregnancy outcomes in GDM. GDM
310 patients who were randomly allocated to receive 233 mg zinc gluconate (containing 30 mg zinc)
311 for six weeks had reduced serum high-sensitivity C-reactive protein (hs-CRP) and increased
312 plasma total antioxidant capacity compared with placebo, but there was no effect of the supplement

on pregnancy outcomes [109]. 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 [110].

Fiber

There has been one study of fiber supplementation in GDM, which was published in 1993 [111]. 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 fiber supplementation does not improve GDM, although additional studies would be beneficial.

Fatty acids

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 or prevent GDM. In STZ pregnant rats, omega-3 fatty acids reduce hyperlipidemia and fetal macrosomia [112–114]. A double-blind, placebo controlled RCT of women with GDM randomly assigned to either 1000 mg omega-3 fatty acid supplements or placebo for six weeks found beneficial effects on maternal serum hs-CRP, malondialdehyde, incidence of newborn's hyperbilirubemia, and newborn hospitalization [115]. Another study examined vitamin D (50,000 IU) and omega-3 fatty acid (1000 mg) supplementation taken both together and separately on glucose metabolism and lipid concentrations in GDM patients [116]. After six weeks of intervention, the combination of vitamin D and omega-3 fatty acids was associated with decreased fasting plasma glucose, serum insulin, HOMA-IR, serum triglycerides compared with both control and the individual groups (vitamin D or omega-3 alone). In contrast, another study of women 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 [117]. Further, a meta-analysis encompassing six RCTs of omega-3 fish oil in healthy pregnant women found no beneficial effect on risk of GDM or any other maternal or infant outcomes, with the exception of an increase in the duration of pregnancy [118]. 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 [119,120]. Therefore, the use of omega-3 supplements during pregnancy remains contentious.

Probiotics

Modifying the gut microbiome has become a popular new area of research in many medical disciplines, including type 1 and type 2 diabetes [121,122]. Probiotic supplementation involves ingesting capsules of “live microorganisms that confer a health benefit on the host” [123]. 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) [124]. GLP-1 both slows intestinal transit time and increases insulin sensitivity [125]. SCFAs may also decrease gut permeability by upregulating expression of tight junction proteins such as zonula occludens-1 (ZO-1) in the gut lining [124]. 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 [126], lipid profile [127], and inflammation [128]). In all three of these trials, fasting glycaemia and insulin resistance (HOMA-IR) were significantly reduced in the probiotic group. Further, probiotics reduced gestational weight gain [126], serum VLDL-cholesterol and triglyceride concentrations [127], and serum triglyceride, IL-6, TNF α , and hs-CRP concentrations [128]. A recent study which randomized GDM patients to probiotics (*Bifidobacterium bifidum* and *Lactobacillus acidophilus*, 10⁹ 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 [129]. However, an RCT in Ireland that assigned 149 women with GDM to either probiotic (*Lactobacillus salivarius*, 10⁹ CFU per day) or placebo found no significant differences between the groups with the exception of total cholesterol [130]. So far, there is no evidence to suggest that probiotic intervention affects pregnancy outcomes, such as caesarean delivery, preeclampsia or macrosomia [131]. Furthermore, a systematic review of the evidence involving women with GDM found no effect of probiotic supplementation on fasting blood glucose or LDL-cholesterol. However, insulin resistance was significantly reduced – which appeared to be associated mainly with the genus *Bifidobacterium* [124]. The analysis concluded that larger, longer-duration trials, across different strains of probiotics, needed to be performed.

A small number of RCTs have examined the ability of probiotic supplementation to *prevent* GDM. The Finnish “Probiotics and Pregnancy Outcome Study” randomized women 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 [132]. A double-blind, randomized, placebo-controlled probiotic intervention trial in women at risk of GDM in New Zealand was recently published [133]. The authors randomized women to receive either a probiotic (*Lactobacillus rhamnosus*, 6×10^9 CFU per day) or placebo, at 14–16 weeks' gestation, 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.

Summary

In summary, dietary supplementation is an exciting new avenue for GDM treatment and prevention. While current therapies such as lifestyle intervention, insulin therapy, and oral anti-diabetics can be effective at managing glycaemia and reducing fetal growth, they can be difficult to adhere to, and questions remain about their 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. Dietary supplements, on the other hand, can be safely used for prevention and are typically easy to administer. While there is promise in MI, vitamin, mineral, fatty acid, and probiotic supplementation, there is a need for further studies, both in animals and humans, to strengthen the evidence, and ensure the safety of both the mother and child.

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