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# Nutrition Therapy Within and Beyond Gestational Diabetes

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## Summary

With the global rising prevalence of gestational diabetes (GDM), an adaptable, economical approach to nutrition therapy that effectively controls maternal glycemia while promoting normal fetal growth will have far-reaching implications. The conventional focus has been to rigidly limit all types of carbohydrate. While controlling glucose, this approach fosters maternal anxiety and is a primary barrier to adherence. Many mothers substitute fat for carbohydrate, which may unintentionally enhance lipolysis, promote elevated free fatty acids (FFA), and worsen maternal insulin resistance (IR). Nutrition that worsens IR may facilitate nutrient shunting across the placenta, promoting excess fetal fat accretion. Evidence suggests that liberalizing higher quality, nutrient-dense carbohydrates results in controlled fasting/postprandial glucose, lower FFA, improved insulin action, vascular benefits, and may reduce excess infant adiposity. Thus, a less carbohydrate-restricted approach may improve maternal adherence when combined with higher quality carbohydrates, lower fat, appropriate caloric intake, and ethnically acceptable foods. Such a diet can be culturally sensitive, socioeconomically attentive, minimize further weight gain in GDM, with potential relevance for pregnancies complicated by overweight/obesity. Future research is needed to better understand the effect of macronutrient composition on the placenta and gut microbiome, the benefits/risks of nonnutritive sweeteners, and whether precisionnutrition is beneficial in pregnancy.

### Keywords

Pregnancy; Gestational diabetes; Obesity; Nutrition; Diet

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## Introduction

The high prevalence of obesity in young women has changed the pregnancy landscape to one commonly characterized by over-nutrition. Over the first and second decades of the female lifespan, key metabolic factors and behaviors contribute to insulin resistance (IR) and glucose intolerance, often manifesting in pregnancy. This risk begins with a high birthweight or excess adiposity, followed by accelerated postnatal growth potentially promoted by formula feeding, leading to early adiposity rebound, childhood overweight or metabolic syndrome. This phenotype is subsequently compounded by years of poor diet quality, over-nutrition, a sedentary lifestyle and poor sleep[1] resulting in worsening puberty IR that does not normalize[2] after adolescence. By young adulthood, these influences culminate in a prepregnancy phenotype characterized by obesity and pre-existing IR, where mild hyperglycemia and hyperlipidemia are already present, only to manifest and be amplified with superimposed pregnancy metabolic adaptations[3].

Seminal leaders in the field of diabetes in pregnancy recognized that fetal overgrowth is a primary concern in pregnancies affected by diabetes[4], and Freinkel[5] advocated that lessons from diabetes in pregnancy apply to all pregnancy. Twenty-five[6] to nearly 40%[7] of young women are obese worldwide, and although women with obesity alone account for the highest number of pregnancies complicated by fetal overgrowth[8], nutrition therapy is instituted only once gestational diabetes mellitus (GDM) has been diagnosed. However, as more women are diagnosed with GDM accompanied with milder degrees of hyperglycemia[9], now estimated at ~20% of pregnancies[10], more overweight and obese women will qualify for the diagnosis. Nutrition therapy is the single management component applicable to every woman with the GDM diagnosis, regardless of phenotypic severity. Although the optimal approach to nutrition therapy remains elusive and may require a personalized strategy, it is critical to identify therapeutically efficacious components that minimize the need for medical therapy in this growing population of mothers. Further, adaptable, economical options effective for GDM might impart benefits for mothers who are overweight or obese, who often share a milder metabolic phenotype and deliver the largest number of large-for-gestational age (LGA) infants[8].

Over a century of clinical experience supports dietary manipulation in the treatment of diabetes[3, 11], thus the conventional approach to treatment of GDM is restriction of carbohydrate[4]. In GDM, restriction of carbohydrate, particularly simple carbohydrate, reduces postprandial hyperglycemia and decreases fetal glucose exposure, reducing fetal overgrowth[12]. Unfortunately, the restrictive approach to nutrition has been identified as the primary barrier to treatment adherence in GDM[13]. Moreover, there is a lack of evidence supporting all carbohydrate restriction in GDM[14, 15] and concerns focused on its unintended consequences have been raised[15–17]. In environments that promote over-nutrition and reduced physical activity, with rigid carbohydrate restriction comes a tendency to replace carbohydrate calories with those from fat. We[18, 19] and others[17, 20–28] have shown that maternal lipids (triglycerides [TG], free fatty acids [FFA]) are positively associated with excess fetal growth and that high total and saturated fats, which increase FFA exposure, can worsen maternal IR resulting in prolonged hyperglycemia. Although

there remains a critical need for RCTs designed to understand the physiologic effects of nutrition in GDM[14, 16], the purpose of this paper is to illuminate the high potential for a less restrictive but higher-quality macronutrient approach to choices in nutrition therapy. Evidence from RCTs in GDM suggests this approach may effectively optimize intrauterine conditions and fetal growth patterns, potentially applying to obesity and all pregnancies.

## Targeting Metabolism in Pregnancy using Nutrition

It has been recognized for decades that in-utero conditions are formed by maternal nutrition[5]. Orchestrated by placental hormones, normal pregnancy metabolism is characterized by reduced insulin sensitivity, increased postprandial glucose[29], 2–3 fold increased insulin production[30, 31], and increased plasma FFA, TG, total cholesterol and phospholipids[31–33]. When fetal growth increases in the 3rd trimester, IR heightens with each gestational week to ensure nutrient shunting to the fetus[34–36]. Pre-conception obesity is commonly associated with impairments in insulin-stimulated glucose uptake, insulin-suppression of hepatic gluconeogenesis, and insulin-suppression of lipolysis that intensify by the third trimester[33, 37, 38]. In fact, nearly 50% of GDM in the United States can be explained by overweight/obesity[39], and is a result of a combination of IR and insufficient beta cell reserve[31, 40].

Recently, we demonstrated that women with diet-controlled GDM randomized to a higher-complex carbohydrate, lower fat diet (vs. carbohydrate restriction with higher fat) demonstrated greater insulin action after 6–7 wks of provided diet. The estimates of IR across both groups were strongly correlated with infant adiposity[41] (Figure 1). Although women with GDM have higher patterns of glycemia[42, 43], we have shown using eucaloric fixed diets that healthy obese women also have higher patterns of 24-hr glycemia than normal-weight mothers (by ~9%, using continuous glucose monitoring) early and later in pregnancy[18, 19]. Fasting TG are higher in GDM throughout gestation compared to obese and normal-weight women[44]. However, in our controlled studies (all meals were provided), meal studies at 28–31 wks gestation demonstrated *postprandial* TG were similar in diet-controlled GDM (interventional study)[45] and otherwise healthy obese mothers without GDM (controlled observational study)[19]. Although nutrition therapy in GDM has focused on control of maternal glycemia[12], mounting data suggest that maternal lipids, especially TG, may be stronger drivers of fetal growth than glucose in GDM[21, 28] and in pregnant women with normal glucose tolerance[17–20, 22–28]. In our studies of obesity alone, both fasting and 1-hr postprandial TG at only 16wks gestation were strongly associated with neonatal adiposity[19], and more so than maternal glucose. Maternal TG can be hydrolyzed to FFA by placental lipoprotein lipase (pLPL), increasing FFA availability to the fetus for fetal fat accretion. We have recently shown that pLPL activity correlates with newborn fat mass[46]. Maternal glucose, FFA, and TG, factors driven by maternal IR, are sensitive to nutritional patterns (Figure 1). Therefore, these data highlight the potential of nutrition therapy to target maternal glucose *and* TG or FFA to mitigate fetal overgrowth in GDM, potentially extending to overweight and obesity outside of GDM.

## Glycemic Index and Higher Quality Carbohydrates

GIycemic index is a property of a carbohydrate food that describes its ability to raise blood glucose: a low-GI food has a lesser ability to raise postprandial glucose, while high-GI foods acutely raise blood glucose[47]. Lower-GI foods produce higher satiety, while higher-GI foods are associated with increased hunger, insulin levels, and energy intake[47]. Over the last decade, low-GI foods have been increasingly recommended for nutrition in pregnancy[48]. Freinkel[5] demonstrated that the postprandial glucose increases the maternal-fetal glucose gradient, facilitating placental glucose transport. Because postprandial glycemia is higher with heightened IR and impaired glucose tolerance (i.e., obesity, GDM, pre-existing diabetes), low-GI foods have high potential to help reduce the risk of LGA/macrosomia[48]. Glycemic load (GL) describes the insulin demand created by a carbohydrate food[49]. When considering a less restrictive approach for carbohydrate intake in GDM, international consensus supports that complex carbohydrates should be of higher quality[47, 50] to reduce insulin demand. A nutrition pattern including *higher quality* carbohydrates liberalizes those that tend to be nutrient dense (more vitamins/minerals), have higher fiber, and are lower in calories and GI/GL[47, 50–52].

## Anxiety and Fear Undermine Nutrition Therapy in GDM

A diagnosis of GDM generates anxiety and fear. At ~28 wks gestation, the diagnosis is often a surprise to women, who until then perceived a normal pregnancy[53]. Quite suddenly, the pregnancy is 'high-risk'; women are asked to self-monitor blood glucose, conform to a rigid restriction of dietary carbohydrate, read food labels and count grams of carbohydrate, attend more doctor visits, and they face the potential for treatment with insulin and increased fetal surveillance. The need for insulin has been associated with feelings of failure, guilt[54], and anxiety[55]. Once the diagnosis is assigned, women have reported fear for the baby's wellbeing, anxiety and depression[53, 55]. They have expressed that nutrition therapy is culturally insensitive[54–56], intrusive[53], and hard to follow late in pregnancy[53, 57, 58]. In particular, food selection is mentally exhausting[57]. In general, a restrictive approach to diet creates internal conflict and a focus on prohibited foods[59]--a mindset that undermines weight and nutrition interventions. On the other hand, a less restrictive approach allows a range of acceptable foods, alleviating the feeling of rigid control and inner conflict, and instead allowing a range of acceptable foods. A flexible, less restrictive approach has been associated with better health/psychological well-being, higher self-confidence, and commitment to personal health goals, all of which predict success for nutrition programs[59].

In the authors' clinical experience, some women are so fearful of macrosomia that they consume extreme carbohydrate-restricted diets, freely consuming fat instead, reasoning that less will improve infant outcomes. Although their glycemia is typically controlled, they are anxious, unhappy, and consume only a narrow range of suitable foods and are at risk for ketosis. Others are so stressed by the nutrition plan that they simply do not follow it, and consistent with recent experience in China[58], self-monitoring of glucose is less than recommended as it provides feedback of their perceived failure. A less restrictive approach

to nutrition therapy in GDM could increase self-confidence, compliance, and avoid compensatory higher fat intake.

## Unintended Consequences: Carbohydrate Restriction in GDM

Rather than limiting all carbohydrate, a focus on which macronutrients might influence maternal IR may be an alternative and beneficial approach. This is based on the premise that the degree of IR increases fetoplacental nutrient exposure (glucose, lipids, amino acids)[5] (Figure 1). We have demonstrated that pregnancy-induced IR can be attenuated by a lower fat diet[41, 45] and excessive fetal growth might be favorably modified using a liberalization of high-quality carbohydrates with lower fat[13, 41, 45, 60]. Because amplified maternal IR and lipolysis are fundamental adaptations to maternal physiology, dietary manipulations that increase FFA (which interfere with insulin signaling[61]), may actually result in protracted hyperglycemia due to increasing IR. If carbohydrate energy is replaced by fat, given that it is difficult and not advantageous to increase protein to ≥20%, there is potential for increased peripheral and hepatic IR, a finding supported in human studies[41, 62]. Recently, pre-conception carbohydrate restriction was linked to a higher incidence of neural tube defects, probably due to lower intake of nutrient-fortified foods with folic acid[63]. Outside of pregnancy, rigid carbohydrate restriction (20g/day) with high fat intake resulted in blunted 24-hr insulin secretion and worsening IR. This was accompanied by sustained elevated FFA over 24hrs and very low insulin levels were inadequate to suppress lipolysis [64]. These conditions associated with high dietary fat intake suggest increased IR that, in pregnancy, would promote in-utero over-nutrition, setting the stage for overgrowth (Figure 1).

Lipids and FFA are potent fetal growth substrates now also recognized to have negative intrauterine programming effects associated with excess fetal growth and poorer long-term offspring health[65]. Intensified carbohydrate restriction to minimal intake carries a risk for maternal ketosis[66] from increased lipolysis and generation of FFA (Figure 1). With severe carbohydrate restriction, the obligate fetoplacental glucose supply which depends on higher maternal glucose, could challenge placental-fetal glucose transfer [67]. Pregnant women are advised to consume an average of 175g of carbohydrate/day, which includes the necessary 33g to support fetal brain development[68]. However, newer evidence suggests the recommended ~175g/day does not account for *placental* glucose requirements, which likely exceed 135g alone in the 3$^{rd}$ trimester in a NW mother and would be increased with higher BMI[67]. Extremes in protein intake should also be carefully considered as both restricted and excessive protein intake have been associated with low birthweight[69, 70]. Differential effects of dietary carbohydrate on postprandial glucose[71] support that although simple carbohydrates acutely raise blood glucose[47], complex nutrient-dense carbohydrates (polysaccharides and starches primarily from grains, vegetables, and legumes)[50] result in an attenuation of the postprandial glucose excursion[29]. With optimal dietary carbohydrate and lower fat intake, nutrition therapy could safely support a less restrictive plan that meets glycemic targets, weight stabilization goals[72], supports appropriate fetal growth, and, importantly, avoids the need for medication and expensive fetal surveillance.

## Evidence Supporting Less Restrictive Carbohydrate Intake for GDM

### Effects on Maternal Glucose Metabolism

Treatment of GDM has aimed to keep maternal glucose within treatment targets of: fasting ≤90–95 mg/dL, and ≤140 or ≤120 mg/dL for 1- and 2-hour postprandial glucose, respectively[3, 9]. Women who attain a fasting glucose ≤95 mg/dL within 2 weeks of diet prescription are less likely to require insulin or oral hypoglycemic therapy[73, 74]. Two highly controlled randomized crossover studies (all food provided) showed that nutrition with 60–70% of total intake from higher-quality complex carbohydrates controlled postprandial glucose to within treatment targets within 3 days (n=4 women)[45] and 4 days (n=16)[75]. Although maternal glucose control in the former study might in part be explained by fiber intake (70g fiber, 70% carbohydrate vs. 31g, 35% carbohydrate)[75], fiber was similar in the latter study (29g, 60% carbohydrate vs. 24g, 40% carbohydrate)[45]. In the latter study, performed by our group[45], the 24-hr glucose area-under-the-curve (AUC) by continuous glucose monitoring (CGM) was minimally higher by 6% on the 60% higher complex carbohydrate diet (vs. 40% carbohydrate), but both diets controlled maternal glycemia to well below therapeutic targets. In Poland[76], it was similarly demonstrated within a 60% total carbohydrate diet group that postprandial glucose was lower than baseline after 2 weeks. In Iran, women were randomized to a dietary approach to stop hypertension (DASH, low-sodium) diet (~65% carbohydrate, mainly complex) vs. a ~55% carbohydrate diet Although women with GDM demonstrated a decreased fasting glucose[77] and improved response to an oral glucose tolerance test[78], the findings are surprising given the intervention was only 4 weeks, immediately after GDM diagnosis, and was not maintained for the last 8–10 weeks of pregnancy.

In our study, we examined the glucose and FFA response after 6–7 weeks of diet and until delivery (all meals were provided to the mothers). Surprisingly, women randomized to the complex carbohydrate diet (60% of total calories, similar in carbohydrate, sugars and fiber to DASH) actually had a *decrease* in fasting glucose while those randomized to the lower-carbohydrate (40% of total calories) diet demonstrated *increased* fasting glucose. In these trials, protein ranged 15–20%, and total fat was lower (10–25%) with lower saturated fat in the higher carbohydrate arm. The lower total fat content could have added to beneficial effects on glucose metabolism due to lessened FFA-induced worsening of IR[79]. Overall, these trials underscore that women with GDM achieved good glycemic control with a less carbohydrate-restrictive approach to nutrition therapy.

### Effects on Lipids, Insulin Resistance, Inflammation

In the short-exposure randomized crossover studies, the higher complex carbohydrate diets resulted in lower fasting total cholesterol, fasting FFA (70% carbohydrate/10% fat)[75], and postprandial FFA response to a controlled meal (60% carbohydrate/25% fat)[45], which may attenuate IR. Women who consumed the DASH diet (65% carbohydrate/18% fat) for only 4 wks appeared to have a lower lipids, HbA1c, systolic blood pressure[78], increased total glutathione and antioxidant capacities, as well as an improved IR index (HOMA-IR)[77], presumably from consuming more nutrient-dense carbohydrates with increased vitamins and minerals. However, there was no evidence that the mothers actually consumed this diet by

urinary sodium or other biomarkers. Further, the intervention was not maintained for the remaining 8–10 weeks of pregnancy and the women were not directly followed, warranting caution in the interpretation of the results[77, 78]. In our study[41], we biopsied maternal adipose tissue and demonstrated a nearly doubled suppression of isoproterenol-stimulated lipolysis (56% suppression), a biomarker of adipose tissue IR, in those following the higher complex carbohydrate diet (60% carbohydrate/25% fat) compared to only 31 % suppression in the lower carbohydrate (40% carbohydrate/45% fat). Adipose tissue gene expression in mothers on the higher complex carbohydrate/lower fat diet also suggested less inflammation, although in this small study we did not show decreased plasma inflammatory biomarkers[41]. These data suggest better insulin action in adipose tissue with the more liberal complex carbohydrate (with lower fat) exposure after 6–7 wks. Overall, the studies suggest that less restrictive higher-quality complex carbohydrate with lower total fat, possibly lower sodium and higher antioxidant activity, lowered FFA and improved insulin action despite the inevitable increase in pregnancy-induced IR.

## Effect on Gestational Weight Gain (GWG)

It has been suggested that a 50–60% carbohydrate diet leads to excessive GWG and postprandial hyperglycemia[80], which fuels a focus on rigid carbohydrate restriction in GDM. Weight gain might be expected in the setting of caloric excess and high consumption of simple carbohydrates that acutely increase blood glucose, where higher insulinemia would promote lipid storage[81]. In Spain[82], women randomized to a low-carbohydrate (40% carbohydrate/40% fat) gained 1.4 kg vs. 2.3 kg in the control group (55% carbohydrate/25% fat). However, only total GWG was reported and weight gained during the intervention is unclear. In Australia[83], 42% of those in a higher-GI group had excessive GWG[84], compared to 25% of women randomized to low-GI. Again, only total GWG was reported and weight gained before the intervention is unknown. The higher proportion of insulin therapy in both groups could further confound the GWG observation because insulin administration is clearly associated with weight gain. Even more of a confounder is if mothers consume more carbohydrate in order to avoid hypoglycemia from too much insulin administration. Three trials have reported weight gained during the diet intervention[41, 77, 78, 85], which was ~1–2 kg on either a higher- or lower-carbohydrate eucaloric diet, supporting that a less restrictive consumption of complex, lower-GI carbohydrates does not promote excess GWG.

## Need for Insulin Therapy

Historically, non-randomized studies in GDM demonstrated that glycemic control could be achieved using diet+insulin[4], and consumption of <42% carbohydrate might avoid the need for insulin therapy[86]. Two published RCTs were powered on the need for insulin. In Australia[87], 29% of women randomized to a low-GI diet (GI=48) required insulin versus 59% with a higher-GI diet (GI=56). In fact, 50% of women who failed the higher-GI diet were able to avoid insulin by switching to the low-GI option. Fiber was similar in the low-GI (26g) and high-GI (23g) arms. In Spain[82], 55% of women randomized to a low-carbohydrate (~40% carbohydrate/40% fat) or a higher carbohydrate diet (~55% carbohydrate/25% fat) required insulin, showing no difference. Intakes of total energy, fat and protein were not reported. Women did not decrease simple sugar intake over the 6–12

wk intervention in either group. In the DASH diet studies, fewer women randomized to DASH for 4 wks (65% carbohydrate/18% fat vs. 54% carbohydrate/28% fat) required insulin; however, this is curious given the intervention was not continued for the last 8–10 weeks of pregnancy. Overall, the data support that in GDM, less restrictive intake of higher quality low-GI carbohydrates can potentially reduce the need for insulin therapy.

## Effect on Maternal and Infant Outcomes

Two published RCTs were powered on a difference in infant birth weight. An Australian RCT (n=92)[83] designed to compare the impact of a low-GI diet with 27g fiber (GI=47, 37% carbohydrate/33% fat) to a higher-GI diet (GI=53, 40% carbohydrate/35% fat) with similar fiber on infant birth weight (powered on 260g difference) was stopped early because a difference in birthweight remained undetectable between groups; neither group met the GI targets. Although in the Iran[85] DASH vs. control trial, a lower birth weight was reported with DASH, this was an unusually large difference (3223g vs. 3819g) given the sample size was only 58, the intervention was only 4 weeks duration, and the women were simply sent back for routine care by their individual providers for the remaining 8–10 weeks of pregnancy. Our data[41] (all food was provided) supported a trend for lower infant adiposity in women randomized to the higher complex carbohydrate (lower fat) diet for 6–7 wks through delivery.

Birthweight and infant adiposity at birth, however, are not the only important outcomes GDM, obesity, or diet may affect. Our group recently demonstrated that infants from obese GDM mothers were born with 68% more intrahepatic lipid at 2 weeks of life. This underscores concerns about excess FFA availability to the fetus, who early in pregnancy has insufficient subcutaneous fat and may store excess energy as visceral fat[88]. Excess intrahepatic lipid could serve as a “first hit,” increasing later risk for non-alcoholic fatty liver disease (NAFLD), present in 40% of obese children and the leading cause of liver transplant[89].

## Effect of Fiber and Low-GI Diets

It is difficult to isolate the independent effects of fiber and low-GI diets since both are often manipulated when trying to influence each separate component. One RCT formally compared a high-fiber (80g fiber/ 60% carbohydrate/20% fat) to a lower-fiber (20g fiber/50% carbohydrate/30% fat) diet in GDM. However, women self-monitored their glucose only 2 days/wk, self-reported compliance was poor (40–60%) due to GI intolerance (high-fiber goal was 80 grams), and the drop-out rate was unreported. In the early short-term crossover study[75] fiber intolerance was also described (70g fiber/70% carbohydrate vs. 31g fiber/35% carbohydrate), but the improvement in glycemic control could be due to differences in carbohydrate, fat, or by higher fiber. Viscous fiber is thought to attenuate postprandial glycemia due to its absorptive properties[90]. In Type 2 diabetes, this concept was recently supported whether the source of fiber was dietary or by supplementation[91]. Outside of pregnancy, controlled studies have also shown that glycemic load (total insulin demand) is a stronger driver of glycemic response in single foods and mixed meals than total carbohydrate or fiber[29, 92, 93]. Across the remainder of RCTs in GDM[41, 45, 78, 82, 83, 85, 87, 94, 95], the difference in fiber between higher- and lower carbohydrate diets was so

small (2–7g) that it was unlikely to explain improved glucose tolerance. Higher-quality complex carbohydrates tend to have higher fiber content if they are from vegetable, legume, or whole grain sources, and higher fiber diets are linked with lower cancer, diabetes and CVD risk[47, 96]. By meta-analysis, there was a suggestion that increased fiber intake alone could influence fetal growth; a low-GI diet with higher fiber alone (vs. low-GI with lower fiber) in pregnancy reduced the risk for macrosomia[97].

In support of low-GI nutrition patterns, the aforementioned meta-analysis of 5 RCTs[97] showed that in addition to reducing the need for insulin, a low-GI diet (vs. higher-GI) in GDM reduced the risk of macrosomia. In China[95], Asian women with GDM and a much lower BMI of 20–21 $kg/m^2$ admitted to a metabolic ward were randomized to 4-days of either replacement of rice in meals with a low-GI staple food (brown rice) vs. control (white rice)(total carbohydrate/energy content held constant). Women randomized to the low-GI staple had decreased fasting glucose (−3.7% vs. −1.2%, respectively) and a greater reduction in postprandial glucose (−19 to −22% vs. −7 to −12%, respectively). Overall, the studies suggest a benefit of low-GI diets in GDM on fasting/postprandial glucose and infant birthweight, particularly when fiber intake is increased.

Outside of pregnancy, mounting evidence supports low-GI/low-GL diets with higher-quality carbohydrates for control of postprandial glycemia in obesity and impaired glucose tolerance[47]. In pregnant mothers *without* GDM, a recent meta-analysis of 11 trials demonstrated that a low-GI diet (vs. control) was associated with a reduction in fasting and postprandial glucose, and LGA[98], although the trials were highly heterogeneous. In mothers with either GDM or impaired glucose tolerance a low-GI (vs. high-GI) diet resulted in a higher percentage of postprandial glucose values in the target range, but there was no significant difference in glycemia between groups[99]. In 800 pregnant women at risk for macrosomia[100], women randomized to a low-GI (vs. high-GI diet) had lower GWG by 1.5kg, less incidence of a higher fasting glucose (>92 mg/dL) or a 50g glucose challenge >140mg/dL[101] but no significant difference in infant birthweight In Australia, in women at risk for GDM, a low-GI diet did not produce a difference in pregnancy outcomes[102] although in a subgroup analysis of women who appeared to be able to slightly reduce GI, the *offspring* had slightly lower birthweight/length z-scores with evidence of lower aortic intima-medial thickness at 12 months of life[103]. As a whole, the evidence implicates low-GI diets in improved postprandial glucose, insulin action, and vascular health, with reduced GWG. These benefits may be linked to increased consumption of higher-quality complex carbohydrates, which overall are lower in GI, may contain higher fiber, are more nutrient dense[104] and have been linked with greater satiety[47].

### Unknown or Poor Compliance in Nutrition Therapy for GDM

Compliance to nutrition therapy in GDM remains one of the largest confounding factors across studies[16]. To increase compliance, investigators have implemented strategies where all food is provided to participants[41, 45, 75, 95], a sample food basket is provided[83], and phone follow-up, meetings with a registered dietitian, and menus for participants to follow were used. Compliance has been measured with scoring tools using a questionnaire, and self-reported intake (food records). Despite these strategies, compliance continues to

undermine trial outcomes[15]. In the RCT where fiber was manipulated, there was no difference in glycemic control but compliance marginally despite being reported as “good” when only 60% self-reported compliance and “acceptable” when only 40% reported compliance and there was significant attrition[105]. In Poland[94] a 60% to 45% total carbohydrate content was compared and although improved glycemic control within groups was reported, self-reported compliance was ~50%. Despite providing sample food baskets, participants in the Australian RCT of low- vs- higher-GI diets failed to achieve the GI targets[83], resulting in little difference between diets (GI: 53 vs. 47), likely explaining the negative trial outcome. In Spain[82], where higher vs. low-carbohydrate diets were compared, about 2/3 of women returned diet records, only the low-carbohydrate group reported they met the carbohydrate target, and attrition within the control group was 20%. In the 4-week DASH studies, urinary sodium was not included as a compliance metric[77, 78, 85]. Even in our study where food was provided for 6–7 wks through delivery[41, 45], full compliance cannot be guaranteed. These illustrations demonstrate the critical need to consider compliance as a major factor in the interpretation of trial outcomes, especially when self-reported by questionnaires. Trials that provide all meals, as in our pilot RCT[41, 45](larger trial ongoing), are likely to be the most rigorous method to maximize compliance, but is expensive and labor intensive.

## Cultural Adaptability of a Less Restrictive Approach to Nutrition Therapy in GDM

For an approach to nutrition therapy in GDM to be truly optimal, it must be adaptable and economical (Table 1). One of the leading factors that undermines nutrition therapy in GDM is its cultural unacceptability[54–56]. Linked to a restrictive approach, women believe they cannot consume many foods consistent with their regional culture. Clearly, different regions of the world have varied dietary patterns defined by local food availability, cultural/traditional practices, and socio-economic factors. Consequently, dietary recommendations must vary across the globe to suit the local dietary patterns. In Table 1, we offer examples of foods that are culturally sensitive which can be incorporated in nutrition approaches for GDM across wide-ranging ethnic populations. The global nutrition transition, mainly affecting the developing parts of the world such as Asia, Latin America and Africa, is causing a shift from traditional diets to patterns of eating that highly depend on processed foods, high fat/high caloric meals, and eating away from home[106]. A consequent increase in incidence of non-communicable diseases, such as obesity and diabetes, is posing major health and economic challenges in these relatively poor parts of the world.

Dietary interventions from across the globe suggest beneficial effects of traditional foods high in complex carbohydrates and fiber, with lower GI and that are low in fat. In a study with immigrant GDM mothers in Italy, an ethnic meal plan resulted in better maternal and fetal outcomes than a standard meal plan, due to better adherence to ethnic foods[107]. Outside of pregnancy in Type 2 diabetes, a rice and beans combination was found to be effective in controlling postprandial glycemia when compared to rice alone[108]. Similarly in Asia, a brown rice-based Vegan diet yielded greater reductions in HbA1C when compared to conventional diet [109]. Also in a Type 2 population in India, a millets-based regional

dish was shown to significantly reduce postprandial glycemia compared to its rice-based counterpart [110]. These foods have not yet been tested in studies of GDM women. Adherence to a prescribed therapeutic diet is hindered by many barriers including elimination of culturally familiar foods and a perceived inability to eat same food as the rest of the family[111, 112]. Hence, a promising dietary approach in GDM would be the one that targets an optimal maternal weight goal and is delivered in the form of culturally sensitive foods, potentially improving patient acceptability and adherence to these diets.

## Conclusions and Recommendations

Nutrition therapy is the single treatment component that will reach every woman with GDM across diagnostic criteria. Despite the advancing IR of pregnancy, the evidence to date suggests that an optimal mixture of higher-quality complex carbohydrates with less glycemic potential, lower fat, and appropriate protein supports good glycemic control and insulin action, improves lipemia, and may have beneficial vascular effects. A less carbohydrate-restrictive approach to nutrition therapy in GDM can be adapted to fit cultural diet preferences, lessening diagnosis-provoked anxiety, boosting compliance, and avoiding unintended consequences associated with compensatory higher fat intake. Low-GI diets may reduce the need for insulin and lessen postprandial hyperglycemia. Future prospective RCTs are suggested to include: use of provided foods; consistent reporting of total GWG vs. weight gained during intervention; inclusion of infant adiposity as a marker of in-utero nutrition exposure given its better prediction of childhood obesity than birthweight[113]; control of confounders such as medication, disparate energy intake, and physical activity between diets; improved biomarkers of dietary adherence; inclusion of homogeneous samples of women (ethnicity, glucose metabolism)[3, 40]; reporting of achieved glycemia[3]; and more reliable reporting of foods consumed. Data suggest that women with GDM do not require any additional weight gain for adequate fetal growth[72]. Appropriate focus on minimizing additional weight gain by prescribing eucaloric diets is essential.

Nutrition directly affects the maternal gut microbiome, which is passed to the infant and has been shown to promote an obesigenic phenotype with a high fat simple carbohydrate diet[114]; extensive research is underway and will likely be highly informative. Additionally, there is speculation that a higher fat, high simple sugar diet that leads to excess FFA availability to the fetus could result in increased intrahepatic lipid stores and potentially increase the risk of NAFLD[89], underscoring the need for offspring measures beyond birthweight or percent fat at birth. The use of non-nutritive sweeteners have recently been linked with later obesity risk and poor cardiometabolic health[115]. Because women with GDM are typically counseled to substitute sugar with non-nutritive sweeteners, how the use of these products impact the gut microbiome in pregnancy and maternal and infant outcomes remains unstudied but is critically important. Identifying a diet the optimal diet for GDM mothers is likely to apply to mothers with obesity, from which the largest numbers of LGA infants are born. Importantly, earlier adoption of a healthier diet in pregnancy may be critical to improve pregnancy outcomes given fetal hyerperinsulinemia occurs by 16 weeks, placental transporters are likely to be set early in pregnancy, and exposure to high levels of free fatty acids before fetuses develop later subcutaneous fat depots could result in increased

visceral or hepatic fat. More study on how particular macronutrients directly affect placental function and transport are needed.

The evidence to date supports a less restrictive approach including higher-quality complex carbohydrates, but lower fat, which may be adopted beyond the window of GDM by the mother and her family, serving as a foundation for a lifetime higher diet quality in mother and offspring[70]. Newer research in personalized medicine may revolutionize our ability to optimize nutrition therapy in GDM. However, until this is achievable, we can at least attempt to maximize cultural adaptability, better address the socioeconomic considerations, and adopt a less restrictive approach that allows greater flexibility in choosing healthier foods designed to stabilize weight and promote good metabolic health far beyond the gestational window.

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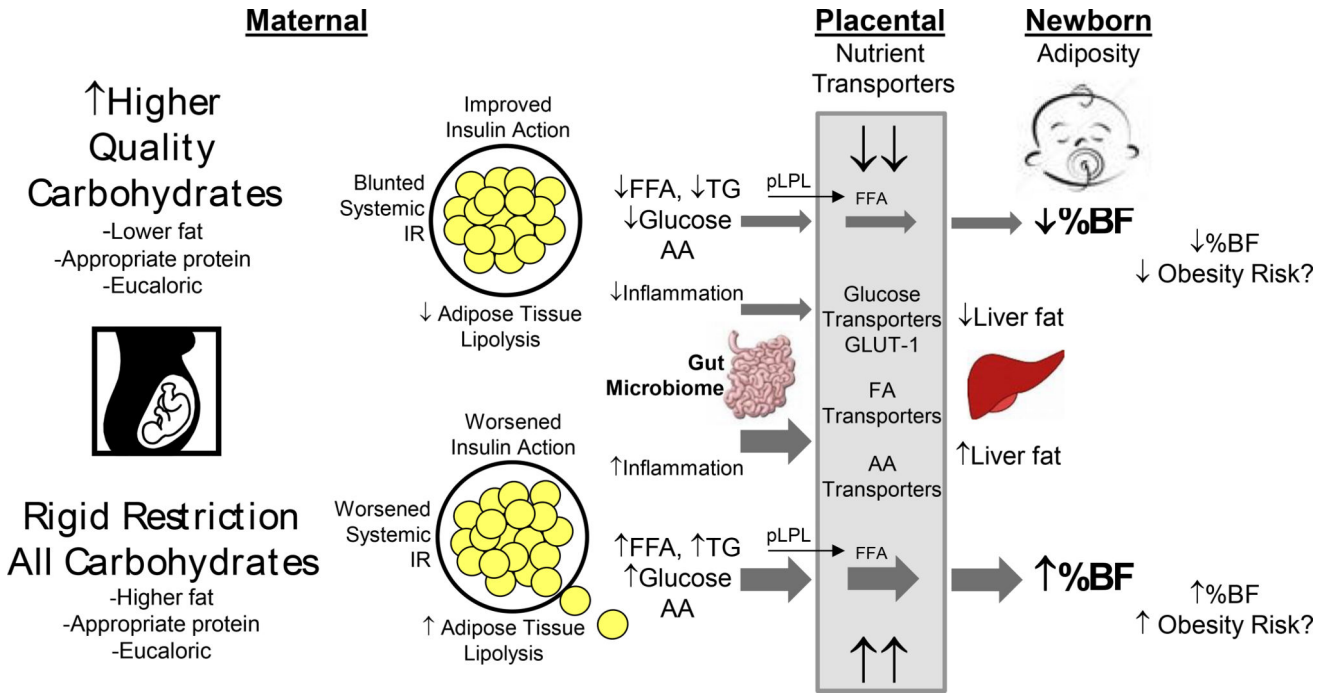


**Figure 1.**

The impact of rigid restriction and less-restrictive approaches on maternal metabolism in GDM. In environments promoting over-nutrition and physical inactivity, with rigid carbohydrate restriction comes a tendency to replace carbohydrate energy with calories from fat. Higher total and saturated fat intake amplify maternal adipose tissue lipolysis, worsening FFA and dampening insulin signaling, leading to higher systemic and hepatic insulin resistance (IR). In maternal circulation, IR results in higher levels of free fatty acids (FFA), glucose, and amino acids (AA) available to the placenta and fetus. Higher inflammation linked to adipose tissue and the gut microbiome with IR promote nutrient shunting through placental nutrient transporters, promoting fetal overgrowth and excess fat accretion. Maternal obesity and GDM has been associated with increased intrahepatic lipid accumulation[88], higher birthweight and newborn adiposity, all risk factors for childhood obesity. Modification of maternal metabolism using a less carbohydrate-restrictive approach that liberalizes higher-quality complex carbohydrates in combination with lower fat may attenuate maternal IR and promote appropriate fetal growth, setting the stage for lifetime health and lower obesity risk. (TG = triglycerides; pLPL = placental lipoprotein lipase; GLUT-1 = glucose transporter; %BF = percent body fat)

## Table 1

Local/Traditional foods from varied geographical regions that qualify for a less carbohydrate-restricted dietary approach in GDM.

| Geographical region | Examples of traditional foods that qualify for less restricted GDM Nutrition therapy approach |
|---|---|
| North America | - Whole grain breads, pasta, brown or parboiled rice, oats<br>- Vegetables, fruits, beans, lentils<br>- Low-fat dairy, lean poultry and fish<br>- Occasional meats, cheese and nuts |
| Latin America | - Whole grains like amaranth, maize, quinoa, brown rice<br>- Vegetables, fruits, beans<br>- Lean poultry, fish, low-fat dairy<br>- Occasional meats, nuts and cheese |
| Mediterranean Region | - Whole grain bread/pasta, brown rice, couscous<br>- Vegetables, fruits, beans, lentils<br>- White fish, lean poultry, low-fat dairy<br>- Occasional nuts, cheese, meats and shellfish |
| Africa | - Whole grains like millets, sorghum, teff, parboiled rice<br>- Vegetables, fruits, roots, tubers, beans<br>- Fish, eggs, poultry<br>- Occasional meats and dairy |
| South Asia | - Whole wheat, millets, barley, rye, buckwheat, parboiled rice, wheat rotis<br>- Vegetables, roots, tubers, fruits<br>- Beans, lentils, dals, low-fat dairy, lean poultry, fish<br>- Occasional meats, nuts and cottage cheese (paneer) |
| East Asia | - Noodles and brown rice<br>- Soybeans, fish, seafood, vegetables, wild plants, seaweed, mushrooms<br>- Occasional lean meats, shellfish, dairy |