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Strategies in the Nutritional Management of Gestational Diabetes

Teri L. Hernandez, PhD, RN[1,2,3], **Molly A. Anderson, MS, RD**[4], **Catherine Chartier-Logan, MPH**[1], **Jacob E. Friedman, PhD**[5], and **Linda A. Barbour, MD, MSPH**[1,6]

[1]Department of Medicine, Division of Endocrinology, Metabolism, and Diabetes; University of Colorado, Anschutz Medical Campus, Aurora, CO

[2]College of Nursing, Division of Women, Children, and Family Health; University of Colorado, Anschutz Medical Campus, Aurora, CO

[3]Center for Women's Health Research, University of Colorado, Anschutz Medical Campus, Aurora, CO

[4]Department of Geriatric Medicine, University of Colorado, Anschutz Medical Campus, Aurora, CO

[5]Department of Pediatrics, University of Colorado, Anschutz Medical Campus, Aurora, CO

[6]Department of Medicine, Division of Obstetrics and Gynecology; University of Colorado, Anschutz Medical Campus, Aurora, CO

Abstract

Elucidating the optimal macronutrient composition for dietary management of gestational diabetes mellitus(GDM) has enormous potential to improve perinatal outcomes. Diet therapy may result in significant cost savings if effective in deterring the need for expensive medical management within this growing population. In only 6 randomized controlled trials(RCTs) in 250 women, data suggest that a diet higher in complex carbohydrate and fiber, low in simple sugar, and lower in saturated fat may be effective in blunting postprandial hyperglycemia, preventing worsened insulin resistance and excess fetal growth. The use of diet in GDM remains an area in grave need for high-quality RCTs.

The rapidly rising prevalence of gestational diabetes mellitus (GDM) could affect nearly one in five pregnant women if the American Diabetes Association (ADA) and International Association of Diabetes in Pregnancy Study Group diagnostic criteria are adopted. This necessitates an effective diet strategy to avoid the higher costs of treatment with insulin or other medications. Yet, there is still no consensus about the optimal macronutrient diet composition that could improve maternal glycemia, and potentially prevent a worsening maternal metabolic profile with excessive fetal growth. Although a lower carbohydrate (CHO) diet has traditionally been recommended to blunt postprandial excursions, increasing concern over a diet in which fat is often substituted for CHO has resulted in a lack of any clear guidelines for the optimal management of GDM using diet. As the GDM and obese maternal populations continue to rise, mounting evidence underscores the potential influence

Corresponding Author: Teri L. Hernandez, PhD, RN, Assistant Professor of Medicine and Nursing, Division of Endocrinology, Metabolism, and Diabetes, College of Nursing, 12801 E. 17th Avenue, MS8106, P.O. Box 6511, Aurora, CO 80045, Phone: (303)724-3943, Fax: (303)724-3920, teri.hernandez@ucdenver.edu.

of the intrauterine metabolic environment on the risk of offspring obesity and glucose intolerance. Unfortunately most, if not all, published human studies pertaining to GDM and diet therapy have been conducted with little attention paid to comparing controlled diets and infant body composition. Thus, identifying a diet that can improve both maternal and infant outcomes is of paramount importance.

Diet therapy is the first line of defense in the treatment of women with GDM. Women who fail diet not only require more intensive medical management, but are often offered increased fetal surveillance, which adds substantial cost to treatment. In papers published 15–20 years ago it was reported that a low CHO diet could blunt postprandial glucose excursions[1] and decrease the need for insulin therapy[2]. However, a focus on CHO restriction necessitates an increase in dietary fat when protein intake is constant. Outside of pregnancy, diets higher in fat, particularly saturated fat, have been shown to promote insulin resistance. Increasing maternal insulin resistance in pregnancy could further result in increased substrate delivery to the fetus and worsening of fetal hyperinsulinemia. Emerging data in both animal and non-human primate models support an intrauterine influence of dietary fat in promoting offspring adiposity, abnormal growth patterns, and hepatic steatosis as an early manifestation of the metabolic syndrome [3]. Data in humans have also shown that maternal triglycerides (TG) and free fatty acids (FFA) can be used by the placenta and may be a stronger predictor of excess fetal fat accretion than maternal glucose [4, 5], raising the question as to whether glycemia should be the sole criteria for medical therapy.

As a result of the growing appreciation for the metabolic impact of dietary macronutrients beyond CHO, consensus panels continue to withhold specific diet recommendations for women with GDM due to insufficient evidence[6]. The field of GDM has moved from establishing that *treatment of GDM is effective*, to the current state where the challenge is to identify *which treatments of GDM are most effective*. Cost effectiveness is a paramount consideration given the prevalence of women being diagnosed with GDM continues to increase. It is hoped that effective diet therapy can prevent the need for more expensive management by insulin or medication(s). The intent of this article is to first offer an historical perspective supporting the rationale behind a lower CHO diet for the management of GDM. Then, we will systematically review the literature focusing on randomized controlled trials (RCTs) which varied the macronutrient distribution to discuss why there is no consensus on the optimal GDM diet. As important aspects of diet therapy, RCTs exploring the use of dietary supplements will also be reviewed, and new considerations surrounding the macronutrients will be discussed.

Historical Perspective: Diet Prescription in Gestational Diabetes

Dietary advice in pregnancy is given with several goals for the mother, assuming subsequent benefits for the offspring: control of hyperglycemia; adequate weight gain; and appropriate nutritional status [7]. The issue of adequate weight gain in pregnancy and prevention of exacerbated weight gain through hypocaloric diets has been thoroughly reviewed elsewhere[8]. Most GDM is diagnosed between 24–28 weeks of gestation when maternal insulin resistance begins to increase with each passing week. Dietary advice as a treatment modality in GDM is given primarily during the last trimester, when fetal growth and development are maximized before birth. During the decade between 1950–1960, O'Sullivan, and Carpenter and Coustan demonstrated that the use of diet + insulin was effective in reducing maternal glycemia, likely accomplished through a focus on CHO restriction as was consistent during the time period[8]. In 1990, Jovanovic-Peterson and Peterson[1] defined a diet prescription (40% CHO, 20% protein, and 40% fat) that supported appropriate maternal weight gain based on levels of BMI as defined by the Institute of Medicine. Subsequent evidence supported a strong association between maternal

postprandial glycemia and infant size[9, 10]. The CHO-restricted diet was associated with a reduction in macrosomia incidence[1], although reported informally. The ADA formally recommended CHO restriction (≤40% of total daily caloric intake) in mothers with GDM in 1995 [11], despite the fact that dietary advice for non-pregnant persons with diabetes no longer included such a restriction. In 2007, however, the ADA withdrew formal diet recommendations for mothers with GDM due to a paucity of evidence from randomized trials[6].

Other evidence from non-randomized studies mostly supported the use of CHO restriction. In a descriptive study (n = 14, obese women with GDM, 32–36 wk gestation) Peterson and Jovanovic-Peterson[12] identified a correlation between the percentage of CHO in a meal and the 1-hour postprandial glucose (r=0.95; p<0.001). They recommended that CHO content should be <45% for any meal to keep the postprandial glucose level < 120 mg/dL. In 1999, Ilic [13] administered 2 single test meals (randomized cross-over design, n=10, diet-controlled GDM, weeks 29–34 gestation, 40% CHO, 40% fat, 20% protein) that differed in SFA vs. MUFA content for the fat composition. The results demonstrated a blunted insulin response, smaller glucose area-under-the-curve, and lower FFA concentrations on the SFA diet. Major[2] conducted a non-randomized, descriptive study in which 42 women with GDM were placed in groups based on their free-living CHO intake (<42% lower CHO[LC, n = 21] *vs*. > 42% but < 50% higher CHO[HC, n = 21] of total energy). On the LC (lower CHO) diet, fewer women required insulin therapy, and 1-hour postprandial glucose was significantly lower (110 ± 18 mg/dL vs. 132 ± 19 mg/dL; p<0.04). Fewer infants born to mothers in the LC group were LGA, and there was less incidence of Cesarean delivery. However, the mean difference in CHO was only 5% between the diets, there was no description of fat content, and the indications for Cesarean delivery were not given. In contrast, Romon[14] conducted a correlational study in which 80 women (France) with GDM or mild hyperglycemia followed a diet that was 43% CHO, 38% fat, and 19% protein. The unexpected outcome was that infant birth weight was ***negatively*** correlated with CHO intake (p < 0.03); no LGA infants were born in mothers whose CHO intake was >210 g/day. In fact, women with CHO intake <39.4% had infants in the highest quintile for birth weight. Unfortunately, 38% of the women required insulin therapy, and 24% were “under-reporters” who did not adhere to the diet. Thus, the effect the intervention is confounded and therefore difficult to determine.

Randomized Controlled Diet Trials in GDM Exploring Macronutrient Diet Composition

Given the ambiguity and limitations of studies using an observational and retrospective design, we performed a broad PubMed and OVID search from 1950–2012 using keywords and their combinations, such as “GESTATIONAL DIABETES,” “GDM DIET,” “GESTATIONAL HYPERGLYCEMIA,” “DIET,” “LIFESTYLE INTERVENTION,” “RCT,” and “HYPOCALORIC DIETS.” Reference lists in review papers, manuscripts reporting original data, and expert reports were examined and the references cross-checked to findings in PubMed. Studies must have met the following criteria for inclusion: 1) Prospective randomized study, 2) Women diagnosed after 24 weeks gestation but by the 3rd trimester of pregnancy, 3) Diet exposure was the independent variable, 4) Diet exposure was required to last >24 hours, 5) Macronutrient prescription and/or actual consumed macronutrient distribution consumed was reported, 6) A measure of dietary adherence was included in the study, or food was provided to research participants, 7) Diets were eucaloric, and 8) If medication was administered, it was required that the analysis was conducted without those women or that use of insulin or medication was prospectively defined as the main outcome of interest. Studies of women with pre-existing diabetes were not included.

Due to the lack of uniformity in reported outcomes across the studies, it was impossible to attempt a meta-analysis.

Only 6 studies across 4 countries (Australia, Denmark, Poland, Iran) met criteria for inclusion. Two RCTs were excluded because the exposure length was 1 meal[13] or the outcomes were confounded by the use of insulin[15]. The oldest study was published in 1984[16] and the most recent was published in 2012[17] (Table 1). The 6 studies included only a sum of *n*=250 women with diet-controlled GDM. The criteria by which the women were diagnosed varied from those of the American Diabetes Association[17], the World Health Organization[18], and the Australian Diabetes in Pregnancy (ADIPS) guidelines[19, 20]. In general, the diet interventions began during gestational week 28–34. Across studies, the BMI range was 24–35 kg/m^2. Approximately 50% of the 250 women were Caucasian; the remaining 50% were Asian-Australian[20] and Iranian[17] (~25% each). The women were overweight or obese (BMI≥27 kg/m^2), but in the study of Louie[20] in which >50% of the women were Asian, the mean BMI was ~24 kg/m^2. Two of the studies compared 2 different macronutrient distributions (HC vs. LC)[16, 18], 1 investigated the effect of varying the type of dietary fat (higher monounsaturated fatty acid [MUFA] content diet vs. lower MUFA)[21], 2 compared degrees of glycemic index (GI) (lower GI [LGI] vs. higher GI [HGI]) [19, 20], and 1 compared a low-sodium DASH (Dietary Approaches to Stop Hypertension) diet to a higher-sodium control diet[17]. In the first study wherein varying GI was the independent variable[19], the need for insulin was the main outcome and was compared when a low vs. higher GI was randomized (LGI, 48 vs. HGI, 56). In the second GI study[20], although not a main outcome, the need for insulin was a pre-defined outcome for comparison between 2 degrees of GI (LGI, 53 vs. a higher-fiber diet with GI, 47).

The diet interventions and study designs varied. As Table 1 outlines, the macronutrient distributions ranged 37–70% CHO of total calories[16, 1719]. Dietary fat intake ranged 10–45% of total calories [16]. Protein intake varied between 16–24% of total calories. All of the diets were eucaloric and supported appropriate maternal weight gain. Exposure to diet as the independent variable ranged 4 days[16] to 10 weeks[19].

Compliance with Diet Therapy in RCTs

In the 5 of the 6 studies where food was not provided, all but one[18] evaluated dietary compliance using self-reported intake through food records. Other strategies for monitoring compliance included use of a compliance questionnaire[18], weighing foods[21], meeting with a registered dietitian either in person or over the phone[17, 20], and providing sample foods[20]. Lauszus[21] confirmed adherence to a low vs. higher MUFA diet using the fatty acid distribution in a blood sample, but unfortunately, the diet records were also reported to be a 20–30% underestimation of total calories. In the study of Moses[19], diet records revealed that women were able to achieve a modest difference in GI (LGI of 48 vs. HGI of 56). Asemi[17] reported that a low-sodium DASH diet was achieved, but no measure of urinary sodium was reported as a confirmation. In the intervention of Cypryk[18](HC vs. LC), reported compliance was only ~50%. In the study of Louie[20] the women were not able to achieve the targets for GI in either the LGI or HGI[higher fiber] group. In fact, the groups did not achieve a statistically different GI or fiber content between groups.

Maternal Glucose Response to Diet Therapy

Because the historical approach to diet therapy in GDM has focused on control of fasting and postprandial glucose, we examined the studies within the context of maternal glucose outcomes (Table 1). Two studies [16, 18] reported the postprandial glycemic response to the diet interventions tested. Nolan[16] reported no difference in postprandial glucose between a HC vs. LC diet (70% unrefined CHO/10% fat vs. 35% unrefined CHO/40% fat) treatment

after 4 days, but only 3 plasma glucose values were reported per diet treatment. This was a small study (n=4) but the HC diet showed superiority over the LC diet in improving glucose tolerance to a 50g oral glucose load after only 4 days of treatment in a highly controlled setting (hospital admission/all food provided). Urinary glucose output was reported also ***lower*** on the HC diet but this is not a conventional measure of glycemia. Cypryk[18] conducted a randomized, 2- week diet intervention in which they also compared a HC vs. LC diet (60% vs. 45%, consecutively). Postprandial glucose fell within each diet compared to the baseline level, but no between-diet comparisons were reported. An improvement in glucose response to an oral glucose load was also reported on a DASH diet (67% CHO/18% fat)[17] compared to lower-CHO diet (54% CHO/29% fat). The effects of the various diets on fasting glucose across the studies was unclear, but Nolan[16] and Louie et al[20] reported no differences. Fasting glucose appeared lower on the HC vs. LC treatment (76±7 vs. 81±7 mg/dL, mean±SD, consecutively) in the study of Cypryk[18], but between-diet statistical comparisons were not provided.

Other Maternal Outcomes in Response to Diet Interventions in RCTs

The studies reported a number of maternal outcomes, and a limited number of neonatal outcomes in the context of diet therapy in GDM (Table 1). Nolan[16] reported that fasting total cholesterol was 6% lower and fasting FFA were 14% lower on a HC diet vs. LC. Lauszus[21] reported a 15% improvement in insulin sensitivity (via intravenous glucose tolerance testing [IVGTT]) on the HC treatment compared to a 34% decline in insulin sensitivity after 4 weeks of a higher MUFA diet. However, they reported a lower 24-hour diastolic blood pressure (BP) on the higher MUFA diet compared to HC (126/75 vs. 128/80, consecutively). Moses[19] demonstrated that with similar macronutrient distribution, less women required insulin following an LGI vs. HGI diet for 8–10 weeks (29% vs. 59%, $p<0.05$, respectively). Louie[20] reported a lower number of women needing insulin therapy on LGI vs. higher fiber (53.2% vs. 65.1%). However, there were no statistical differences in the GI content of the diets, and the number of women needing insulin did not reach statistical significance. Asemi[17] reported a lower A1c, total cholesterol, LDL cholesterol, plus a decreased systolic BP in women who followed a DASH diet (higher in complex CHO and lower in fat) vs. control for 4 weeks.

Birth and Infant Outcomes in Response to Diet Interventions in RCTs

Overall there were no notable differences in birth or infant outcomes across the diet treatments. Investigators reported infant birth weight and/or frequency of LGA in 5 of the studies[17–21], but with one exception, no statistical differences were found between diet comparisons. Asemi[17] reported a statistically significant lower infant birth weight in offspring of women who followed a DASH diet vs. control (Table 1), as well as a lower rate of Cesarean delivery in the DASH diet group. However, gestational age (GA) at delivery was not reported. In fact, GA at the time of delivery was not reported by 3 investigators[17, 19, 21], making it difficult to interpret the birth and infant outcomes reported. The main outcome in study of Louie[20] was a difference in infant birth weight between the LGI and HGI[higher fiber] groups, but the trial was stopped early because it was underpowered to detect such a difference.

Review of Evidence and Discussion of RCTs

A salient finding across these randomized studies of nutrition interventions in women with GDM is that improvements in glucose tolerance can be seen in as little as 4 days[16], and that women were able to tolerate higher CHO diet treatments when the type of CHO was unrefined or of the complex variety. This is significant because the historical approach to diet therapy in GDM has been one of CHO restriction[1] and these findings would suggest

that any benefit from lowering the CHO content could be negated by the obligatory increase in dietary fat. It may be that the strict focus on CHO restriction due to fear of macrosomia leads to high dietary fat consumption in order to avoid CHO, which may worsen insulin resistance. It is encouraging that the evidence shows higher CHO diet interventions, when complex CHO or CHOs with low glycemic indices are used, yielded favorable glucose control/glucose tolerance[16–18] including an improvement in insulin sensitivity[21](15% improvement compared to 34% decrement in a higher-MUFA diet). In 2 of the studies this finding might be explained by higher fiber intake[16, 17]. However, Moses[19] demonstrated in a strong study design that when fiber, calories, and macronutrients were similar, the LGI diet yielded less need for insulin treatment. Other notable outcomes from higher CHO diet treatments included improved fasting FFAs[16] and lipids[16, 17], and systolic BP[17].

Despite the use of randomized assignment in these studies, the evidence is limited. Over nearly 30 years, evidence across the RCTs includes only 250 women with GDM, diagnosed with varying diagnostic criteria. Half of the women were Caucasian and the other half included Asian[20] and Iranian[17] women. There is minimal representation from Black or Hispanic/Latino women among the RCTs. There is a lack of consistency across the outcomes reported and exposure time to the interventions. The lack of dietary compliance among the women with GDM in half of the studies[18, 20, 21] taints the outcomes that are reported. Moreover, with two exceptions[16, 19] the studies are not highly controlled. In clinical practice, postprandial self-monitored blood glucose (SMBG) using a glucometer is the single available glycemic metric used to assess the day-to-day efficacy of diet therapy in women with GDM. Yet, only 2 investigators reported the response to the diet interventions in terms of plasma glucose [16] or SMBG[18]. Despite these limitations, protein intake tended to be held constant across the studies with variance among CHO and fat intake being the major difference between treatments. Moreover, the reported outcomes are not confounded by insulin administration. It should be noted, however, that the frequency for insulin therapy was high in two studies of[19, 20], raising the question of whether these women were representative of most diet-controlled GDM women. Surprisingly, women in the sample of Asemi[17] required insulin therapy ***after*** delivery (DASH diet vs. control, 12% vs. 59%), which is inconsistent with GDM in clinical practice, since the vast majority of GDM women revert to normal glucose tolerance postpartum and rarely need insulin. The favorable effects of the DASH diet[17] might be explained by differences in the amount of saturated fat and added sugars, which were both higher in the control diet, especially given there was no objective evidence by urinary sodium excretion that DASH was truly lower in sodium.

The Contribution of Glycemic Indices and Fructose in Diet Prescriptions

Recent attention in the diet literature both within and outside of pregnancy has focused on the quality of CHO in terms of its glycemic index or ability to increase blood glucose. Consumption of CHOs that are digested more slowly and attenuate postprandial hyperglycemia might be a favorable approach to diet therapy in GDM that avoids the need for CHO restriction [22]. Although 3 randomized trials have been published in which levels of GI were compared in pregnant women with GDM[15, 19, 20], the strongest evidence in terms of both study design and statistical analysis was the study of Moses[19], who demonstrated that women who consume LGI carbohydrates require less insulin compared to those who consume HGI carbohydrates. They further demonstrated that in 19 women who met criteria for insulin therapy, 9 were able to avoid insulin use by switching to a LGI diet. Walsh[23] conducted a randomized trial comparing a LGI diet to no diet intervention in 800 pregnant women without DM with the goal of reducing fetal macrosomia. All 800 women were in their second pregnancy and had previously delivered an infant weighing >4000 g. There was no significant difference between the two groups in birth weight at delivery. However, women consuming the LGI diet had significantly less gestational weight gain, and they

reported a significantly higher proportion of women in the control arm had a higher incidence of glucose intolerance (a glucose challenge >140 mg/dL at 28 weeks gestation) compared to the women in the intervention arm. Overall, evidence supports the use of GI and it appears to hold promise within diet therapy for women with GDM.

Due to its low glycemic index and independence from insulin, fructose initially appeared to be an attractive option in aiding the glycemic control of those with DM, extending to women with GDM. Although glucose and fructose are structurally similar, their metabolic fates differ greatly. In summary, fructose is almost completely extracted by the liver and undergoes rapid conversion into glucose, glycogen, lactate and fat[24]. In rodent models, marked increases in comorbidities such as insulin resistance, obesity, and T2DM in addition to increased production of uric acid and hypertension resulted from chronically high levels of fructose consumption[24]. Additionally, the lipogenic effects of fructose through the favoring of de novo lipogensis and attenuation of lipid oxidation has been observed in healthy, insulin resistant and those with T2DM. Although the underlying mechanisms of GDM have not been fully elucidated, the downstream effects of high fructose consumption could exacerbate CHO intolerance within these women. Animal models have shown that high fructose intake induces a phenotype similar to GDM, with obesity as a consequence in the offspring. The increasing intake of fructose over the past several decades taken in combination with recent animal research underlining the adverse metabolic effects of fructose intake mandates further research to better understand such impacts and develop guidelines for safe levels of intake, if any, for these women. There is currently no evidence supporting or refuting fructose consumption within diet therapy for GDM.

Dietary Supplements in GDM

Myo-inositol, fish oils, and probiotics have recently been used in RCTs to either treat or prevent GDM by improving insulin resistance. Two trials[25, 26] by the same investigators in Italy randomized pregnant women to myo-inositol 4g with 400 ug of folic acid vs. folic acid alone. In the first study, 24 Caucasian women (mean BMI, 24–25kg/m^2) received open-label treatment for 8 weeks compared to 45 controls (mean GA= 26 weeks). Insulin and glucose levels fell in both groups after 8 weeks but there was a greater improvement in insulin sensitivity (HOMA-IR) in the myo-inositol group (50% improvement vs. 29%, respectively). Adiponectin was reported to increase in the myo-inositol group by 28%. In the 2nd study[26], the same investigators randomized pregnant women (Caucasian, mean BMI 23kg/m^2, no conventional GDM risk factors) with a first degree relative with T2DM to treatment (n=99) or folic acid alone (n=98) at 12–13 weeks in an attempt to prevent GDM. The women receiving myo-inositol had a lower rate of GDM compared to the controls (6% vs. 15.3%; p= 0.04) and infant BW was lower (3111 ± 447 vs 3273 ± 504g; mean GA= 39 weeks). Whether these results could be duplicated in women with more conventional GDM risk factors (history of GDM, obesity, non-Caucasian, history of PCOS) remains to be studied, as does the mechanism by which myo-inositol might act to improve insulin sensitivity.

In a double-blind multicenter RCT of ~2400 Australian pregnant women (mean age 29 yrs; 32% smokers)[27], DHA-enriched fish oil (800 mg/day) was found to be no different than vegetable oil capsules without DHA in preventing GDM or preeclampsia. The concentration of DHA in cord blood, as a biomarker for compliance, was higher in the treatment group. In addition to the absence of a benefit on GDM or preeclampsia outcomes, there was no difference in the risk for SGA or LGA. However there was a slightly lower but statistically significant perinatal death rate and neonatal convulsion rate in the DHA-rich fish oil group. This may have been in part due to the lower rate of early preterm birth in the treatment group. It is likely that both the excess of n-6 PUFA and paucity of n-3 PUFA, characteristic

of more Western-style high-fat diets, play a functional role in adverse obese pregnancy outcomes. Given that n-3 and n-6 PUFA are both broken down to their most biologically active eicosanoid products by the same enzymatic pathways, it follows that a 1:1 ratio of the two is ideal. Thus, balancing this ratio should be the primary goal, and potential therapies should focus on not only increasing maternal n-3 PUFA intake, but correspondingly reducing dietary n-6 PUFA and overall saturated fat intake as well.

Lastly, given recent data suggesting that aberrant compositional development of the gut microbiota can result in obesity, 238 Finnish women (mean age 30 years, double-blind) were successfully randomized during the first trimester of pregnancy to a diet intervention + probiotics (Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12), a diet intervention + placebo, or a control group to examine whether probiotics could decrease the development of GDM[28]. GDM was diagnosed at a rate of 13% the diet +probiotics group, compared to 36% in the diet + placebo and 34% in the control group. The intervention extended to the end of exclusive breast feeding; 191 mother/infant pairs completed 24 months of follow-up. The 10-yr follow-up of these infants[29] revealed that probiotic treatment had a tendency to reduce the birth-weight-adjusted mean body mass index at the age of 4 years. Although modulation of the gut microbiota could be beneficial, the prevalence of GDM was unusually high in the diet-alone and control group. Moreover, the mean glucose values on the 75g OGTT and gestational weight gain were not reported. This novel therapy calls for further epidemiological and clinical trials, with precise data on the gut microbiota and confounding factors influencing weight development.

New Insight into Dietary Macronutrients

The current challenge before us in the field of diabetes in pregnancy is to identify which diet treatments of GDM are effective, and to identify effective treatment strategies from well-designed RCTs. Although limiting carbohydrate can reduce postprandial hyperglycemia[10], dietary carbohydrate and fat are not all alike. “Carbohydrate” can be an ambiguous term, since it includes sugars (including fructose), starches (including the concept of glycemic index), and fiber and all have varying degrees of effect on plasma glucose. Fiber that occurs naturally in foods is not digestible, and has little effect on blood glucose or insulin levels[30]. At the same time, “fat” can be ambiguous; monounsaturated, polyunsaturated, and saturated fats (MUFA, PUFA, and SFA) do not directly influence plasma glucose, but exert other effects on insulin action that are not equivalent[30].

New insights into the metabolic effects of the macronutrients warrant consideration in women with GDM as novel trials of diet intervention are planned and executed. With dominant approach to diet therapy in GDM focused on CHO restriction, there has been emphasis on increasing the 2 macronutrients that do not increase blood glucose per se: fat and protein[30]. Outside of pregnancy, it has been shown that diets high in SFA decrease insulin sensitivity through a defect in insulin signaling. Higher plasma concentrations of FFA secondary to insulin resistance stimulate the secretion of TNF-alpha which further promotes inflammation. High dietary saturated fat consumption in insulin resistant individuals have also been shown to increase the release of intestinal lipopolysaccharide (LPS), a potent inducer of inflammation and oxidative stress as well as hypertriglyceridemia[31]. Dietary fat may further overload mitochondrial oxidative capacity resulting in increased oxidative stress. Emerging evidence outside of pregnancy supports an interaction effect between dietary fat and protein (particularly branched-chain amino acids) in promoting an insulin resistant phenotype[32], highlighting that increasing fat and protein to control postprandial glucose might further exacerbate it over time.

As early as 2001, data in humans have demonstrated that maternal TGs and FFA can be used by the placenta and may be a stronger predictor of excess fetal fat accretion than maternal glucose, especially in GDM women with adequate glycemic control[4, 5]. Our group has also demonstrated that although obese pregnant women who are given a controlled diet have higher glycemic profiles compared to normal-weight women, they also have higher maternal TGs and FFAs both early and late in gestation[33]. Furthermore, the maternal TGs and FFAs were a stronger predictor than glycemic profiles for infant adiposity. It has been shown in human pregnancy that in the setting of insulin resistance and inflammation, placental FA binding proteins are up-regulated; this could result in excess transport of maternal dietary FA across the placental to serve as substrates that promote excess fetal fat accretion.

Liberalizing complex CHO to avoid adding fat to the diet is the focus of our own research in which we are currently using a highly controlled randomized cross-over design to carefully compare the effects of 2 different diets (HC: 60% CHO, 25% fat, 15% protein vs. LC: 40% CHO, 45% fat, 15% protein) within women with diet-controlled GDM. We provide precisely prepared food to the women in our research kitchen from the time of GDM diagnosis through delivery. Our preliminary findings show that glycemic control is within current treatment guidelines on both diets, despite postprandial glucose being marginally but statistically higher on the HC treatment[34]. Consistent with Nolan's[16] report of lower fasting FFA concentrations in women on a HC treatment after only 4 days; we similarly have demonstrated a statistically significantly lower FFA area-under-the-curve on the HC vs. LC treatment (n=15, paired data). Also consistent with Lauszus'[21] report of a 15% improvement in insulin sensitivity on the HC vs. MUFA diet after 4 weeks of treatment, we similarly demonstrated improved insulin sensitivity (HOMA-IR) after ~7 weeks of treatment with HC (vs. LC). This is further supported by data in adipose tissue samples that show a reduction in insulin suppression of isoproterenol-stimulated lipolysis in the LC diet group (LC 32% vs. HC 59%) (unpublished data). Preliminary data also suggest lower adiposity in infants born to mothers on the HC (lower fat) diet (unpublished).

Evidence from epidemiological and animal experiments highlights that maternal dietary fats, and their constituent FFA, play a key role in the programming of early growth and development[35]. Thus, intrauterine exposure to nutrient excess in the overweight mother with GDM may not be limited to the short-term adverse neonatal sequellae associated with excess abnormal growth and metabolic abnormalities. Fetal metabolic programming from excess maternal nutrient availability (glucose, TG, FFA) has been strongly associated in human epidemiologic studies as an independent predictor for the development of IGT, DM, childhood obesity, and poorer intellectual/psychomotor development [36, 37]. Therefore, manipulating the intrauterine environment using a maternal diet intervention that limits simple sugars but also limits saturated fat in order to favorably affect fetal programming, highlights the potential for altering maternal nutrition as a mechanism for improving the offspring's future health.

Conclusions

Diet therapy for women with GDM has historically focused on CHO restriction. Evidence from the randomized trials, however, supports the idea that women with GDM tolerate higher complex CHO diets. In fact the data from RCTs would suggest that a diet which liberalizes complex CHO (using higher fiber and lower glycemic index carbohydrates) and limits saturated fats may be optimal in improving glycemia, preventing further insulin resistance, and attenuating excess fetal fat accretion. Larger, highly controlled randomized prospective trials are gravely needed to identify the optimal diets in GDM women. The elucidation of the most favorable diet to improve maternal and infant outcomes in this rapidly increasing population of GDM women has far reaching implications. Such a diet

might also be validated in obese women, given both of these populations are at high risk for adverse pregnancy outcomes as well as long-term health risks to both mother and offspring.

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Table 1

Randomized controlled trials of nutrition interventions in diet-treated GDM.

Study	Design/N	Maternal BMI, kg/m^2[a]	Intervention	Exposure Length	Compliance	Maternal Outcome[b]	Infant Outcome[b]	Conclusion/ Comment
Nolan, 1984[16] Australia	Randomized Crossover N=4	26.9±8	HC: 70/10/20 70g fiber LC: 35/45/20 31g fiber - Unrefined CHO on both	4d each Begin 33.4±1.4 wk No Washout	Food provided Hospital admission	HC: - Fasting TC 6% lower - Fasting FFA 14% lower - Improved 50g OGTT response (day-4)	--	- HC diet associated with improved glucose tolerance, FFAs, TC compared to LC - Plasma glucose (p=NS) between diets but only 3/day
Lauszus, 2001[21] Denmark	Randomized unpaired N=27 13 MUFA 14 HC	MUFA: 35.3±2.4 HC: 32.2±1.5 (p<0.05)	MUFA: 46/37/16 22% MUFA 34g fiber HC: 50/30/19 11% MUFA 32g fiber	4 wk Begin 34 wk	- Food records + weighed food - Adherence demonstrated by ↑MUFA in blood. - Diet records 20–30% underestimated	*IVGTT* HC: −15% improvement in Si MUFA: −34% reduction in Si *Oscillometric DBP* MUFA: - Lower DBP at wk38 126/75 vs. 128/80	*BW* MUFA: 3743±602g HC: 3742±501g (Mean±SD, p=NS) GA not reported	- CHO/fiber similar - HC associated with improved Si - MUFA associated with lower DBP
Cypryk, 2007[18] Poland	RCT N=30 15 LC 15 HC	BMI not reported	LC: 45/30/25 HC: 60/15/25	14 days Begin 29.2±5.4 wk	- Compliance questionnaire ~50% compliance on each diet	LC/HC: Postprandial glucose across meals lower vs. baseline - Glucoses lower on HC but was not compared to LC	*BW* LC: 3407±309 38.9±1.4 wk HC: 3385±418 38.8±1.2 wk (Mean±SD, all p=NS)	- Postprandial glucose fell on both diets; Break-fast fell more on LC – Postprandial glucose better on HC, but no stats provided
Moses, 2009[19] Australia	RCT N=63 LGI 31 HGI 32	LGI: 32.0±1.2 HGI: 32.8±1.4	LGI: 37/33/24 26g fiber GI=48 HGI: 38/34/24 23g fiber GI=56	8–10 wk[c] Begin 29.9–30.3±0.2 wk	- 7-d food records x2 - Achieved modest difference in GI targets	LGI: - 29% required insulin HGI: 59% required insulin	*LGA* LGI: 3 women HGI:3 women GA not reported (p=NS)	- LGI: Less women required insulin; - 50% of those on HGI who failed diet avoided insulin by switching to LGI diet - High insulin frequency on both
Louie, 2011[20] Australia	RCT N=92 LGI 47 Fiber 45 50% Asian	LGI: 23.9±4.4 Fiber: 24.1±5.7 Pre-pregnancy	LGI: 39/35/24 27g fiber GI= 53 Fiber: 40/35/22 25g fiber GI= 47	6–7 wk Begin 29–29.7 ±3.5–4.0 wk	- 3-d food records 36–37wk - 3 visits with RD; 24-hr recall - Sample food baskets provided	- 53.2% on LGI vs. 65.1% on Fiber required insulin (p>0.05) - GI similar between diets (p>0.05)	*BW* LGI: 3.3±0.1kg at 39.1wk Fiber: 3.3±0.1kg at 39.2 wk *LGA* LGI: 12.8% Fiber: 4.4% (Mean±SEM; all p=NS)	- Trial stopped early; lack of power in BW outcome - Women did not reach GI targets - High insulin frequency in both - 68% of sample with BMI<25kg/m^2
Asemi, 2012[17] Iran	RCT N=34 DASH 17 CON 17	DASH 29.0±3.2 CON 31.8±5.9	DASH: 67/18/17 Fiber 23g Sodium 1379 mg SFA 19% Added sugar: 9g CON: 54/29/18 Fiber 16g	4wk Begin 24–28 wk	- 3-d food records - Phone follow-up - 7d menus provided	DASH: - Improved response OGTT - lower A1c, TC, LDL - decreased SBP	*BW* DASH: 3083±402 CON: 3641±579 (Mean±SD) GA not reported	- DASH had lower SFA, added sugar, fiber - No reasons for C/S noted - RD not blinded; administered both diets

Study	Design/N	Maternal BMI, kg/m^2[a]	Intervention	Exposure Length	Compliance	Maternal Outcome[b]	Infant Outcome[b]	Conclusion/ Comment
			Sodium 3859 mg SFA 26% Added sugar: 20g		- Reported sodium lower on DASH	- lower C/S rate - 12% on DASH and 59% on CON needed insulin AFTER delivery		- No urine sodium - High requirement for insulin after delivery

Macronutrients are (Carbohydrate/Fat/Pro). Percent distributions are as reported and may not total 100%. HC=high carbohydrate; LC=low carbohydrate; CHO=carbohydrate; TC=total cholesterol ; FFA=free fatty acids; OGTT= oral glucose tolerance test; MUFA=monounsaturated FA; IVGTT = intravenous glucose tolerance test; Si=insulin sensitivity; DBP=diastolic blood pressure; BW=infant birth weight GA=gestational age at delivery; LGI=lower-glycemic index; HGI= higher-glycemic index; LGA = infant birth weight≥90th centile; SFA=saturated FA; C/S=caesarean section.

[a] BMI at time of intervention start, unless specified

[b] All differences are $p<0.05$ unless specified.

[c] Gestational age at delivery not reported; exposure based on 40 week gestation.