Effects of a modestly lower carbohydrate diet in gestational diabetes: a randomized controlled trial

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ABSTRACT

Background: Lower carbohydrate diets have the potential to improve glycemia but may increase ketonemia in women with gestational diabetes (GDM). We hypothesized that modestly lower carbohydrate intake would not increase ketonemia.

Objective: To compare blood ketone concentration, risk of ketonemia, and pregnancy outcomes in women with GDM randomly assigned to a lower carbohydrate diet or routine care.

Methods: Forty-six women aged (mean ± SEM) 33.3 ± 0.6 y and prepregnancy BMI 26.8 ± 0.9 kg/m^2 were randomly assigned at 28.5 ± 0.4 wk to a modestly lower carbohydrate diet (MLC, ∼135 g/d carbohydrate) or routine care (RC, ∼200 g/d) for 6 wk. Blood ketones were ascertained by finger prick test strips and 3-d food diaries were collected at baseline and end of the intervention.

Results: There were no detectable differences in blood ketones between completers in the MLC group compared with the RC group (0.1 ± 0.0 compared with 0.1 ± 0.0 mmol/L, $n = 33$, $P = 0.31$, respectively), even though carbohydrate and total energy intake were significantly lower in the intervention group (carbohydrate 165 ± 7 compared with 190 ± 9 g, $P = 0.04$; energy 7040 ± 240 compared with 8230 ± 320 kJ, $P < 0.01$, respectively). Only 20% of participants in the MLC group met the target intake compared with 65% in the RC group ($P < 0.01$). There were no differences in birth weight, rate of large-for-gestational-age infants, percent fat mass, or fat-free mass between groups.

Conclusions: An intervention to reduce carbohydrate intake in GDM did not raise ketones to clinical significance, possibly because the target of 135 g/d was difficult to achieve in pregnancy. Feeding studies with food provision may be needed to assess the benefits and risks of low-carbohydrate diets. This trial was registered at www.anzctr.org.au as ACTRN12616000018415. *Am J Clin Nutr* 2020;112:284–292.

Keywords: lower carbohydrate, gestational diabetes, ketones, diet, MAMI study, metabolism

Introduction

Dietary carbohydrates have played an important role in human evolution, exemplified by marked changes in gene frequency related to starch and lactose intake (1). Glucose derived from digestion and absorption of starches and sugars is also the primary determinant of postprandial glycemia and insulinemia (2). In pregnancy, maternal glucose concentrations below those previously considered diagnostic of diabetes are also associated with effects on fetal growth (3). Both high and low dietary carbohydrate intake are therefore relevant to pregnancy and gestational diabetes (GDM). In the context of obesity and type 2 diabetes (T2D), meta-analyses show that low-carbohydrate diets can produce significant improvements in glycated hemoglobin (HbA1c) and greater weight loss in comparison to conventional higher carbohydrate diets (4). However, relatively few trials

The University of Sydney's internal funding was used to conduct the MAMI 1 (macronutrient adjustments in mothers with gestational diabetes study 1) trial. Aside from the authors, no other entity took part in the design, implementation, analysis, and interpretation of data.

Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Data described in the manuscript, code book, and analytic code will be made available upon request pending ethical approval.

Abbreviations used: BGC, blood glucose concentration; BHB, β-hydroxybutyrate; GDM, gestational diabetes mellitus; GWG, gestational weight gain; HbAc1, glycated hemoglobin, HC, head circumference; IOM, Institute of Medicine; LGA, large-for-gestational-age; MAMI 1, macronutrient adjustments in mothers with gestational diabetes study 1; MLC (diet), modestly lower carbohydrate; NRV, Nutrient Reference Values; OGTT, oral-glucose-tolerance test; RC (diet), routine care; RCT, randomized controlled trial; RPAH, Royal Prince Alfred Hospital; T2D, type 2 diabetes.

Received September 7, 2019. Accepted for publication May 15, 2020.

First published online June 15, 2020; doi: https://doi.org/10.1093/ajcn/nqaa137.

have investigated the effects in GDM. Limited studies report improvements in postprandial glucose concentration (5–8), but only 1 showed a lower risk of large-for-gestational-age infants (LGA) (6).

The lack of high-quality clinical evidence has led to a lack of consensus on the most effective diet for GDM (9). This is a concern given the rising prevalence of GDM and its association with adverse pregnancy outcomes including macrosomia and cesarean section (10, 11). Currently, Medical Nutrition Therapy (MNT) for GDM focuses on carbohydrate quality, quantity, and distribution throughout the day to achieve euglycemia (12). Some guidelines suggest a minimum of 175 g/d of carbohydrate (13), but the American Endocrine Society and the American College of Obstetrics and Gynecologists advise women with GDM to follow a "lower" carbohydrate diet, where carbohydrates comprise 150–200 g/d (~33–45% of total energy intake), respectively (14, 15).

One concern of low-carbohydrate diets in pregnancy is the potential to increase maternal ketone concentration because of a reported inverse association with the intelligence of the offspring, even in the absence of ketoacidosis (16). In principle, a moderate level of carbohydrate restriction is not normally associated with elevated blood ketone concentrations. However, in early pregnancy, the maternal blood glucose concentration typically falls, increasing dependence on fat oxidation as the source of energy (17). Even with adequate energy intake, restricted carbohydrate intake increases the ratio of glucagon to insulin, promoting the oxidation of free fatty acids to β-hydroxybutyrate (BHB) and other ketones (18). Maternal ketone concentration can rise 3-fold within 24 h, increasing more rapidly in pregnant compared with nonpregnant women (19). As <50 g/d of carbohydrate is required to induce ketonemia in a nonpregnant population (20, 21), we hypothesized that modestly lower carbohydrate intake (~135 g/d) would not increase ketonemia, particularly if it is adequately spread throughout the day. In MAMI 1 (Macronutrient Adjustments in Mothers wIth gestational diabetes study 1) we aimed to conduct a randomized controlled trial (RCT) comparing blood ketone concentration and risk of ketonemia in women with GDM assigned to either a moderately low-carbohydrate diet or conventional dietary management.

Methods

The MAMI 1 study was conducted at the antenatal clinics of the Royal Prince Alfred Hospital (RPAH) and Campbelltown Hospital, Australia. The protocol was approved by the South-Western Sydney Local Health District (HE16/367) and the Human Research Ethics Committee of the Sydney South West Area Health Service (RPA Hospital Zone HREC/15/RPAH/397). All participants gave written informed consent. At ~26–28 wk, GDM was confirmed by a 75-g oral-glucose-tolerance test (OGTT) using 1 of the following diagnostic criteria: *1*) 1998 The Australasian Diabetes in Pregnancy Society (ADIPS) [fasting blood glucose concentration (BGC) ≥5.5 mmol/L or 2 h ≥8.0 mmol/L (22)]; *2*) 2010 The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [fasting BGC ≥5.1 mmol/L, 1 h ≥10.0 mmol/L, or 2 h ≥8.5 mmol/L (23)] diagnostic criteria. The hospitals differed in blood glucose monitoring targets, with a fasting BGC target of ≤5.3 mmol/L and 2-h postmeal ≤6.8 mmol/L used by the Campbelltown Hospital, and a fasting BGC ≤5.2 mmol/L and 1-h postmeal ≤7.5 mmol/L at RPAH.

MAMI 1 was a 6-wk, 2-arm, parallel RCT conducted April 2016 to May 2018. Pregnant women aged 18–45 y with a singleton pregnancy, between 24 and 32 weeks of gestation with a GDM diagnosis were eligible to take part. Women were excluded if they consumed alcohol, smoked cigarettes, followed a gluten-free, vegetarian, or vegan diet, had assisted reproduction, could not understand English, had major surgery (e.g., gastric bypass) in the previous 5 y, or had comorbidities other than obesity, hypertension, or dyslipidemia. Eligible participants were randomly allocated to either a modestly lower carbohydrate diet (MLC) or the routine care (RC) diet using block randomization, stratified according to age ($18 \leq$ age ≤ 30 or $30 <$ age ≤ 45) and BMI ($\leq$27 or >27 kg/m^2) category (4 blocks). Allocation to treatment was concealed in an opaque envelope and revealed to the dietitian on the first visit. An enrollment form was used to collect demographic data including age, parity, past and present medical conditions, self-reported prepregnancy weight, physical activity habits, and nutrition education exposure. Gestational age was based on last menstrual period and confirmed by an ultrasound scan. The trial was registered at www.anzctr.org.au as ACTRN12616000018415.

Diets

The MLC diet aimed for an absolute carbohydrate target of 135 g/d without energy restriction, based on the estimated average requirement for carbohydrate intake during pregnancy (24). The RC diet aimed for an absolute carbohydrate target of 180–200 g/d. To assist in achieving the target, a pictorial booklet, showing carbohydrate content, a target number of portions, and glycemic index (GI), was provided to both groups. Participants who had lower carbohydrate intake at baseline were encouraged to eat more high-fiber, low-GI foods, and this particularly applied to those allocated to the control group. Study visits were every 2 wk and made to coincide with those to the antenatal clinic. At baseline and end of the intervention, participants completed a 3 × 24-h food diary (including 2 weekdays and 1 weekend day) and a 2-d blood ketone diary as described below.

Biochemistry

The primary outcome, blood ketone concentration (as BHB), was determined using a handheld Optium™ meter and Optium™ β-ketone test strips (Abbott). Participants were instructed to test their blood for ketones in the morning after an overnight fast, and before the midday and evening meals for 2 nonconsecutive days. Ketone concentration was defined as normal: <0.5 mmol/L, mildly elevated: 0.5–1.0 mmol/L, hyperketonemia: >1.0 mmol/L, and ketoacidosis: >3.0 mmol/L (25). Monitoring of blood glucose concentration (a secondary outcome) was instituted as part of routine care with 4 finger prick tests each day, the first in the morning following an overnight fast, and remainder at 1-h (RPAH) or 2-h (Campbelltown Hospital) after each of the 3 main meals, to coincide with blood glucose monitoring.

As safety was primary, the research dietitian closely monitored patient medical symptoms and biochemistry, with specific focus

on blood ketone concentration. If participants were feeling unwell or dizzy, they were instructed to assess both blood ketone and glucose concentrations. If the ketone concentration was >0.5 mmol/L, they were advised to consume a carbohydrate-containing snack and repeat the blood ketone measurement. If the blood ketone concentration remained elevated (i.e., >0.5 mmol/L) for >2 d, the patient was advised to contact the hospital to arrange an immediate clinical review to establish the cause of the elevated blood ketones. They were also instructed to increase their dietary carbohydrate to 180 g/d and monitor blood ketones daily until the concentration stabilized (~48 h).

Process measures

At each visit, the endocrinologist reviewed the glucose concentration and instituted or adjusted insulin treatment as indicated. At visits 1–3, 24-h recall was collected. On visit 3, participants were asked to complete a second 3 × 24-h food diary and 2-d blood ketone diary. Glucose control during the intervention period was assessed using HbA1c and daily blood glucose concentration recorded by participants. Dietary information from food diaries (baseline and end of intervention) and 24-h recall were entered into an Australian nutrition analysis computer software (FoodWorks Professional Version 8, 2015, Xyris Software) based on the Australian Food, Supplement, and Nutrient Database (AUSNUT 2011–2013). GI values were cross-checked and compared with the international table of GI and glycemic load (GL) values (26).

Secondary outcomes

The 24-h recalls were used to assess compliance with the prescribed diets at each visit and final 3-d food diaries were compared to the baseline to determine if the overall dietary instructions were successful. To determine the proportion of carbohydrate restriction at baseline, we defined the minimum target as 175 g/d (13) for both groups. Similarly, to determine the proportion of women meeting their prescribed carbohydrate targets at the end of the intervention, ≥175 g/d was applied to the RC group and ≤135 g/d for the MLC group. Micronutrients were assessed against the Nutrient Reference Values (NRV) for pregnant women (27).

Body composition (RPAH only), including fat mass (%FM) and fat-free mass (%FFM), assessed using air displacement plethysmography (PEA POD®, COSMED) (28), infant birth weight, and mode of delivery were obtained from medical records. WHO growth charts (weight-for-gestational-age, gender-specific) and the Australian national birthweight percentiles (29) were used to determine small-for-gestational-age (SGA, <10th percentile) or large-for-gestational-age (LGA, >90th percentile) infants. Macrosomia was defined as birthweight >4000 g. Full term pregnancy was defined as ≥37 weeks of gestation. Participants and all personnel other than the research dietitian were blinded to allocation.

Additional exploratory outcomes

Pregnancy outcomes, including induction rates, insulin treatment and dosing, and infant outcomes such as length, head circumference (HC), HC percentiles, and ponderal index (obtained from medical records), were explored in the present study. HC percentiles were determined using CDC data and an Australian database (30, 31). Gestational weight gain (GWG) was calculated as the difference between the last measured weight before delivery and prepregnancy weight and compared with the 2009 Institute of Medicine (IOM) weight gain guidelines (32), specific for each BMI category.

Statistical analysis

MAMI 1 was designed to have 80% statistical power to detect 0.04 mmol/L difference in blood ketones with 25 participants in each arm based on previous data (33). Assuming a 25% drop-out rate, we aimed to enroll a total of 65 participants. The primary analysis (modified intention-to-treat) included all women who attended the first dietary education session and ≥1 other visit. The primary outcome was calculated as the marginal mean estimated by the linear mixed model (34), which explored the interaction between timepoints (5 level category) and diet (2 level category) and a random effect for patient identification (restricted maximum likelihood estimation). Secondary analyses included participants who completed the full protocol by providing the last set of 3-d food diaries and blood ketone/glucose charts. Descriptive data are presented as mean ± SEM for continuous variables and percentages for frequency variables (e.g., emergency cesarean delivery). Independent sample t-tests and Mann–Whitney U tests were used to assess differences in continuous variables. A general linear model was employed to assess the effect of the dietary intervention assignment on ketone and glucose concentrations. We also conducted a general linear model using univariate analysis to assess the relation between diet and HC, while adjusting for confounding variables including GWG, infant sex, and weeks of gestation at delivery. In a second-step analysis, insulin status (categorical, yes/no) at the end of the intervention period was included in the model to assess its effect on ketone and glucose concentrations. Pearson's chi-square test of independence was used to compare categorical data. Spearman correlation coefficients were used to assess the association between selected maternal variables and infant outcomes.

Results

Of the 297 women screened, 75 women were eligible and 46 were randomly assigned (29 withdrew before assignment) (**Figure 1**). We excluded an extreme outlier from further analysis in the control group due to nausea that persisted throughout her pregnancy, resulting in very low energy intake (>2 SD below the mean of the group). Age and prepregnancy BMI were similar in the 2 groups (**Table 1**). Baseline characteristics were comparable between women who completed the study versus those who withdrew (**Supplemental Table 1**). Based on the initial number randomized ($n = 46$), and exclusion of 1 extreme outlier (final $n = 45$), 67% ($n = 16$) of women in the MLC group completed the full study protocol versus 81% ($n = 17$) in the RC group ($P = 0.28$). The final sample size had 77% power to detect a 0.04 mmol/L difference in blood ketone concentrations.

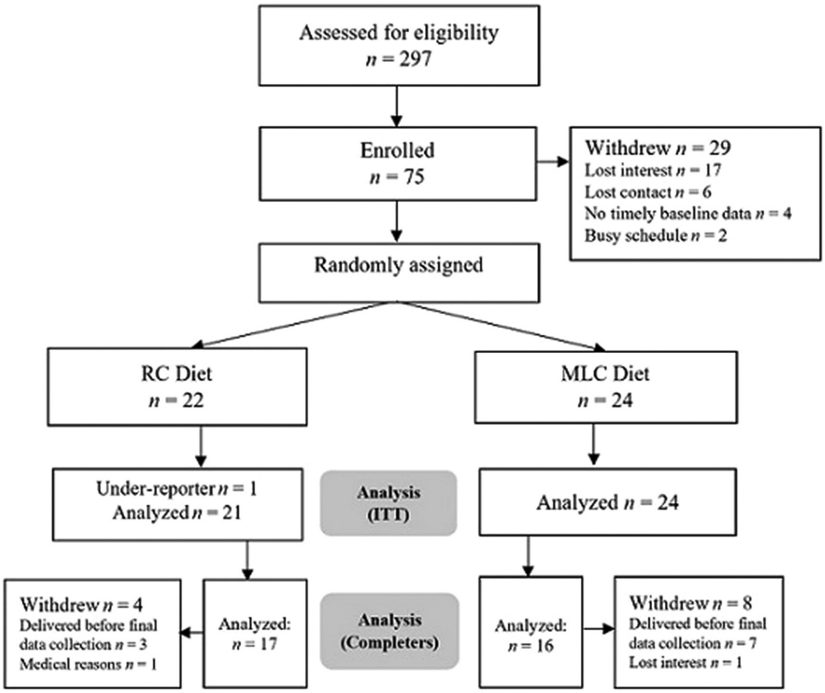

FIGURE 1 An amended CONSORT flow diagram depicting the progress of a 2-group parallel randomized trial, MAMI 1. CONSORT, Consolidated Standards of Reporting Trial; ITT, modified intention-to-treat; MAMI 1, macronutrient adjustments in mothers with gestational diabetes study 1; MLC, modestly lower carbohydrate (diet); RC, routine care (diet).

Nonetheless, we found no detectable differences in blood ketone concentrations between the dietary groups (MLC 0.1 ± 0.0 compared with RC 0.1 ± 0.0 mmol/L, $P = 0.31$) (**Table 2**). Dietary intake was comparable at baseline (**Table 3**), but a high proportion of women were already restricting their carbohydrate intake, i.e., consuming less than the recommended minimum of 175 g/d (71% in MLC compared with 57% in RC, $P = 0.34$). By the end of the study, completers in the intervention group reported lower carbohydrate intake (MLC compared with RC, respectively: 165 ± 7 compared with 190 ± 9 g/d, $P = 0.04$), lower protein (85 ± 4 compared with 103 ± 4 g/d, $P < 0.01$), and 9% lower overall energy intake (Table 3). Only 20% of participants in the MLC group met their carbohydrate target at the end of the intervention, compared with 65% in RC ($P < 0.01$). There were no differences in gestational age at delivery, birth weight, rate of LGA, macrosomia, %FM, or %FFM (**Table 4**). Adjusting for infant sex did not change the fat mass outcome ($P = 0.19$), although the final sample size was small ($n = 15$), partially due to body composition measurements not being collected in infants that were born overnight.

Additional exploratory analysis

Two critical dietary micronutrients, iron and iodine, were lower in the completers of the intervention compared with those having RC (iron: 8.7 ± 0.4 compared with 10.6 ± 0.4 mg/d, $P < 0.01$; iodine: 147 ± 11 compared with 196 ± 14 μg/d, $P < 0.01$). Only 32% of the women in the MLC group met the NRV for iron versus 67% for iodine, compared with 39% and 89%, respectively, in the RC group. We observed no difference in glycemia (MLC 6.1 ± 0.1 compared with RC 6.0 ± 0.1 mmol/L, $P = 0.31$, Table 2); insulin was prescribed to the majority of women in both groups and the dose of insulin was similar (MLC 14.6 ± 1.8 compared with RC 21.2 ± 3.9 units, $P = 0.13$, **Supplemental Table 2).**

Between the groups, ketonemia was not affected by exogenous insulin use ($P = 0.97$). Although exogenous insulin status at the end of the study showed a trend toward influencing the difference in the average daily glucose concentrations ($P = 0.06$), we found no difference in the final HbA1c concentrations ($P = 0.98$). Mean GWG was also comparable, although the lower carbohydrate diet group had a ~3-fold higher proportion of women meeting the IOM weight gain guidelines ($P = 0.10$, Table 4). Surprisingly, infants in the MLC group had a significantly smaller HC (33.9 ± 0.3 compared with 34.9 ± 0.3 cm, $P = 0.05$) (Table 4), which remained significant after adjustment for GWG, gestational age, and infant sex ($P = 0.04$).

Discussion

The present study suggests a need for larger, appropriately powered studies with food provision to determine the benefits and risks associated with recommending modestly lower carbohydrate intake in the management of GDM. We found that women assigned to the lower carbohydrate intervention had similar blood ketone concentration and glucose control to women assigned to routine dietary management. However, the lack of difference is potentially related to the difficulty in achieving a low-carbohydrate intake in pregnancy. Only 1 in 5 women in the intervention group met the target of only 135 g carbohydrates per day. Conversely, we also found that a high proportion (2 in 3 of all the women) had already adopted some degree of carbohydrate

TABLE 1 Baseline characteristics of MAMI 1 participants randomly assigned to MLC and RC diets

	n	MLC	*n*	RC
Age, y	24	32.5 ± 0.9	22	34.2 ± 0.9
Weeks of gestation at enrollment	24	28.4 ± 0.5	22	28.6 ± 0.6
Prepregnancy BMI, kg/m^2	24	25.8 ± 1.0	22	27.8 ± 1.5
Prepregnancy BMI category				
Underweight, *n* (%)	24	0 (0)	22	2 (9.0)
Normal, *n* (%)	24	12 (50.0)	22	8 (36.4)
Overweight, *n* (%)	24	8 (33.3)	22	6 (27.3)
Obese I, *n* (%)	24	2 (8.3)	22	4 (18.2)
≥ Obese II, *n* (%)	24	2 (8.3)	22	2 (9.0)
Ethnicity				
Asian, *n* (%)	24	13 (54.2)	22	16 (72.7)
East Asian, *n* (%)	24	1 (7.7)	22	5 (31.3)
South Asian, *n* (%)	24	9 (69.2)	22	4 (25.0)
Southeast Asian, *n* (%)	24	3 (23.1)	22	7 (43.7)
Caucasian, *n* (%)	24	11 (45.8)	22	7 (31.8)
Nulliparous, *n* (%)	24	14 (58.3)	22	10 (45.5)
Weeks at GDM diagnosis	24	20.2 ± 1.1	22	20.7 ± 1.2
75-g OGTT results				
Fasting, mmol/L	23	4.8 ± 0.1	21	4.7 ± 0.1
1 h, mmol/L	23	9.4 ± 0.3	20	10.1 ± 0.4
2 h, mmol/L	23	8.0 ± 0.4	20	8.3 ± 0.3
HbA1c, %	20	5.1 ± 0.1	20	5.0 ± 0.1
Education				
Secondary, *n* (%)	24	4 (16.7)	22	3 (13.6)
Tertiary, *n* (%)	24	10 (83.3)	22	19 (86.4)
Marital status				
Single, *n* (%)	24	1 (4.2)	22	1 (4.5)
Defacto, *n* (%)	24	1 (4.2)	22	6 (27.3)
Married, *n* (%)	24	22 (91.7)	22	15 (68.2)
Smoking history, *n* (%)	24	5 (20.8)	22	5 (22.7)
GDM history, *n* (%)	24	2 (8.3)	22	1 (4.5)
Family history				
T2DM, *n* (%)	24	18 (75.0)	22	15 (68.2)
HT, *n* (%)	24	18 (75.0)	22	13 (59.1)
Ow/Ob, *n* (%)	24	7 (29.2)	22	6 (27.3)
Insulin use at baseline, *n* (%)	24	6 (25.0)	22	7 (31.8)
Thyroid medication, *n* (%)	21	5 (25.0)	22	1 (4.5)
Metformin, *n* (%)	24	1 (4.2)	22	1 (4.5)
Aspirin, *n* (%)	24	1 (4.2)	22	1 (4.5)
Supplement use, *n* (%)	24	24 (100)	22	22 (100)
Pregnancy multivitamin, *n* (%)	24	24 (100)	22	22 (100)

Values presented as mean ± SEM or *n* (%). GDM, gestational diabetes mellitus; HbAc1, glycated hemoglobin; HT, hypertension; MAMI 1, macronutrient adjustments in mothers with gestational diabetes study 1; MLC, modestly lower carbohydrate (diet); OGTT, oral-glucose-tolerance test; Ow/Ob, overweight/obesity; RC, routine care (diet); T2DM, type 2 diabetes mellitus.

restriction at baseline. Taken together, our findings suggest that a modestly lower carbohydrate intervention in pregnancy (38–39% energy, 165 g/d) is not associated with clinically important levels of ketonemia.

In T2D and GDM, reducing carbohydrate intake is recommended on the assumption that this will improve glycemic control. However, in the present study, the MLC diet did not provide any additional benefit for glucose management, with the average glucose concentration and HbA1c being comparable in the 2 groups. This is in line with the findings of a recent systematic review of carbohydrate restriction in T2D, where HbA1c concentration was reduced with both moderate and high carbohydrate diets (35). In GDM specifically, Hernandez and colleagues concluded that higher carbohydrate intake (60% energy) can provide benefits for fasting glucose (8), insulin sensitivity, and inflammatory markers (36) when compared with low-carbohydrate intake (40% energy). However, the quality of carbohydrate may be critical. Using continuous glucose monitoring (CGM), Kizirian and colleagues (37) demonstrated a markedly lower blood glucose concentration and reduced glucose variability in GDM when carbohydrate intake was reduced from 50% to 40% of energy intake and low-GI foods were substituted for high-GI foods.

Ketonemia in pregnancy may be a sign of deliberate energy restriction or of low-carbohydrate intake per se without the restriction of total energy intake. In practice, it may be difficult to distinguish between the 2. In trials in women with GDM instructed to restrict energy by ≤33%, there was no evidence of ketogenesis (38). However, when energy restriction reached 50%, ketonuria increased by 2- to 3-fold. More modest carbohydrate

TABLE 2 Blood ketones and glucose control at baseline and end of study in women with GDM randomly assigned to MLC compared with RC

	Baseline					End of intervention				
	n	MLC	*n*	RC	*P*	*n*	MLC	*n*	RC	*P*
Ketone, mmol/L (average)	24	0.1 ± 0.0	21	0.2 ± 0.0	0.19	21	0.1 ± 0.0	19	0.1 ± 0.0	0.31
Fasting	24	0.1 ± 0.0	21	0.2 ± 0.0	0.01	14	0.1 ± 0.0	18	0.1 ± 0.0	0.18
Noon	24	0.2 ± 0.0	21	0.2 ± 0.0	0.24	15	0.1 ± 0.0	18	0.1 ± 0.0	0.77
Evening	24	0.1 ± 0.0	21	0.2 ± 0.0	0.24	13	0.1 ± 0.0	18	0.1 ± 0.0	0.75
HbA1c, %	20	5.1 ± 0.1	20	5.0 ± 0.1	0.52	16	5.1 ± 0.1	15	5.3 ± 0.1	0.21
Glucose,[1] mmol/L (average)	22	6.0 ± 0.1	17	6.2 ± 0.1	0.26	13	6.1 ± 0.1	15	6.0 ± 0.1	0.31
Fasting glucose, mmol/L	21	4.9 ± 0.1	17	5.0 ± 0.1	0.97	13	4.9 ± 0.1	16	4.9 ± 0.1	0.88
Postprandial glucose, mmol/L	22	6.4 ± 0.1	17	6.6 ± 0.2	0.39	13	6.5 ± 0.1	16	6.2 ± 0.1	0.17

GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; MLC, modestly lower carbohydrate (diet); RC, routine care (diet).
Values presented as mean ± SEM.
P values obtained from independent samples t-test.
[1]Average glucose concentration as the mean ± SEM of 4 finger prick tests per day, the first in the fasting state and then at 1 h (Royal Prince Alfred Hospital) or 2 h (Campbelltown Hospital) after each of the 3 main meals.

restriction (i.e., 150 g carbohydrate/d, comparable to that in MAMI 1) produces mixed findings. In obese women with GDM, Potter and colleagues reported a detectable rise in ketone concentration to ∼0.26 mmol/L (39). However, in other studies, only a small number of participants tested positive (6, 40). In the present study, carbohydrate intake in the intervention group was still 3-fold greater than the amount suggested to induce ketosis in a nonpregnant population (∼50 g) (21). However, it appeared that our MLC instructions inadvertently resulted in at least some energy restriction, a phenomenon also reported in short-term weight loss trials. Carbohydrate and energy restriction may, therefore, be common in pregnancy, particularly in GDM where both the scientific literature and social media have debated the benefits of low-carbohydrate intake.

TABLE 3 MAMI 1 maternal dietary intake at baseline and end of the intervention

				End of intervention					
	Baseline			Modified intention-to-treat[1]			Completers		
	MLC	RC	*P*	MLC	RC	*P*	MLC	RC	*P*
n	24	21		24	21		16	17	
Energy, kJ	7480 ± 320	7510 ± 370	0.95	7180 ± 350	8230 ± 340	0.03	7040 ± 240	8230 ± 320	< 0.01
Carbohydrate, g	167 ± 6	164 ± 12	0.86	166 ± 9	190 ± 9	0.05	165 ± 7	190 ± 9	0.04
Sugars, g	62 ± 4	61 ± 5	0.80	65 ± 5	79 ± 5	0.07	65 ± 4	78 ± 5	0.08
Starch, g	104 ± 4	102 ± 9	0.84	100 ± 7	109 ± 7	0.33	99 ± 7	110 ± 7	0.25
Dietary fiber, g	25 ± 1	24 ± 1	0.81	24 ± 2	26 ± 2	0.34	24 ± 1	26 ± 2	0.26
Protein, g	100 ± 6	99 ± 5	0.88	87 ± 6	105 ± 6	0.04	85 ± 4	103 ± 4	< 0.01
Total fat, g	74 ± 5	77 ± 6	0.73	73 ± 6	81 ± 6	0.35	71 ± 5	82 ± 5	0.14
Saturated, g	24 ± 2	27 ± 2	0.73	25 ± 2	29 ± 2	0.20	24 ± 2	29 ± 2	0.11
Long chain FA–3, g	0.6 ± 0.2	0.5 ± 0.1	0.68	0.4 ± 0.2	0.4 ± 0.2	0.90	0.4 ± 0.1	0.4 ± 0.1	0.26
Carbohydrate, %EI	38 ± 1	36 ± 2	0.53	38 ± 2	38 ± 2	0.91	39 ± 2	38 ± 1	0.61
Protein, %EI	23 ± 0.8	23 ± 0.9	0.96	21 ± 1	22 ± 1	0.44	21 ± 1	21 ± 1	0.33
Total fat, %EI	36 ± 1	37 ± 2	0.51	37 ± 2	36 ± 2	0.69	37 ± 2	37 ± 1	1.00
MUFA, %total fat	45 ± 1	45 ± 2	0.99	46 ± 1	44 ± 1	0.33	46 ± 1	44 ± 1	0.24
PUFA, %total fat	19 ± 1	18 ± 1	0.77	17 ± 1	17 ± 1	0.96	17 ± 1	17 ± 1	0.84
SFA, %total fat	36 ± 1	36 ± 1	0.85	37 ± 2	39 ± 2	0.44	37 ± 1	39 ± 1	0.29
SFA, %EI	12 ± 1	12 ± 1	0.62	13 ± 1	13 ± 1	0.79	12.3 ± 0.7	13.0 ± 0.6	0.49
GI	54 ± 1	52 ± 1	0.34	52 ± 1	51 ± 1	0.60	53 ± 1	51 ± 1	0.31
GL	92 ± 3	88 ± 7	0.62	88 ± 5	99 ± 5	0.11	87 ± 4	98 ± 6	0.14
Iron, mg	10 ± 1	11 ± 1	0.58	8.9 ± 0.6	10.7 ± 0.6	0.04	8.7 ± 0.4	10.6 ± 0.4	< 0.01
Iodine, μg	161 ± 11	144 ± 10	0.26	147 ± 14	195 ± 14	0.02	147 ± 11	196 ± 14	< 0.01
Total folate, μg	490 ± 40	440 ± 30	0.51	455 ± 36	487 ± 35	0.41	451 ± 25	488 ± 31	0.37

EI, energy intake; FA, fatty acid; GI, glycemic index; GL, glycemic load; MAMI 1, macronutrient adjustments in mothers with gestational diabetes study 1; MLC, modestly lower carbohydrate (diet); RC, routine care (diet).
[1]The data in the modified intention-to-treat analysis is the mean ± SEM of all the dietary data collected during the intervention, irrespective of whether the participant completed the full protocol (or not), as estimated by the linear mixed model. The completers are only those participants who completed the full protocol.
Independent samples t-test; Mann–Whitney tests were also performed, where appropriate.
Values presented as mean ± SEM.

TABLE 4 Pregnancy and infant outcomes in MAMI 1 participants with GDM randomly assigned to MLC and RC

	n	MLC	*n*	RC	*P*
Pregnancy outcomes					
Total weight gain, kg	24	10.9 ± 0.9	21	8.2 ± 1.5	0.21
Meeting target vs. not meeting weight gain target					
Below target,[1] *n* (%)	24	10 (41.7)	21	12 (57.1)	0.19†
Within target,[1] *n* (%)	24	10 (41.7)	21	3 (14.3)	0.10†
Above target,[1] *n* (%)	24	4 (16.7)	21	6 (28.6)	0.81†
Gestational age, wk	24	38.7 ± 0.2	21	38.6 ± 0.2	0.97
Mode of delivery					
Vaginal vs. cesarean	24		21		0.20†
Vaginal delivery, *n* (%)	24	17 (70.8)	21	11 (52.4)	
Normal, *n* (% vaginal)	24	15 (88.2)	21	8 (72.7)	0.10†
Vacuum extraction, *n* (% vaginal)	24	1 (5.9)	21	2 (18.2)	0.47†
Forceps-liftout, *n* (% vaginal)	24	1 (5.9)	21	1 (9.1)	0.92†
Elective cesarean, *n* (%)	24	3 (12.5)	21	8 (38.1)	< 0.05†
Emergency cesarean, *n* (%)	24	4 (16.7)	21	2 (9.5)	0.48†
Infant outcomes					
Sex	23		19		0.98†
Male, *n* (%)	23	12 (52.2)	19	11 (57.9)	
Female, *n* (%)	23	11 (47.8)	19	8 (42.1)	
Birthweight, g	24	3125 ± 101	20	3278 ± 79	0.25
Within vs. outside normal range	24		20		0.41†
SGA, *n* (%)	24	6 (25.0)	20	3 (14.3)	0.25†
LGA, *n* (%)	24	0 (0)	20	1 (4.8)	0.28†
Macrosomia, *n* (%)	24	1 (4.2)	20	1 (4.8)	0.55†
Fat mass, %	7	7.2 ± 2.2	8	10.1 ± 1.0	0.23
Fat-free mass, %	7	92.8 ± 2.2	8	89.9 ± 1.0	0.23

LGA, large-for-gestational age; MAMI 1, macronutrient adjustments in mothers with gestational diabetes study 1; MLC, modestly lower carbohydrate (diet); PI, ponderal index; RC, routine care (diet); SGA, small-for-gestational age. *P* value obtained from independent samples t-test; †Pearson's chi-square test of independence.

Values presented as mean ± SEM.

[1]Institute of Medicine gestational weight gain criteria.

Energy restriction in overweight and obese pregnancies is usually recommended to restrict maternal weight gain and reduce the incidence of macrosomia (41). Nonetheless, concerns over safety have been raised (42). In the present study, despite all women having received dietetic counseling, those on the MLC diet had significantly lower dietary intakes of 2 critical micronutrients, iron and iodine. Furthermore, many women in both groups failed to meet the NRVs (35% in the case of iron and 80% for iodine). Although pregnancy multivitamins are recommended, this advice may not always be followed. In future studies, assessment of biomarkers of these micronutrients is warranted.

Despite the observed lower energy intake in the intervention group, we were unable to detect any differences in pregnancy outcomes such as birth weight, LGA rates, and infant %FM. This was surprising as some studies have reported that higher dietary GI and higher carbohydrate intake during the third trimester of pregnancy were associated with a lower %FFM and %FM index, respectively (43). Other studies have reported that female infants often have higher %FM at birth when compared with males (44, 45). However, the lack of difference in values in the present study could be related to small sample size, especially the body fatness measurements ($n = 15$).

Our study has strengths and limitations. We stratified participants according to BMI and age. Diet allocation was concealed, and the 2 treatment groups were comparable in baseline characteristics, including diet. Both groups received the same treatment intensity, all women having 3–4 visits with the dietitian. However, the target carbohydrate intake of only 135 g/d was difficult to achieve. An important constraint was the precision of the ketone meter which was unable to distinguish between differences <0.1 mM. At present, small changes in ketonuria and ketonemia are not considered clinically important, although evidence is lacking (46). Although exogenous insulin is likely to suppress ketone formation, in the context of the present study, this may not be relevant. On the other hand, insulin status appeared to influence the average daily glucose concentrations and may, therefore, be a more relevant factor in glucose metabolism. Caution should be applied when interpreting blood glucose concentrations obtained from finger prick glucose handheld monitors, as the readings can be affected by a number of factors including inappropriate storage and usage of test strips and interaction of medications (47).

In summary, a modest reduction in carbohydrate and overall energy intake did not result in greater blood ketone concentration or improved glucose control. However, the lower carbohydrate dietary target was not achieved, despite lower overall energy intake. Future studies should consider provision of all carbohydrate foods to increase dietary compliance.

We thank the hospital staff at the Royal Prince Alfred and Campbelltown Hospitals. We are grateful to David Simmons who facilitated recruitment at Campbelltown, Alistair Senior for his guidance on statistical analysis, and

Roslyn Muirhead and Shannon Brodie for their assistance with the coding of dietary data.

The authors' contributions were as follows—JM: conducted the studies, analyzed the data, and wrote the manuscript as part of her doctorate thesis; JCYL, JB-M, and GPR: conceived the study; GPR and TM: were responsible for clinical management; MB: contributed to statistical analyses; all authors: interpretation of the data and drafting of the manuscript; and all authors: read and approved the final manuscript. The authors declare no conflicts of interest. JB-M is the President of the nonprofit Glycemic Index Foundation and oversees a glycemic index testing service at the University of Sydney. She is the coauthor of The Low GI Diet (DeCapo Press) and other books on healthy eating.

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