Association of Pre-pregnancy low-carbohydrate diet with maternal oral glucose tolerance test levels in Gestational Diabetes

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Research Article

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Abstract

Background

Limited evidence exists on the correlation between the pre-pregnancy low-carbohydrate (LC) diet and maternal oral glucose tolerance test (OGTT) levels during pregnancy. Our aim was to compare the differences in maternal OGTT levels among women who had been diagnosed with gestational diabetes mellitus (GDM) during pregnancy and adopted different dietary patterns in the pre-pregnancy period.

Methods

This was a case-control study in 20 GDM women with LC diet during pre-conception (LC/GDM), using 80 GDM women with conventional diet (Con/GDM) and 80 women with conventional diet but without GDM as reference (Con/Healthy), respectively. Potential risk factors of GDM were controlled. We used unadjusted raw data to compare the dietary composition data and biomarkers of the three study groups.

Results

Compared with the Con/GDM group, the OGTT-1h and OGTT-2h values in LC/GDM group were significantly higher (10.36 ± 1.28 mmol/L vs. 9.75 ± 0.98 mmol/L; 9.12 ± 0.98 mmol/L vs. 8.29 ± 1.06 mmol/L). Furthermore, 40% of the LC/GDM group participants had abnormal values in both OGTT-1h and OGTT-2h, significantly higher than 16.3% of the Con/GDM group.

Conclusions

We observed a relationship between the pre-pregnancy LC diet and more detrimental OGTT values in patients with GDM. This finding warrants further studies to understand the effect of pre-pregnancy LC diet behavior on maternal glucose tolerance.

Introduction

Gestational diabetes mellitus (GDM), characterized by glucose intolerance first diagnosed during pregnancy, is one of the most common maternal complications[1]. In China, a recent systematic review and meta-analysis including 79,064 participants showed a total incidence of 14.8%, while the Shanghai Birth Cohort found 14.2% (585 women) with GDM [2,3]. Epidemiologic data have shown that GDM is associated with both short- and long-term adverse health consequences for the mother and the offspring [4]. Risk factors of developing GDM include those with advanced maternal age, pre-pregnancy overweight/obesity, family history of diabetes, and excessive weight gain during pregnancy[5]. Poor dietary behaviors before and during pregnancy, such as excessive consumption of sugary drinks and higher intake of animal fat and cholesterol, were also associated with an increased risk of GDM [6].

Low-carbohydrate (LC) diet, a dietary pattern with carbohydrate restriction, is a popular approach in weight loss and glucose control[7]. It was originated from the Ketogenic Diet used as a treatment for epilepsy proposed by the Mayo Clinic in 1921 [8,9]. Due to the difficulty of implementing very low carbohydrate intake for a long time, currently the limits for daily carbohydrate intake on LC diet range from 20 to 130g[10]. In 2014, Bao et al. found that, compared with the highest pre-pregnancy carbohydrate intake group, the lowest pre-pregnancy carbohydrate intake group had a 27% higher risk of GDM (relative risk [RR] = 1.27, 95% CI: 1.06, 1.51) [11].The Australian Longitudinal Study on Women's Health's results also suggested that relatively LC diet and high fat intakes may increase the risk of GDM [12]. However, the above studies compared the differences between the lowest (lowest quintile of carbohydrate score) and highest (highest quintile of carbohydrate score) carbohydrate intake groups based on the LC-diet scores rather than by absolute intakes of carbohydrate, fat, and protein; the lowest carbohydrate intakes (of 178 g/d and 162 g/d, respectively) did not meet the strictly defined LC diet (< 130 g/d); In addition, the detailed glucose levels were not reported. Despite the increasing popularity of strictly LC diets for weight loss in women of childbearing age, little is known about their effects on maternal blood glucose levels.

The purpose of this case-control study was to evaluate the differences in OGTT levels between GDM patients on an LC diet (LC/GDM) and GDM on a conventional diet (Con/GDM) during pre-conception, and healthy pregnant women on a conventional diet (Con/Healthy) for healthy control.

Methods

Study design and participants

This case-control study included the LC/GDM, Con/GDM, and Con/Healthy groups. Participants were classified into LC/GDM group if they were diagnosed as GDM at 24–28 gestational weeks and went on an initiative limit-carbohydrate diet (carbohydrate intake <130 g/d) for weight management before pregnancy for at least 12 months. Participants, diagnosed as GDM at 24–28 gestational weeks and having an conventional diet (carbohydrate intake >130 g/d) before pregnancy , were classified into Con/GDM group. The Con/Healthy group included healthy women on a conventional diet (carbohydrate intake >130 g/d). The two control groups (Con/GDM and Con/Healthy) were matched to the LC/GDM group by 1:4 for age, pre-pregnancy BMI (underweight, normal, overweight, obese), parity and family history of diabetes, and they were enrolled in the nutrition clinic and obestetrical clinic, respectively. All participants were recruited at the clinic in the International Peace Maternity and Child Health Hospital (**Figure 1** Patient workflow).

Subjects with the following criteria were excluded: 1) those with religious dietary restrictions or dietary intervention for other; 2) those diagnosed with type 2 diabetes mellitus (T2DM) before pregnancy ;3) those with history of polycystic ovary syndrome, unexplained recurrent spontaneous abortion, and other digestive tract disease, liver disease, and kidney disease.

Eventually, 20 participants were included in the LC/GDM group. 80 participants were included in the Con/GDM and Con/Healthy, respectively. After diagnosed as GDM, the LC/GDM and Con/GDM groups received medical nutritional treatment according to the diabetes medical treatment guidelines[13]. No intervention was performed in the Con/Healthy group.

The case-control study was conducted at Shanghai International Peace Maternity and Child Health Hospital (IPMCH) between January 2019 and January 2020. All participants were local residents of Shanghai, and had completed pregnancy diagnosis and treatment records. Cut-off points of BMI were adopted based on the Chinese population standards[14].

Written informed consent was obtained from all participants. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involing human subjects/patients were approved by the Institutional Review Board of the International Peace Maternity and Child Health Hospital (IPMCH) affiliated with the School of Medicine, Shanghai Jiao Tong University (GKLW2018-35).

Diagnosis of GDM

GDM was diagnosed by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria between 24 and 28 weeks of gestation. A one-step approach using 75-g OGTT was performed after at least an 8-h fast (cutoff values: fasting ≥5.1 mmol/L; 1 h ≥10.0 mmol; 2 h ≥8.5 mmol/L). GDM was defined as one or more abnormal OGTT values [15].

Dietary Assessment

Information on habitual dietary intake before pregnancy was collected through a 24-h dietary recall about the average intake of major foods or food groups. Participants were also invited to complete a 24-h dietary recalls between 24 and 28 weeks of gestation. If a participant reported during a 24-h recall that she did not eat or drink normally the day before (e.g., because of fasting, illness, or other reasons), dietary data from that 24-h recall will be performed at another visit.

Trained dietitians administered the interview, using food models to access the food intake. The interview was conducted between 24 and 28 weeks of gestation. The intakes of energy and macronutrients were calculated by nutrient calculation software ZHEN DIN *2.0*.

Clinical examinations

All participants underwent standard clinical care which included biomedical blood tests. Fasting blood glucose, serum glycated haemoglobin (HbA1c) and lipid profiles [total cholesterol (TC), triacylglycerol (TG), high density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC)]were measured in the first trimester of pregnancy (10-12 weeks of gestation). Serum HbA1c, glycated albumin (GA) and levels of OGTT test were performed between 24-28 gestational weeks. All the blood samples were detected with Cobas 8000 modular analyzer series. The detection of ketones in the urine was performed through Sysmex UC-3500 urine chemistry analyzer.

Anthropometric measurements

The participants were weighed barefoot using a standardized digital height and weight scale calibrated to 0.1 kg (SECA-285). After resting for 5 min, an automated system (OMRON-HEM-1020) was used to measure the blood pressure once. Weighing and blood pressure measurements were performed during every routine check-up.

Statistical analysis

Given the exploratory nature of this study (the sample size of women with a strict LC diet was limited), we did not conduct a priori sample size estimation. We only used unadjusted data to compare the dietary composition data and biomarkers of the three study groups because we have matched the potential confounders in different groups. One-way analysis of variance was used to analyze difference in continuous variables, and pairwise comparisons between the three groups were performed using Tukey's studentized range test. Continuous variables were showed as means and SD. Chi-square test was used to analyze difference in categorical variables, and pairwise comparisons were performed using Bonferroni test. Statistical analysis was performed using SPSS statistical software, version 23. P values < 0.05 was considered statistically significant.

Results

Characteristics of the participants

The main characteristics of the study groupsparticipants were presented in Table 1. As expected, all study participants were comparable in terms of age, parity, educational level, pre-pregnancy BMI, and family history of diabetes. There was no significant difference between the weight gains during pregnancy in the three groups in the first trimester. In the second trimester, the LC/GDM group had the lowest weight gain (5.72 kg) followed by the Con/GDM group (7.01 kg); the Con/Healthy group gained the most weight (8.33 kg). There was no difference in weight gain among women in the LC/GDM and Con/GDM groups in the third trimester, while the gestational weight gain in GDM groups were significantly lower than that in the Con/Healthy group ($P < 0.001$). No other significant differences were observed, including infant birth weight and macrosomia rate.

Table 1
Characteristics of the study population

	LC/GDM (N = 20)	Con/GDM (N = 80)	Con/Healthy (N = 80)	*P*-value
Maternal characteristics				
Maternal age(years)				
Mean (SD)	31.35 ± 3.98	30.09 ± 3.38	31.06 ± 3.59	0.147
N (%)				1.000
≤35	19 (95)	76 (95)	76 (95)	
>35	1 (5)	4(5)	4 (5)	
Parity, n (%)				1.000
Nulliparous	18 (90)	72 (90)	72 (90)	
Multiparous	2 (10)	8 (10)	8 (10)	
Education, n (%)				0.595
High school and lower	3 (15)	15 (18.75)	19 (23.75)	
College and above	17 (85)	65 (81.25)	61 (76.25)	
Pre-pregnancy BMI (kg/m^2)				
Mean (SD)	19.12 ± 2.00	19.65 ± 2.32	19.53 ± 2.30	0.647
n (%)				1.000
<18.5	10 (50)	40 (50)	40 (50)	
18.5–23.9	9 (45)	36 (45)	36 (45)	
≥24	1 (5)	4 (5)	4 (5)	
Race, n (%)				1.000
Han	20 (100)	78 (97.5)	77 (96.25)	
Non-Han	0 (0)	2 (2.5)	3 (3.75)	
Blood pressure				
Systolic (mmHg)	107.8 ± 16.65	112.7 ± 11.1	109.2 ± 11.5	0.102
Diastolic (mmHg)	69.6 ± 12.9	70.6 ± 11.1	70.2 ± 10.0	0.923
Family history of diabetes, n (%)				1.000
NO	18 (90)	72 (90)	72 (90)	

	LC/GDM (N = 20)	Con/GDM (N = 80)	Con/Healthy (N = 80)	*P*-value
Yes	2 (10)	8 (10)	8 (10)	
Lipid profile				
TG (mmol/L)	1.28 ± 0.79	1.32 ± 0.50	1.21 ± 0.44	0.345
TC (mmol/L)	4.31 ± 0.94	4.57 ± 0.71[1]	4.19 ± 0.82	0.009
LDLC (mmol/L)	2.45 ± 0.81	2.46 ± 0.65	2.23 ± 0.75	0.104
HDLC (mmol/L)	2.19 ± 0.49	2.08 ± 0.49	1.99 ± 0.44	0.182
Gestational weight gain				
1st trimester	1.95 ± 2.72	2.18 ± 2.60	1.92 ± 2.32	0.798
2nd trimester	5.72 ± 2.08[2]	7.01 ± 2.41[1]	8.33 ± 2.56[3]	< 0.001
3rd trimester	3.11 ± 1.75	3.31 ± 2.30[1]	5.26 ± 2.54[3]	< 0.001
Total weight gain	10.77 ± 3.93	12.50 ± 4.42[1]	15.51 ± 4.45[3]	< 0.001
Preeclampsia, n (%)				0.792
No	19 (95)	78 (97.5)	78 (97.5)	
Yes	1 (5)	2 (2.5)	2 (2.5)	
Thyroid dysfunction				0.904
No	19 (95)	75 (93.75)	74 (92.5)	
Yes	1 (5)	5 (6.25)	6 (7.5)	
Mode of delivery				0.102
Vaginal birth	6 (30)	47 (58.75)	42 (52.5)	
Cesarean section	14 (70)	33 (41.25)	38 (47.5)	
Child characteristics				
Gestational age (weeks)	39.1 ± 0.7	39.2 ± 1.6	39.7 ± 1.6	0.072
Birth weight (g)	3113.4 ± 289.5	3193.7 ± 493.4	3267.9 ± 471.3	0.354
LGA, n (%)	0 (0)	4 (5)	5 (6.25)	0.534
SGA, n (%)	0 (0)	2 (2.5)	1 (1.25)	0.690

[1]The value for the Con/GDM group is significantly different from the value for the Con/Healthy group (P < 0.05).

	LC/GDM (N = 20)	Con/GDM (N = 80)	Con/Healthy (N = 80)	*P*-value
[2]The value for the LC/GDM group is significantly different from the value for the Con/GDM group (P < 0.05).				
[3]The value for the LC/GDM group is significantly different from the value for the Con/Healthy group (P < 0.05).				
LC, low carbohydrate diet; GDM, gestational diabetes mellitus; Con, conventional diet; SD, standard deviation; TG, triglyceride; TC, total cholesterol; LDLC, low-density lipoprotein-cholesterol; HDLC, high-density lipoprotein-cholesterol; LGA, Large-for gestational age; SGA, small-for gestational age				

Ditary Intake

Table 2 shows the dietary intake data of the study groups before pregnancy and at the second trimester of pregnancy. The LC/GDM group had the lowest intake of carbohydrates (95.3 g/d; energy supply ratio, 33.4%) compared to the other two groups before pregnancy, with minimum and maximum intakes of 52.8 g/d and 126.6 g/d, respectively, which met the LC intake standard of < 130 g/d. All study groups showed increased carbohydrate intake during the second trimester. The intake in the LC/GDM and Con/GDM groups increased by an average of 64.4 g and 31.3 g, respectively. Although the LC/GDM group had the highest increase in carbohydrate intake, that in the second trimester was still lower than that in the other two groups (P < 0.001), and six (30%) participants in the LC/GDM group still followed an LC diet in the second trimester.

In the pre-pregnancy period, the protein intake level (58.1 g/d) of the LC/GDM group was lower than that of the Con/GDM group (69.9 g/d). The protein energy supply ratio of the LC/GDM group was 21%, which was higher than the 17.6% of the Con/GDM group in the pre-pregnancy period. There was no difference in the total fat intake among the three groups during the pre-pregnancy period (P = 0.729), but the fat energy supply ratio of the LC/GDM group was significantly higher than that of the Con/GDM and Con/Healthy groups (P < 0.001). The total energy intake before pregnancy in the LC/GDM group was 1078.5 kcal/d, which was much lower than the 1585.5 kcal/d in the Con/GDM group (P < 0.001) and 1532.5 kcal/d (P < 0.001) in the Con/Healthy group. The increase in energy intake of the three groups, during the second trimester, was highest in the Con/Healthy group (366.7 kcal) compared to the LC/GDM (297 kcal) and Con/GDM (241.4 kcal) groups.

The dietary patterns of the Con/GDM and Con/Healthy groups were similar before and during pregnancy in terms of the energy and macronutrient intakes and ratio, which were consistent with the recommended range of the Chinese food pagoda [16]. Compared with the Con/GDM and Con/Healthy groups, the LC/GDM group followed a typical LC diet before pregnancy.

Table 2

Changes in dietary intake pre-pregnancy and during the second trimester of pregnancy according to the diet group, with or without gestational diabetes mellitus

	LC/GDM (N = 20)	**Con/GDM (N = 80)**	**Con/Healthy (N = 80)**	***P*-value**
Variable				
Energy (kcal/d)				
Pre-pregnancy	1078.5 ± 209.0[1]	1585.5 ± 254.2	1532.5 ± 285.3[3]	< 0.001
2nd trimester of pregnancy	1375.6 ± 192.9[1]	1826.9 ± 268.3	1899.2 ± 364.0[3]	< 0.001
Carbohydrate				
Dietary Intake < 130g/d				
Pre-pregnancy n (%)	20(100)[1]	0(0)	0(0)[3]	< 0.001
2nd trimester of pregnancy n (%)	6(30)[1]	0(0)	0(0)[3]	< 0.001
Dietary Intake (g/d)				
Pre-pregnancy [mean (SD)]	95.3 ± 20.2[1]	213.1 ± 46.8	204.2 ± 40.9[3]	< 0.001
Pre-pregnancy [Median (min, max)]	97.1 (52.80,126.60)[1]	206 (132.70,334.10)	200.4 (133,325.30)[3]	
2nd trimester of pregnancy [mean (SD)]	159.7 ± 45.2[1]	244.4 ± 50.8	242.9 ± 56.7[3]	< 0.001
2nd trimester of pregnancy [Median (min, max)]	179.55 (74.80,233.20)[1]	243.45 (141.50,360.20)	237.45 (143.70,436.00)[3]	
Dietary Intake (% of energy)				

[1]The value for the LC/GDM group is significantly different from the value for the Con/GDM group ($P < 0.05$).

[2]The value for the Con/GDM group is significantly different from the value for the Con/Healthy group ($P < 0.05$).

[3]The value for the LC/GDM group is significantly different from the value for the Con/Healthy group ($P < 0.05$).

	LC/GDM (N = 20)	Con/GDM (N = 80)	Con/Healthy (N = 80)	*P*-value
Pre-pregnancy	33.4 ± 8.6[1]	52.0 ± 7.6	51.9 ± 7.3[3]	< 0.001
2nd trimester of pregnancy	43.5 ± 11.2[1]	51.8 ± 7.3	49.4 ± 7.1[3]	< 0.001
Protein				
Dietary Intake (g/d)				
Pre-pregnancy	58.1 ± 22.0[1]	69.9 ± 17.5	68.2 ± 19.2[3]	0.043
2nd trimester of pregnancy	70.2 ± 19.9[1]	79.9 ± 17.6	84.8 ± 19.9[3]	0.008
Dietary Intake (% of energy)				
Pre-pregnancy	21.0 ± 4.9[1]	17.6 ± 3.4	17.7 ± 3.3[3]	< 0.001
2nd trimester of pregnancy	20.6 ± 6.1[1]	17.5 ± 2.9	17.9 ± 2.7[3]	0.001
Animal Protein				
Dietary Intake (g/d)				
Pre-pregnancy	43.71 ± 21.53	37.98 ± 15.59	40.05 ± 16.87	0.375
2nd trimester of pregnancy	47.75 ± 23.92	45.44 ± 14.82	49.48 ± 17.05	0.325
Dietary Intake (% of energy)				
Pre-pregnancy	15.6 ± 5.4[1]	9.67 ± 3.85	10.34 ± 3.69[3]	< 0.001
2nd trimester of pregnancy	14.06 ± 7.41[1]	9.98 ± 3.03	10.5 ± 3.03[3]	< 0.001
Fat				
Dietary Intake (g/d)				
Pre-pregnancy	55.2 ± 15.8	53.5 ± 13.6	52.3 ± 16.2	0.729

[1]The value for the LC/GDM group is significantly different from the value for the Con/GDM group ($P < 0.05$).

[2]The value for the Con/GDM group is significantly different from the value for the Con/Healthy group ($P < 0.05$).

[3]The value for the LC/GDM group is significantly different from the value for the Con/Healthy group ($P < 0.05$).

	LC/GDM (N = 20)	Con/GDM (N = 80)	Con/Healthy (N = 80)	*P*-value
2nd trimester of pregnancy	55.0 ± 13.2	62.1 ± 15.8	69.3 ± 22.4[3]	0.004
Dietary Intake (% of energy)				
Pre-pregnancy	45.6 ± 6.4[1]	30.4 ± 5.9	30.4 ± 6.3[3]	< 0.001
2nd trimester of pregnancy	35.9 ± 7.3[1]	30.7 ± 6.5	32.6 ± 7.0	0.007
Animal Fat				
Dietary Intake (g/d)				
Pre-pregnancy	19.65 ± 9.93	22.02 ± 10.68	21.97 ± 10.49	0.643
2nd trimester of pregnancy	19.23 ± 8.53[1]	27.69 ± 12.7	32.27 ± 18.36[3]	0.002
Dietary Intake (% of energy)				
Pre-pregnancy	16.11 ± 7.19[1]	12.61 ± 6	12.61 ± 4.82[3]	0.035
2nd trimester of pregnancy	12.67 ± 5.57	13.73 ± 6.06	15.07 ± 6.73	0.211
Fiber				
Dietary Intake (g/d)				
Pre-pregnancy	9.7 ± 4.3	11.0 ± 4.0	10.6 ± 4.2	0.436
2nd trimester of pregnancy	12.5 ± 3.9	11.6 ± 4.1[2]	14.1 ± 8.4	0.049
Cholesterol				
Dietary Intake (mg/d)				
Pre-pregnancy	413.8 ± 209.9	463.1 ± 232.5	478.8 ± 245.9	0.545
2nd trimester of pregnancy	449.2 ± 266.8	521.5 ± 269.1	575.4 ± 217.8[3]	0.095
[1]The value for the LC/GDM group is significantly different from the value for the Con/GDM group (P < 0.05).				
[2]The value for the Con/GDM group is significantly different from the value for the Con/Healthy group (P < 0.05).				
[3]The value for the LC/GDM group is significantly different from the value for the Con/Healthy group (P < 0.05).				

LC, low carbohydrate diet; GDM, gestational diabetes mellitus; Con, conventional diet; SD, standard deviat

Fasting plasma glucose and OGTT

Compared with women in the Con/GDM group, those in the LC/GDM group had a lower HbA1c level in the first trimester (5.14% vs. 5.32%,$P < 0.05$). Compared with the first trimester, the fasting blood glucose level of the three groups in the second trimester showed a downward trend (Table 3).

For comparing the blood glucose levels among the three groups at the three OGTT timepoints (OGTT-0h, OGTT-1h, and OGTT-2h), the OGTT-0h blood glucose levels in the LC/GDM and Con/GDM groups were not significantly different. However, those at OGTT-1h and OGTT-2h in the LC/GDM group were significantly higher than those in the Con/GDM group. The area under the blood glucose curve was also significantly higher than that of the Con/GDM group ($P < 0.001$) (Table 3, Fig. 2). In addition, compared with the Con/GDM group, the ratio of abnormal values in both OGTT-1h and OGTT-2h in the LC/GDM group was significantly higher (LC/GDM: 40.0% ; Con/Healthy: 16.3%). In the first and second trimesters, the HbA1c levels in the LC/GDM and Con/GDM groups were the lowest and highest, respectively, among the three groups. There was no significant difference in HbA1c levels between the LC/GDM and Con/GDM groups in the second trimester. However, in the second trimester, glycated albumin (GA) of the LC/GDM group was significantly lower than that of the Con/GDM group ($P < 0.001$).

There was no significant difference in the rate of positive urine ketone bodies among the three groups in the first trimesters. In the second trimesters, the rate in the LC/GDM greatly increased, which was significantly higher than that in the Con/GDM and Con/Healthy groups ($P < 0.001$). In the third pregnancy, the positive rate of positive urine ketone bodies in LC/GDM group decreased to 5%.

Table 3
Changes in biomarkers according to the diet group, with or without gestational diabetes mellitus

	LC/GDM (N = 20)	**Con/GDM** (N = 80)	**Con/Healthy** (N = 80)	***P*-value**
Variable				
1st trimester of pregnancy				
FBG (mmol/L)	4.41 ± 0.43	4.50 ± 0.35	4.57 ± 0.33	0.165
HbA1c (%) (mmol/mol)	5.14 ± 0.46 (33)[1]	5.32 ± 0.27 (35)[2]	5.19 ± 0.32 (33)	0.011
2nd trimester of pregnancy				
OGTT				
Fasting (mmol/L)	4.15 ± 0.45	4.19 ± 0.48	4.11 ± 0.33	0.411
1h (mmol/L)	10.36 ± 1.28[1]	9.75 ± 0.98[2]	7.15 ± 1.16[3]	< 0.001
2h (mmol/L)	9.12 ± 0.98[1]	8.29 ± 1.06[2]	6.19 ± 1.01[3]	< 0.001
Abnormal values, type				
Fasting (≥ 5.1 mmol/L [92 mg/dL]) (n, %)	1 (5)	5 (6.25)	0 (0)	0.064
1h (≥ 10.0mmol/L [180 mg/dL) (n, %)	14 (70)	43 (53.75)[2]	0 (0)[3]	< 0.001
2h (≥ 8.5mmol/L [153 mg/dL) (n, %)	14 (70)	49 (61.25)[2]	0 (0)[3]	< 0.001
Abnormal values, n				
1	11 (55)[1]	64 (80) [2]	0 (0)[3]	< 0.001

[1]The value for the LC/GDM group is significantly different from the value for the Con/GDM group (P < 0.05).

[2]The value for the Con/GDM group is significantly different from the value for the Con/Healthy group (P < 0.05).

[3]The value for the LC/GDM group is significantly different from the value for the Con/Healthy group (P < 0.05).

LC, low carbohydrate diet; GDM, gestational diabetes; Con, conventional diet; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test; AUC, area under the blood glucose curve; GA, glycated albumin

	LC/GDM (N = 20)	Con/GDM (N = 80)	Con/Healthy (N = 80)	P-value
≧ 2	9 (45)[1]	16 (20) [2]	0 (0)[3]	< 0.001
H-1h-2h (n, %)	8 (40)[1]	13 (16.25) [2]	0 (0)[3]	< 0.001
AUC [mmol/(L˙h)]	17.00 ± 1.13[1]	15.99 ± 0.92[2]	12.59 ± 1.85[3]	< 0.001
HbA1c (%) (mmol/mol)	4.90 ± 0.30 (30)	5.05 ± 0.35 (31)[2]	4.92 ± 0.26 (30)	0.018
GA (%)	12.31 ± 1.23[1]	13.77 ± 1.59	13.49 ± 1.34[3]	< 0.001
Insulin treatment, n (%)				< 0.001
Yes	2 (10)[1]	0 (0)	0 (0) [3]	< 0.001
Detectable urinary ketone bodies (n, % of participants)				
1st trimester of pregnancy	2 (10)	2 (2.5)	5 (6.25)	0.306
2nd trimester of pregnancy	5 (25)[1]	1 (1.25)	1 (1.25)[3]	< 0.001
3rd trimester of pregnancy	1 (5)	1 (1.25)	6 (7.5)	0.158

[1]The value for the LC/GDM group is significantly different from the value for the Con/GDM group ($P < 0.05$).

[2]The value for the Con/GDM group is significantly different from the value for the Con/Healthy group ($P < 0.05$).

[3]The value for the LC/GDM group is significantly different from the value for the Con/Healthy group ($P < 0.05$).

LC, low carbohydrate diet; GDM, gestational diabetes; Con, conventional diet; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test; AUC, area under the blood glucose curve; GA, glycated albumin

Discussion

We found that compared with women with GDM who had a conventional diet before pregnancy, those who adhered to a long time LC diet before pregnancy had not only higher values in OGTT-1h and OGTT-2h but also higher rate of abnormal values both in OGTT-2h and OGTT-2h. This study is the first to explore the relationship between a strict LC diet before pregnancy and glucose tolerance during pregnancy. **First**, the daily carbohydrate intake of the LC/GDM group were less than 130 g, which belong to strict LC diet [10,17]. **Second**, different from studies showing that LC diets were mostly for medical treatment, such as weight loss in obese people and therapy for patients with type 2 diabetes [18,19], participants in this study were healthy women before pregnancy, who followed a long-term (≧ 12 months) LC diet to control body mass. **Third**, different from others LC studies with high fat (40%, 80g/d; 45%,90g/d)[20,21], the absolute intake of fat was relatively low and comparable among participants in our study (LC/GDM:55.2g/d, Con/GDM:53.5g/d, Con/Healthy:52.3g/d). To our best knowledge, both Bao's study in 2014 and Looman's study in 2018 had suggested that pre-pregnancy LC diet may increase the risk of GDM, but the lowest quintile of carbohydrate intakes in these studies were 178 g/d and 162 g/d, respectively, which were higher than the carbohydrate intakes in the LC group our study [11,12].

Studies had suggested that the higher the OGTT glucose levels were, the more severe the imparied glucose tolerance [22]. While the GDM patients with a LC diet (LC/GDM) showed a more severe impaired glucose tolerance than the GDM with a conventional diet (Con/GDM), our study also indicated that long-term LC diet before pregnancy may be associated with impaired glucose tolerance during pregnancy. The possible explanation was that long-term LC diets make the body mobilize fat for energy, and lipolysis produces more free fatty acids (FFAs) which may lead to insulin resistance (or aggravates pregnant insulin resistance). In 1963, Hales's study on healthy men showed a significant increase in OGTT glucose values and serum free fatty acids (FFAs) after 5 days of LC diet [23]. Hernandez's study in 2014 show the concentration of FFAs in the LC diet group (carbohydrates 40%, fat 45%, protein 15%) was significantly higher than that of the high-carbohydrate diet group (carbohydrates 60%, fat 25%, protein 15%)[24]. Existing mechanistic studies also confirmed that the increase in serum FFAs can cause lipotoxicity through endoplasmic reticulum stress [25], reactive oxygen species [26], apoptosis, and inflammatory response [27], which leads to insulin resistance [28,29]. Another possible explanation was degenerated function of pancreatic islet because of long-term low carbohydrate load in the LC group. Our study showed that HbA1c levels in the LC/GDM group were 5.14% (33 mmol/mol) and 4.90% (30 mmol/mol) in the first and the second trimesters, respectively, which were the lowest among the three groups. This proved that the participants in the LC/GDM group had a long-term low carbohydrate load. Animal studies reported in 2014 showed that a reduction in β-cell mass was observed in mice on long-term LC diet (22 weeks) [30]. Our ongoing animal experiments also found that an LC diet for 4 weeks led to a decrease in the number of pancreatic islet β-cells in mice (to be reported separately).

To support the growth of the fetus in the second trimester, the intakes of total energy and carbohydrate in the LC/GDM group increased compared with those before pregnancy, but there were still six participants whose carbohydrate intakes were < 130 g/d. When carbohydrate intake is low, the body consumes its own adipose tissue as energy, which may produce ketone bodies. This was the reason that the rate of positive urine ketone bodies in the LC/GDM group was 25% in the second trimester, which was significantly higher than that in the other two groups. According to the current GDM diagnosis and treatment guidelines [13], the GDM population included in this study was given medical nutritional treatment after diagnosed of

GDM. Participants in the LC/GDM were advised to increase their carbohydrate intake appropriately, so the rate of positive urine ketone bodies decreased to 5% in the third trimester.

Notably, the HAPO study Cooperative Research Group found the higher OGTT levels were associated with adverse outcome, such as macrosomia, cesarean delivery, neonatal hypoglycemia[31]. Furthermore, Hiersch et al. reported the more abnormal OGTT points during pregnancy, the higher the risk of type 2 diabetes after delivery [32]. Nishikawa et al. also found that the higher the level of OGTT-1h, the higher the risk of impaired glucose tolerance after delivery [33]. Therefore, the abnormal glucose metabolism during pregnancy found in the LC/GDM population is particularly worthy of attention, and it provides a warning about the future risk of type 2 diabetes in the population with an LC diet. These findings highlight the urgent need for large-population, long time follow-up cohort studies on the long-term health effects of LC diets.

This study was designed to explore the relationship between a strict LC diet before pregnancy and glucose tolerance during pregnancy. Moreover, all the study participants were included during the similar time period, the food profiles were comparable among them. Different groups were matched by age, pre-pregnancy BMI, parity, conception, family history of diabetes and fasting blood glucose in first trimester of pregnancy to minimize the influence of confounding factors. However, there are several limitations to this study. First, the study sample size of the LC diet group was relatively small; however, given that the participants were a specific group of pregnant women, and based on the strict LC diet inclusion criteria, these inevitably limited the number of eligible women. Therefore, to fully compare the groups, we included a GDM conventional diet control group (Con/GDM group) and a healthy control group (Con/Healthy group) with good comparability. Second, assessment of diets is one of the most challenging behavioral assessments. Self-reporting and 24-hour recall were combined to review the dietary patterns of the study participants before pregnancy. However, there may be recall bias.

Conclusion

In this study, we observed higher values in OGTT-1h and OGTT-2h and higher rate of abnormal values both in OGTT-2h and OGTT-2h in the LC/GDM group, compared with the Con/GDM group. This indicates a relationship between the pre-pregnancy low-carbohydrate diet and imparied glucose tolerance during pregnancy. This finding suggests that it is questionable whether women of childbearing age should adopt a LC diet to control weight. It also warrants further studies to understand the effect of pre-pregnancy low-carbohydrate diet behavior on imparied glucose tolerance and its underlying pathophysiology.

Abbreviations

LC
low-carbohydrate
OGTT
oral glucose tolerance test

GDM
gestational diabetes mellitus
LC/GDM
GDM women with the low-carbohydrate diet
Con/GDM
GDM women with the conventional diet
Con/Healthy
women with conventional diet but without GDM
IPMCH
the International Peace Maternity and Child Health Hospital
IADPSG
the International Association of the Diabetes and Pregnancy Study Groups
HbA1c
glycated haemoglobin
TC
total cholesterol
TG
triacylglycerol
HDLC
high density lipoprotein cholesterol
LDLC
low density lipoprotein cholesterol
LGA
large-for gestational age
SGA
small-for gestational age
FBG
fasting blood glucose
AUC
area under the blood glucose curve
GA
glycated albumin
SD
standard deviation
FFAs
free fatty acids

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the International Peace Maternal and Infant Hospital (IPMCH) of Shanghai (GKLW2018-35).

Consent for publication

Not applicable. Only anonymized data were used.

Declaration of interest

There is no any conflict of interest to declare.

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Author Contribution

WS obtained the funding. YH, LQ, and WS conceived and designed the study. YH, LQ, YG, LM, MG,YZ, YJ, QG, and YZ contributed to the data collection and analysis plans. YH and LQ drafted the manuscript. WS had primary responsibility for final content. All authors have read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Saravanan P, Diabetes in Pregnancy Working G, Maternal Medicine Clinical Study G, Royal College of O, Gynaecologists UK. Gestational diabetes: opportunities for improving maternal and child health. *Lancet Diabetes Endocrinol.* 2020;8(9):793-800.
2. Wang WJ, Zhang L, Zheng T, et al. Fetuin-A and fetal growth in gestational diabetes mellitus. *BMJ Open Diabetes Res Care.* 2020;8(1).
3. Gao C, Sun X, Lu L, Liu F, Yuan J. Prevalence of gestational diabetes mellitus in mainland China: A systematic review and meta-analysis. *J Diabetes Investig.* 2019;10(1):154-162.
4. Grunnet LG, Hansen S, Hjort L, et al. Adiposity, Dysmetabolic Traits, and Earlier Onset of Female Puberty in Adolescent Offspring of Women With Gestational Diabetes Mellitus: A Clinical Study Within the Danish National Birth Cohort. *Diabetes Care.* 2017;40(12):1746-1755.
5. Gestational diabetes mellitus. *Nat Rev Dis Primers.* 2019;5(1):48.
6. Mijatovic-Vukas J, Capling L, Cheng S, et al. Associations of Diet and Physical Activity with Risk for Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Nutrients.* 2018;10(6).

7. Chawla S, Tessarolo Silva F, Amaral Medeiros S, Mekary RA, Radenkovic D. The Effect of Low-Fat and Low-Carbohydrate Diets on Weight Loss and Lipid Levels: A Systematic Review and Meta-Analysis. *Nutrients.* 2020;12(12).
8. Barry D, Ellul S, Watters L, Lee D, Haluska R, Jr., White R. The ketogenic diet in disease and development. *Int J Dev Neurosci.* 2018;68:53-58.
9. Wheless JW. History of the ketogenic diet. *Epilepsia.* 2008;49 Suppl 8:3-5.
10. Goldenberg JZ, Day A, Brinkworth GD, et al. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. *Bmj-British Medical Journal.* 2021;372.
11. Bao W, Bowers K, Tobias DK, et al. Prepregnancy low-carbohydrate dietary pattern and risk of gestational diabetes mellitus: a prospective cohort study. *Am J Clin Nutr.* 2014;99(6):1378-1384.
12. Looman M, Schoenaker D, Soedamah-Muthu SS, Geelen A, Feskens EJM, Mishra GD. Pre-pregnancy dietary carbohydrate quantity and quality, and risk of developing gestational diabetes: the Australian Longitudinal Study on Women's Health. *Br J Nutr.* 2018;120(4):435-444.
13. Obstetrics Group of Chinese Medical Association. Guideline for Diagnosis and Treatment of Gestational Diabetes Mellitus (2014). *Zhonghua Fu Chan Ke Za Zhi 2014.*49(8):561-571.
14. Zhou BF. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults--study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci.* 2002;15(1):83-96.
15. Sacks DA, Hadden DR, Maresh M, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care.* 2012;35(3):526-528.
16. Tian X, Huang Y, Wang H. Deviation of Chinese Adults' Diet from the Chinese Food Pagoda 2016 and Its Association with Adiposity. *Nutrients.* 2017;9(9).
17. Sato J, Kanazawa A, Makita S, et al. A randomized controlled trial of 130 g/day low-carbohydrate diet in type 2 diabetes with poor glycemic control. *Clin Nutr.* 2017;36(4):992-1000.
18. Wang LL, Wang Q, Hong Y, et al. The Effect of Low-Carbohydrate Diet on Glycemic Control in Patients with Type 2 Diabetes Mellitus. *Nutrients.* 2018;10(6).
19. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med.* 2006;166(3):285-293.
20. Moreno-Castilla C, Hernandez M, Bergua M, et al. Low-carbohydrate diet for the treatment of gestational diabetes mellitus: a randomized controlled trial. *Diabetes Care.* 2013;36(8):2233-2238.
21. Blaychfeld-Magnazi M, Reshef N, Zornitzki T, Madar Z, Knobler H. The effect of a low-carbohydrate high-fat diet and ethnicity on daily glucose profile in type 2 diabetes determined by continuous glucose monitoring. *Eur J Nutr.* 2020;59(5):1929-1936.

22. Yerlikaya G, Falcone V, Stopp T, et al. To Predict the Requirement of Pharmacotherapy by OGTT Glucose Levels in Women with GDM Classified by the IADPSG Criteria. *J Diabetes Res.* 2018;2018:3243754.
23. Hales CN, Randle PJ. Effects of low-carbohydrate diet and diabetes mellitus on plasma concentrations of glucose, non-esterified fatty acid, and insulin during oral glucose-tolerance tests. *Lancet.* 1963;1(7285):790-794.
24. Hernandez TL, Van Pelt RE, Anderson MA, et al. A Higher- Complex Carbohydrate Diet in Gestational Diabetes Mellitus Achieves Glucose Targets and Lowers Postprandial Lipids: A Randomized Crossover Study. *Diabetes Care.* 2014;37(5):1254-1262.
25. Legrand-Poels S, Esser N, L'homme L, Scheen A, Paquot N, Piette J. Free fatty acids as modulators of the NLRP3 inflammasome in obesity/type 2 diabetes. *Biochem Pharmacol.* 2014;92(1):131-141.
26. Gao D, Nong SW, Huang XQ, et al. The Effects of Palmitate on Hepatic Insulin Resistance Are Mediated by NADPH Oxidase 3-derived Reactive Oxygen Species through JNK and p38(MAPK) Pathways. *J Biol Chem.* 2010;285(39):29965-29973.
27. Sramek J, Nemcova-Furstova V, Kovar J. Kinase Signaling in Apoptosis Induced by Saturated Fatty Acids in Pancreatic beta-Cells. *Int J Mol Sci.* 2016;17(9).
28. Boden G. Effects of free fatty acids (FFA) on glucose metabolism: Significance for insulin resistance and type 2 diabetes. *Exp Clin Endocr Diab.* 2003;111(3):121-124.
29. Kraegen EW, Cooney GJ. Free fatty acids and skeletal muscle insulin resistance. *Curr Opin Lipidol.* 2008;19(3):235-241.
30. Ellenbroek JH, van Dijck L, Tons HA, et al. Long-term ketogenic diet causes glucose intolerance and reduced beta- and alpha-cell mass but no weight loss in mice. *Am J Physiol-Endoc M.* 2014;306(5):E552-E558.
31. Lowe WL, Jr., Scholtens DM, Kuang A, et al. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Gestational Diabetes Mellitus and Childhood Glucose Metabolism. *Diabetes Care.* 2019;42(3):372-380.
32. Hiersch L, Shah BR, Berger H, et al. Oral Glucose Tolerance Test Results in Pregnancy Can Be Used to Individualize the Risk of Future Maternal Type 2 Diabetes Mellitus in Women With Gestational Diabetes Mellitus. *Diabetes Care.* 2021;44(8):1860-1867.
33. Nishikawa T, Ono K, Hashimoto S, et al. One-hour oral glucose tolerance test plasma glucose at gestational diabetes diagnosis is a common predictor of the need for insulin therapy in pregnancy and postpartum impaired glucose tolerance. *J Diabetes Investig.* 2018;9(6):1370-1377.

Figures

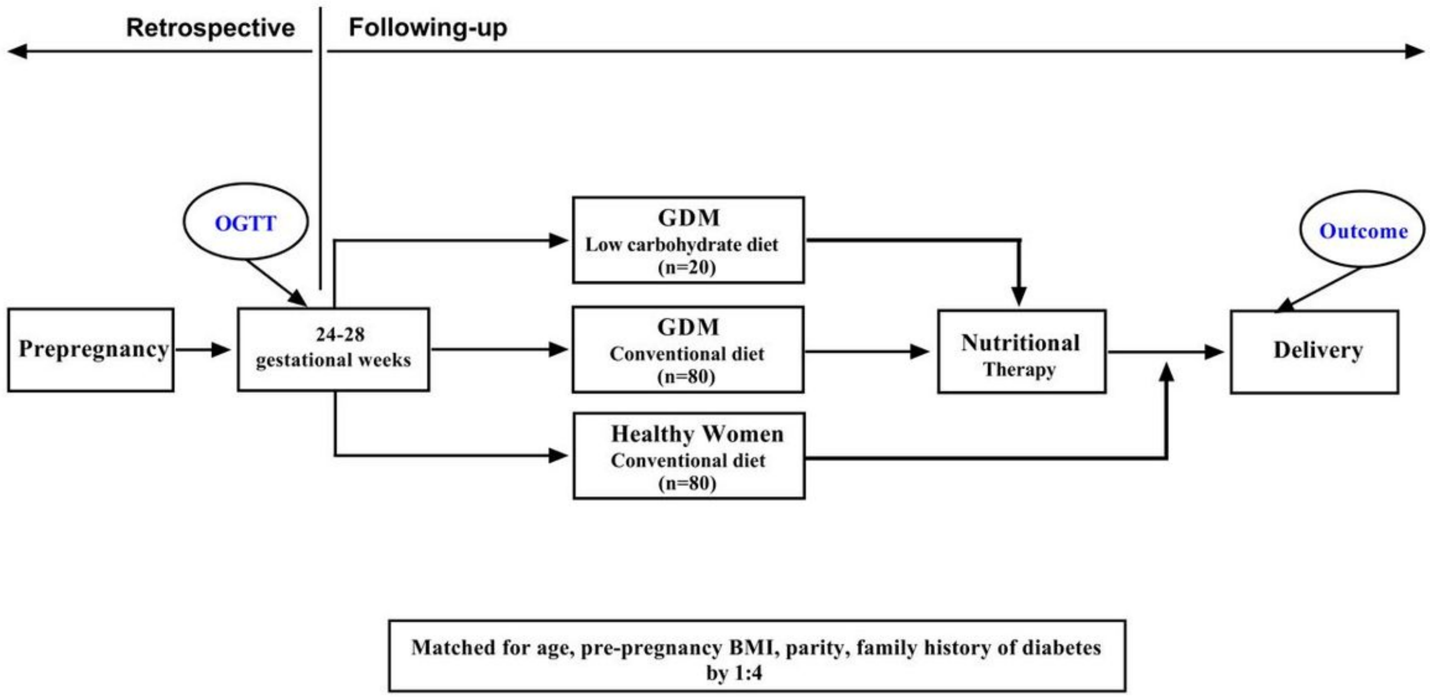

Figure 1

Patient workflow

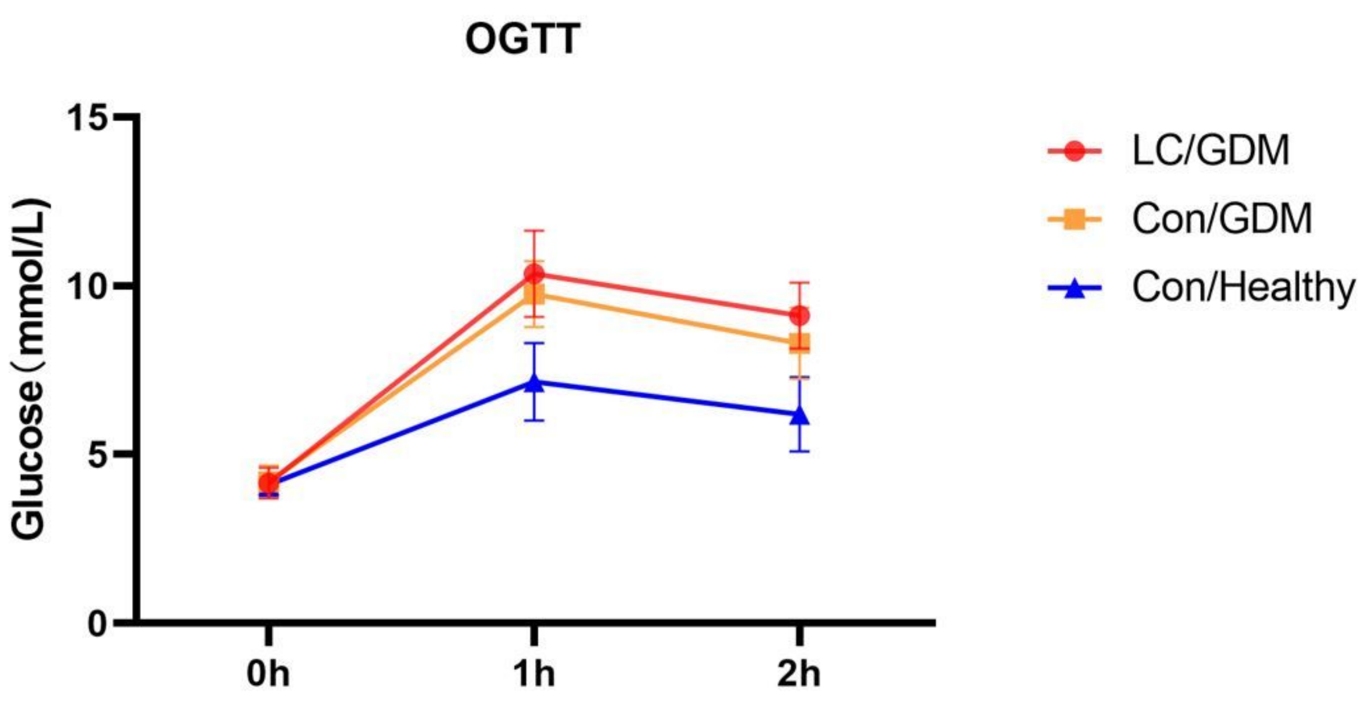

Figure 2

The blood glucose levels of the two groups of participants diagnosed with GDM and the healthy controls at the three time points of the OGTT

LC, low carbohydrate diet; GDM, gestational diabetes; OGTT, oral glucose tolerance test

LC/GDM, patients with GDM on an low carbohydrate diet; Con/GDM, patients with GDM on a conventional diet; Con/Healthy, healthy women on a conventional diet