

# Medical nutrition therapy for gestational diabetes mellitus based on Mediterranean Diet principles: a subanalysis of the St Carlos GDM Prevention Study

Carla Assaf-Balut,<sup>1,2</sup> Nuria Garcia de la Torre,<sup>1,3</sup> Alejandra Durán,<sup>1,2</sup> Manuel Fuentes,<sup>4</sup> Elena Bordiú,<sup>1,2</sup> Laura del Valle,<sup>1</sup> Johanna Valerio,<sup>1</sup> Cristina Familiar,<sup>1</sup> Inés Jiménez,<sup>1</sup> Miguel Angel Herraiz,<sup>2,5</sup> Nuria Izquierdo,<sup>2,5</sup> Maria José Torrejón,<sup>6</sup> Isabelle Runkle,<sup>1,2</sup> Maria Paz de Miguel,<sup>1,2</sup> Inmaculada Moraga,<sup>1</sup> Maria Carmen Montañez,<sup>1</sup> Ana Barabash,<sup>1,3</sup> Martín Cuesta,<sup>1,3</sup> Miguel A Rubio,<sup>1,2</sup> Alfonso Luis Calle-Pascual<sup>1,2,3</sup>

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For numbered affiliations see end of article.

## Correspondence to

Dr Alfonso Luis Calle-Pascual; [acallepascual@hotmail.com](mailto:acallepascual@hotmail.com)

## ABSTRACT

**Objectives** To assess whether Mediterranean Diet (MedDiet)-based medical nutrition therapy facilitates near-normoglycemia in women with gestational diabetes mellitus (GDMw) and observe the effects on adverse pregnancy outcomes.

**Research design and methods** This is a secondary analysis of the St Carlos GDM Prevention Study, conducted between January and December 2015 in Hospital Clínico San Carlos (Madrid, Spain). One thousand consecutive women with normoglycemia were included before 12 gestational weeks (GWs), with 874 included in the final analysis. Of these, 177 women were diagnosed with gestational diabetes mellitus (GDM) and 697 had normal glucose tolerance. All GDMw received MedDiet-based medical nutrition therapy with a recommended daily extra virgin olive oil intake  $\geq 40$  mL and a daily handful of nuts. The primary goal was comparison of hemoglobin A1c (HbA<sub>1c</sub>) levels at 36–38 GWs in GDMw and women with normal glucose tolerance (NGTw).

**Results** GDMw as compared with NGTw had higher HbA<sub>1c</sub> levels at 24–28 GWs ( $5.1\% \pm 0.3\%$  ( $32 \pm 0.9$  mmol/mol) vs  $4.9\% \pm 0.3\%$  ( $30 \pm 0.9$  mmol/mol),  $p=0.001$ ). At 36–38 GWs values were similar between the groups. Similarly, fasting serum insulin and homeostatic model assessment insulin resistance (HOMA-IR) were higher in GDMw at 24–28 GWs ( $p=0.001$ ) but became similar at 36–38 GWs. 26.6% of GDMw required insulin for glycemic control. GDMw compared with NGTw had higher rates of insufficient weight gain (39.5% vs 22.0%,  $p=0.001$ ), small for gestational age (6.8% vs 2.6%,  $p=0.009$ ), and neonatal intensive care unit admission (5.6% vs 1.7%,  $p=0.006$ ). The rates of macrosomia, large for gestational age, pregnancy-induced hypertensive disorders, prematurity and cesarean sections were comparable with NGTw.

**Conclusions** Using a MedDiet-based medical nutrition therapy as part of GDM management is associated with achievement of near-normoglycemia, subsequently making most pregnancy outcomes similar to those of NGTw.

## Significance of this study

### What is already known about this subject?

- The numerous health benefits of the Mediterranean Diet (MedDiet) have been repeatedly reproduced.
- However, there are no published studies evaluating the effect of a MedDiet-based medical nutrition therapy (MNT) on gestational diabetes mellitus (GDM) complications (glycemic control and pregnancy outcomes), nor comparing these women with those with normal glucose tolerance (NGT).

### What are the new findings?

- A MedDiet-based MNT in women with GDM was effective in achieving near-normoglycemia, attaining HbA<sub>1c</sub> levels like women with NGT.
- The rates of several pregnancy outcomes were comparable between women with and without GDM; however, the rates of insufficient weight gain (IWG) and small- for- gestational-age (SGA) newborns were significantly higher in women with GDM

### How might these results change the focus of research or clinical practice?

- MedDiet-based MNT should be considered as a universal first-line therapy in GDM treatment to improve perinatal pregnancy outcomes.
- Dietary strategies need to be designed to reduce IWG and SGA new-borns. For instance, diabetes educators should monitor women's total caloric intake, preventing self-induced reductions.

## INTRODUCTION

Gestational diabetes mellitus (GDM) increases maternal and neonatal morbidity. The Hyperglycemia and Adverse Pregnancy Outcomes study detected a continuous relationship between maternal hyperglycemia

and the incidence of perinatal complications.<sup>1</sup> Even a mildly increased glycemia can have a negative impact on both the mother and the fetus.<sup>1</sup> Based on these findings, new diagnostic criteria of GDM were proposed.<sup>2</sup> Application of these criteria has increased the prevalence of GDM to 10%–25% of gestations.<sup>3</sup> Given its high prevalence and negative pregnancy outcomes, GDM is an important public health issue. Therefore, a need exists to treat more women during pregnancy.<sup>4,5</sup> Treatment of a higher number of pregnant women in turn has been associated with improved perinatal outcomes and is cost-effective.<sup>4</sup> The treatment of GDM has been reported to reduce perinatal morbidity as compared with routine prenatal care.<sup>6</sup> However, whether the intervention can make pregnancy outcomes comparable with those of women without GDM remains unknown.

Medical nutrition therapy (MNT) is first-line therapy in the treatment of GDM.<sup>7–10</sup> Different types of dietary interventions have been compared and evaluated, with inconsistent results.<sup>11–17</sup> The lack of consistent data does not permit evidence-based recommendations, specifically with regard to macronutrient distribution of MNT in GDM management.

Restricting carbohydrates has been the cornerstone to GDM treatment. However, a less restrictive approach, permitting a higher consumption of complex carbohydrates, is being studied as a possible alternative. A higher complex carbohydrate/lower fat versus a low-carbohydrate/higher fat seems to improve maternal insulin resistance and infant adiposity.<sup>11–12</sup> In parallel, low glycemic index diets have also shown benefits in maternal insulin resistance, a lower need of insulin usage and risk of macrosomia.<sup>15–16</sup> Consensus panels have not given specific diet recommendations due to this insufficient evidence. However, both the American College of Obstetricians and Gynecologists and the Endocrine Society still stand behind low-fat diets in GDM treatment. A very recent meta-analysis that included 18 randomized controlled trials showed that dietary interventions as compared with routine care in GDM management improved perinatal outcomes.<sup>18</sup> It highlights the importance of nutritional approaches in GDM treatment and the need to evaluate further its effect on perinatal outcomes in order to find the most appropriate MNT.

The numerous health benefits of the Mediterranean Diet (MedDiet), with a high consumption of extra virgin olive oil and nuts, have been repeatedly reproduced.<sup>19–20</sup> A MedDiet-based MNT needs to be examined since it is a diet that has a low-carbohydrate/higher fat macronutrient distribution, has a low glycemic index diet, and is rich in antioxidants and anti-inflammatory components.

In healthy pregnant women, adherence to this dietary pattern has been associated with a 30% reduction in the incidence of GDM, as well as a reduction in adverse perinatal outcomes.<sup>21</sup> Most studies evaluating MNT focus their attention in assessing different types of MNT as compared with standard-care diets in women with GDM. Only one study group has compared women with

normal glucose tolerance (NGT) with women with GDM treated with diet and exercise.<sup>22</sup> There are no published studies evaluating the effect of a MedDiet-based MNT on GDM complications (glycemic control and pregnancy outcomes) nor comparing these women with those with NGT.

The aim of this study was to explore the clinical, biochemical and body weight parameters, as well as maternal and neonatal outcomes, of women with GDM treated with a MedDiet-based MNT versus women with NGT.

## RESEARCH DESIGN AND METHODS

### Trial design

The study was a secondary analysis of the St Carlos GDM Prevention Study—a prospective, single-center, randomized trial with two parallel groups. It targeted all pregnant women followed by the Obstetrics Department of the Hospital Clínico San Carlos (Madrid, Spain) from January 1 through December 31, 2015. A detailed description of the ‘St. Carlos Gestational GDM prevention study’ has been previously published.<sup>21</sup> In summary, participants were randomized at 12 gestational weeks to a control or intervention group. At this point, the intervention started. The research team did not impose any nutritional recommendations on the control group. This group received nutritional recommendations provided in regular clinical practice by obstetricians and midwives. Current guidelines recommend limiting the consumption of all fats, which by default include extra virgin olive oil and nuts. In contrast, the intervention group was recommended to consume a daily intake of  $\geq 40$  mL of extra virgin olive oil and a handful (25–30 g) of nuts.

The study was registered at ISRCTN84389045.

### Subjects

In this secondary analysis, the inclusion and exclusion criteria were as follows:

#### Inclusion criteria

The inclusion criteria were pregnant women  $\geq 18$  years old, with fasting glucose levels  $< 92$  mg/dL at the first gestational visit (at 8–12 gestational weeks), who agreed to sign the consent form.

#### Exclusion criteria

The exclusion criteria were women with fasting glucose  $\geq 92$  mg/dL at the first gestational visit (at 8–12 gestational weeks), prior diagnosis of diabetes mellitus, multiple pregnancy, nut allergy, lost to follow-up until delivery and/or any medical condition that could prevent the participant from complying with trial follow-up.

#### GDM screening and treatment

GDM was diagnosed at 24–28 gestational weeks with a single 2-hour 75 g oral glucose tolerance test (International Association of Diabetes and Pregnancy Study Group (IADPSG)/WHO criteria).<sup>2</sup> Women from both

the control and intervention groups who were diagnosed with GDM (177/874, 20%) were referred to the Diabetes and Pregnancy Unit and treated according to local guidelines.<sup>4</sup> Regardless of having been previously allocated to the control or intervention group, all women who developed GDM received the same treatment.

Within 1 week of GDM diagnosis, women had their first scheduled appointment at the Diabetes and Pregnancy Unit. Women were asked to self-monitor blood glucose. This included a 6-point daily glycemic profile, with fasting/preprandial and 1-hour postprandial capillary blood glucose. Therapeutic objectives were fasting/preprandial glucose <90 mg/dL (<5 mmol/L) and 1-hour postprandial glucose <120 mg/dL (6.7 mmol/L).

MNT was first-line therapy in GDM treatment. The guidelines provided were based on a MedDiet pattern with an enhanced consumption of extra virgin olive oil and pistachios—a macronutrient distribution of approximately 40% carbohydrates, 40% fats and 20% proteins of total calories. Insulin therapy was initiated when capillary blood glucose monitoring indicated that >50% of fasting or preprandial values were >95 mg/dL (5.3 mmol/L) (basal insulin) or 1-hour postprandial levels were >140 mg/dL (7.8 mmol/L) (bolus insulin). Insulin requirements were adjusted weekly as required. If glycemic control was not achieved but the fasting and preprandial glycemia was 90–94 mg/dL (5–5.2 mmol/L) and postprandial glycemia was 120–139 mg/dL (6.7–7.7 mmol/L), lifestyle changes, including exercise, were reinforced. To regulate postprandial glycemia, dietary changes were advised at each visit. Online supplementary file S1 provides detailed information on the GDM management protocol followed at the Hospital Clínico San Carlos.

Women who did not develop GDM followed the recommendations assigned to them according to the group they were originally randomized to (control or intervention group).

### Study outcomes

The primary objective was to compare glycemic control (as determined by hemoglobin A1c (HbA<sub>1c</sub>) levels at 36–38 gestational weeks) of women with and without GDM.

The following were the secondary outcomes:

1. To compare biochemical and clinical parameters (glucose, insulin, HOMA-IR and blood pressure), lifestyle patterns and gestational weight gain between the GDM and NGT groups. Blood pressure was measured with an adequate armlet after the participants had been seated for 10 min. Lifestyle was assessed using questionnaires evaluating physical activity, general healthy eating habits (Nutrition Score) and adherence to the MedDiet (Mediterranean Diet Adherence Screener (MEDAS) score), as described previously.<sup>21</sup> The questionnaire used to obtain the Nutrition Score contains 15 items, 3 of which evaluate physical activity and 12 food frequency intakes. The Nutrition Score objective

is >5. +1 points are given to habits associated with diabetes mellitus 2 prevention and –1 points to those associated with increased risk. 0 point is given when habits are associated with neither prevention nor risk; it is the minimum objective to be achieved. The MEDAS questionnaire evaluates 14 items. The compliance of each item provides +1 points, considering >10 as ideal. Weight gain was evaluated at 24–28 and at 36–38 gestational weeks. When the latter was unavailable, prepartum weight was recorded. Weights were compared with pregestational body weight. Adequate gestational weight gain was defined according to pregestational body mass index (BMI), as follows: >35 kg/m<sup>2</sup>, 0 kg; 30–34.9 kg/m<sup>2</sup>, 3 kg; 27.6–29.9 kg/m<sup>2</sup>, 6 kg; 25–27.5 kg/m<sup>2</sup>, 9 kg; 20–24.9 kg/m<sup>2</sup>, 12 kg; and <20 kg/m<sup>2</sup>, 15 kg. Insufficient weight gain (IWG) was defined as an increment of 3 kg below the designated target, according to their BMI. Excessive weight gain was when women gained 3 kg above their designated target according to their BMI.<sup>23–25</sup>

2. To compare the rates of prematurity; large for gestational age (LGA) newborns (>90 percentile) and small for gestational age (SGA) newborns (<10th percentile) according to the national chart; pre-eclampsia; pregnancy-induced hypertension; albuminuria; type of delivery; incidence of perineal trauma (any degree of spontaneous tears and episiotomy); urinary tract infections (number of events requiring antibiotic treatment); and neonatal intensive care unit (NICU) admissions.

### Power estimation

Based on the information available at our center of the HbA<sub>1c</sub> levels at 12 gestational weeks of a sample of 1253 women (5.1%±0.2% (32±0.8 mmol/mol)), we have established the limit of non-inferiority based on the variability of the HbA<sub>1c</sub> levels in a large sample of pregnant women. The  $\delta$  value represents the maximum difference tolerable value according to the variability of the parameter at week 12. Considering the current results and sample size (mean GDM group: 5.31% (35 mmol/mol); mean NGT group: 5.23% (34 mmol/mol)), a statistical power >99% permits assumption that treatment in the GDM group would be at least as efficacious as the NGT with a non-inferiority margin of –0.2% (0.8 mmol/mol).

### Statistical analysis

Discrete variables are presented with their frequency and percentage distribution, and continuous variables by their mean and  $\pm$ SD when normally distributed and with median and IQR when not. All primary analyses were performed on an intention-to-treat basis. Comparison between groups for categorical variables was evaluated using the  $\chi^2$  test or Fisher's exact test. For continuous variables, measures were compared with Student's t-test or the Mann-Whitney U test if the distribution of quantitative variables was not normal, as verified by the Shapiro-Wilk test.



The magnitude of association between study groups and binary outcomes was evaluated using OR and 95% CI.

For the primary efficacy endpoint, HbA<sub>1c</sub> levels at 36–38 gestational weeks, the comparison between groups was assessed using analysis of covariance. Non-inferiority of GDM group was demonstrated if the two-sided 95% CI for the difference between the HbA<sub>1c</sub> means was above the predefined non-inferiority margin of  $-0.2\%$  (0.8 mmol/mol).

Logistic regression analyses were used to assess the effect of the GDM for the secondary binary outcomes. Crude and adjusted models were fitted adjusted for BMI (continuous) and ethnicity. To evaluate the effect of the study group on the association of diabetes with the secondary outcome variables, the interaction term was introduced in the model.

All p values are two-tailed at less than 0.05. Analyses were performed using SPSS V.21.

## RESULTS

### Participants' characteristics

In the St Carlos GDM Prevention Study, a total of 1501 women attending their first ultrasound visit were eligible; 1000 accepted participation and signed the consent form. They were randomly allocated to the control (n=500) or intervention (n=500) group. Sixty women in the control group and 66 women in the intervention group were lost to follow-up before GDM screening. Consequently, 874 women were followed through postpartum discharge and were included in the final analysis. A total of 177 (20%; 103 from control group and 74 from intervention group) developed GDM and the remaining 697 (80%; 337 from control group and 360 from intervention group) had NGT (online supplementary figure S1). These were included in this secondary analysis.

Table 1 shows the baseline demographic and clinical characteristics of the women of the two cohorts, according to glucose tolerance. Women with GDM had a higher pregestational BMI, fasting glucose, triglyceride levels and systolic blood pressure (all  $p < 0.05$ ).

### Primary outcome

The 95% CI for the difference between the HbA<sub>1c</sub> mean values at 36–38 gestational weeks ( $-0.00$  to  $0.14$ ) was not above the predefined non-inferiority margin of  $-0.2\%$  (0.8 mmol/mol), showing a non-inferiority target of GDM treatment as compared with NGT women.

### Secondary outcomes

Online supplementary file 1 shows the nutritional questionnaire scores and lifestyle patterns throughout the study period. Nutrition and MEDAS scores and daily intake of nuts and extra virgin olive oil were similar at baseline and 24–28 gestational weeks in both groups and significantly higher in the GDM group at 36–38 gestational weeks ( $p = 0.001$ ). No significant differences were

found between groups with regard to physical activity performance.

Maternal clinical and laboratory data are displayed in table 2. At 24–28 gestational weeks, women of the GDM group as compared with the NGT had significantly higher levels of fasting glucose and 1-hour and 2-hour glycemia after the 75 g glucose load. HbA<sub>1c</sub>, fasting insulin, HOMA-IR, and triglycerides were also higher. At 36–38 gestational weeks, only fasting glucose remained significantly higher. No differences in terms of HbA<sub>1c</sub>, fasting insulin levels and HOMA-IR values were found at 36–38 gestational weeks. Body weight was significantly higher in women with gestational diabetes mellitus (GDMw) at 24–28 gestational weeks. Gestational weight gain was significantly lower in the GDMw measured from pregestational and from 24–28 gestational weeks to 36–38 gestational weeks (both  $p = 0.001$ ). The rates of IWG were significantly higher in GDMw ( $p = 0.001$ ). Online supplementary table S2 shows information on women with GDM, divided into control and intervention group. Women with GDM who had been allocated to the intervention group had lower need for insulin treatment and rates of pregnancy-induced hypertension, urinary tract infections, perineal trauma and newborn SGA.

Crude OR analysis of maternal and neonatal outcomes (table 3) showed that GDM compared with NGTw had an increased risk for IWG (2.37 (1.64 to 3.30),  $p = 0.001$ ), urinary tract infections (1.69 (1.20 to 2.38),  $p = 0.005$ ), SGA newborns (2.05 (1.29 to 3.24),  $p = 0.009$ ) and NICU admissions (3.42 (1.45 to 8.04),  $p = 0.006$ ). However, no differences in others adverse events were found. When adjusted for BMI and ethnicity, GDMw still showed a significantly higher OR for IWG, urinary tract infections, SGA newborns and NICU admissions. There were no interactions between the intervention and control groups in the GDM group. Women with SGA newborns had higher rates of IWG and lower nutrition and MEDAS scores at 24–28 and 36–38 gestational weeks, and higher systolic and diastolic blood pressure at 36–38 gestational weeks (online supplementary table S3).

Multivariate analysis of the maternal risk for SGA newborns is shown in table 4. Having SGA newborns was associated with GDM, insulin-treated GDM, urinary tract infections, gestational age at birth, prematurity and IWG. IWG (n=223) as compared with adequate weight gain (n=488) was associated with GDM (2.48 (1.71 to 3.61)), insulin-treated GDM (2.59 (1.29 to 5.18)) and SGA newborns (3.20 (1.40 to 7.32)).

## DISCUSSION

After 3 months of treatment with a MedDiet as MNT, glycemic control (measured by HbA<sub>1c</sub>) in GDMw was not inferior to that of NGTw. To our knowledge, this is the first study that shows that with GDM management, using a MedDiet-based MNT, GDMw had similar glycemic control at 36–38 gestational weeks to NGTw. As expected, given glycemic control, no significant differences were

**Table 1** Baseline characteristics of the clinical trial population

	NGT group (n=697)	GDM group (n=177)	P values
Age (years)	32.73±5.10	33.44±5.28	0.111
Race/Ethnicity			
Caucasian	470 (67.4)	117 (66.1)	0.032
Hispanic	207 (29.7)	53 (29.9)	
Others	20 (2.9)	7 (4.1)	
Family history			
Type 2 diabetes	138 (19.8)	42 (23.7)	0.450
MetS (>2 components)	145 (20.8)	38 (21.5)	
History			
GDM	15 (2.2)	10 (5.7)	0.043
Miscarriage	225 (32.3)	53 (29.9)	
Educational status			
Elementary education	53 (7.6)	25 (14.2)	0.030
Secondary school	167 (24.0)	45 (25.4)	
University degree	471 (67.6)	106 (59.9)	
UNK	6 (0.9)	2 (1.2)	
Employment	539 (77.3)	135 (76.3)	0.844
Number of pregnancies			
Primiparous	301 (43.2)	77 (43.5)	0.857
Second pregnancy	225 (32.3)	56 (31.6)	
>2 pregnancies	171 (24.5)	44 (25.9)	
Smoker			
Never	384 (55.1)	93 (52.5)	0.786
Current	55 (7.9)	17 (9.6)	
Gestational age (weeks) at entry	12.1±0.5	12.1±0.7	0.261
Body weight (kg)			
Prepregnancy	59.7±10.2	65.1±12.0	0.0001
At entry	61.8±10.5	67.2±12.3	0.0001
Weight gain at entry	2.0±2.9	2.2±2.9	0.508
BMI (kg/m <sup>2</sup> )			
Prepregnancy	22.6±3.5	24.9±4.2	0.0001
At baseline	23.4±3.6	25.7±4.4	0.0001
Systolic BP (mm Hg)	106±11	111±10	0.001
Diastolic BP (mm Hg)	65±10	67±8	0.063
FBG (mg/dL)	81±6	83±6	0.0001
HbA <sub>1c</sub> % (mmol/mol)	5.2±0.3 (33±0.9)	5.0±0.3 (31±0.9)	0.165
Cholesterol (mg/dL)	173±29	177±31	0.288
Triglycerides (mg/dL)	80±41	89±37	0.034
MEDAS score	4.90±1.73	4.89±1.56	0.931
Nutrition Score	0.37±3.2	0.27±3.16	0.699
Physical Activity Score ≥0	80 (12.4)	19 (10.8)	0.694

Data are mean±SD or number (%).

Physical Activity Score ≥0: (1) walking daily (>5 days/week); score 0: at least 30 min; score +1: if >60 min; score -1: if <30 min. (2) Climbing stairs (floors/day, >5 days a week): score 0, between 4 and 16; score +1, >16; score -1: <4.

BMI, body mass index; BP, blood pressure; FBG, fasting blood glucose; GDM, gestational diabetes mellitus; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; MEDAS, Mediterranean Diet Adherence Screener; MetS, metabolic syndrome; NGT, normal glucose tolerance; UNK, unknown.

**Table 2** Maternal clinical, biochemical and anthropometric data at 24–28 and 36–38 GW

	NGT group (n=697)	GDM group (n=177)	Mean differences (95% CI)	P values
75 g OGTT 24–28 GW				
FBG (mg/dL)	82.9±4.7 4.6±0.3	92.9±6.9 5.2±0.4	10.0 (9.1 to 10.9) 0.56 (0.51 to 0.61)	0.001
1-hour blood glucose (mg/dL)	117.9±26.1 6.6±1.5	158.6±35.8 8.8±2.0	40.7 (35.2 to 46.2) 2.3 (2.0 to 2.6)	0.001
2-hour blood glucose (mg/dL)	103.3±20.2 5.7±1.1	137.5±31.7 7.6±1.8	34.2 (29.8 to 38.6) 1.9 (1.7 to 2.1)	0.001
HbA <sub>1c</sub> % (mmol/mol) 24–28 GW	4.9±0.3 (30±0.9)	5.1±0.3 (32±0.9)	0.20 (0.15 to 0 to 24)	0.001
HbA <sub>1c</sub> % (mmol/mol) 36–38 GW	5.2±0.4 (33±1)	5.3±0.4 (34±1)	0.07 (–0.00 to 0.14)	0.060
FBG 36–38 GW (mg/dL)	74.8±7.5 4.2±0.4	79.3±7.3 4.4±0.4	4.5 (2.9 to 6.1) 0.2 (0.1 to 0.3)	0.001
Fasting serum insulin (mcUI/mL)				
24–28 GW	8.9±6.7	12.1±6.1	3.1 (2.0 to 4.3)	0.001
36–38 GW	10.1±10.4	11.0±8.1	0.9 (–1.2 to 3.1)	0.337
HOMA-IR				
24–28 GW	1.9±1.6	2.9±1.6	1.0 (0.7 to 1.2)	0.001
36–38 GW	2.1±2.7	2.2±1.5	0.1 (–0.4 to 0.7)	0.550
Cholesterol (mg/dL)				
24–28 GW	248±44	249±45	0.4 (–7.9 to 8.7)	0.923
36–38 GW	275±52	270±53	–4.7 (–15.9 to 6.5)	0.411
Triglycerides (mg/dL)				
24–28 GW	157±55	169±51	12.1 (2.0 to 22.1)	0.015
36–38 GW	228±79	231±83	4.0 (–13.0 to 21.0)	0.652
Treatment of GDM				
Nutritional		130 (73.4)		
Insulin (total)		47 (26.6)		
Bolus		7 (14.9)		
Basal		35 (74.5)		
Basal/Bolus		5 (10.6)		
Body weight (kg)				
24–28 GW	67.1±10.5	71.8±11.5	4.7 (2.8 to 6.6)	0.001
36–38 GW	72.1±10.7	74.5±12.3	2.3 (–0.0 to 4.7)	0.051
Weight gain (kg) 24–28 to 36–38 GW	5.29±3.19	2.08±3.15	–3.2 (–3.8 to –2.6)	0.001
Weight gain (kg) pregestational to 36–38 GW	10.53±4.39	7.16±4.22	–3.4 (–4.2 to –2.5)	0.001
EWG	132 (18.9)	31 (17.5)		0.001
AWG	412 (59.1)	76 (42.9)		
IWG	153 (22.0)	70 (39.5)		
Systolic BP (mm Hg) 24–28 GW	104±11	109±11	4.6 (2.7 to 6.5)	0.001
Diastolic BP (mm Hg) 24–28 GW	63±9	65±10	2.6 (1.1 to 4.1)	0.001
Systolic BP (mm Hg) 36–38 GW	112±12	112±11	–0.0 (–2.6 to 2.5)	0.983
Diastolic BP (mm Hg) 36–38 GW	73±9	73±9	0.3 (–1.7 to 2.3)	0.752

Data are mean±SD or number (%).

AWG, adequate weight gain; BP, blood pressure; EWG, excessive weight gain; FBG, fasting blood glucose; GDM, gestational diabetes mellitus; GW, gestational week; HOMA-IR, homeostatic model assessment insulin resistance; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; IWG, insufficient weight gain; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

**Table 3** Maternal and neonatal adverse outcomes

	NGT group (n=697)	GDM group (n=177)	Crude OR (95% CI)	Adjusted OR (95% CI)	P† interaction
<b>Maternal outcomes</b>					
IWG	153 (22.0)	70 (39.5)*	2.37 (1.64 to 3.30)	3.29 (2.24 to 4.83)	0.803
Pregnancy-induced hypertension	24 (3.4)	8 (4.5)	1.24 (0.67 to 2.30)	1.09 (0.47 to 2.56)	NA
Pre-eclampsia	11 (1.6)	7 (4.0)	2.57 (0.98 to 6.72)	1.91 (0.70 to 5.16)	NA
Albuminuria	6 (0.9)	2 (1.1)	1.23 (0.37 to 4.13)	0.87 (0.17 to 4.54)	NA
Urinary tract infection	57 (8.2)	27 (15.3)*	1.69 (1.20 to 2.38)	1.77 (1.06 to 2.96)	0.764
<b>Delivery</b>					
Vaginal eutocic	496 (71.2)	132 (74.6)	0.86 (0.43 to 1.71)	0.63 (0.37 to 1.08)	
Instrumental	100 (14.3)	26 (14.7)			
Cesarean section	101 (14.5)	19 (10.7)			
Emergency cesarean section	33 (4.7)	7 (4.0)	0.83 (0.36 to 1.91)	0.75 (0.32 to 1.77)	0.808
Perineal trauma	62 (8.9)	20 (11.3)	1.23 (0.82 to 1.85)	1.25 (0.72 to 2.18)	0.222
<b>Neonatal outcomes</b>					
Gestational age at birth (weeks)	39.6±1.315	39.5±1.48			
<37 GW	15 (2.2)	8 (4.5)	1.75 (0.99 to 3.12)	1.97 (0.78 to 5.14)	0.803
Birth weight (g)	3242±434	3188±472			
Percentile	53.6±35.4	56.5±28.2			
Length (cm)	49.2±2.5	49.0±2.1			
Percentile	39.8±28.2	39.1±28.6			
LGA >90th percentile	14 (2.0)	8 (4.5)	2.31 (0.95 to 5.59)	1.75 (0.70 to 4.36)	0.783
>4500 g	0	2 (1.1)			
SGA <10th percentile	18 (2.6)	12 (6.8)*	2.05 (1.29 to 3.24)	3.27 (1.50 to 7.15)	0.521
Ph cord blood	7.27±0.15	7.28±0.07			
Apgar score at 1 min	8.8±0.7	8.8±0.9			
Apgar score at 5 min	10.0±0.2	10.0±0.5			
Hypoglycemia	7 (1.0)	5 (2.8)	2.86 (0.89 to 9.13)	2.51 (0.75 to 8.39)	NA
Respiratory distress	6 (0.9)	1 (0.6)	0.65 (0.07 to 5.47)	0.61 (0.07 to 5.33)	NA
Hyperbilirubinemia	39 (5.6)	14 (7.9)	1.45 (0.76 to 2.73)	1.44 (0.75 to 2.80)	0.842
NICU/observation	12 (1.7)	10 (5.6)*	3.42 (1.45 to 8.04)	3.47 (1.42 to 8.50)	0.319

Data are mean±SD or number (%).

Adjusted by pregestational body mass index (<25, 25–29.9 and ≥30 kg/m<sup>2</sup>) and ethnicity (Caucasian vs others).

P†: interaction term gestational diabetes mellitus and study group (intervention or control group). NE: not estimable due to the small number of events and the presence of a zero value in some of the cells in the stratified analysis.

\*P<0.01.

GDM, gestational diabetes mellitus; GW, gestational weeks; IWG, insufficient weight; LGA, large for gestational age; NA, not applicable; NGT, normal glucose tolerance; NICU, neonatal intensive care unit; SGA, small for gestational age.

observed in the rates of excessive weight gain, pregnancy-induced hypertension, type of delivery, perineal trauma, prematurity and LGA newborns when comparing GDMw and NGTw.

Only 27% of GDMw needed insulin therapy after failure of MNT. This observed rate is lower than the rates described in other studies, around 56.7% in Caucasian women<sup>26</sup> and 50% in other regions of Spain.<sup>27</sup>

A continuous relationship between maternal glycemia and adverse maternal and neonatal outcomes is well documented.<sup>1</sup> LGA newborns, macrosomia and cesarean

sections are the outcomes most linked to GDM and poor glycemic control, as well as to maternal obesity and gestational weight gain.<sup>28–31</sup> In a large prospective study, high maternal BMI rather than hyperglycemia was associated with LGA newborns.<sup>32</sup> However, our results revealed that, despite GDMw having a higher BMI at baseline, LGA and macrosomia rates were similar in GDMw and NGTw. Therefore, GDM management that includes a MedDiet-based MNT is associated with a lower incidence of these outcomes, possibly by inducing lower rates of excessive weight gain.

**Table 4** Multivariate analysis showing risk factors of having SGA newborns

	AGA (between 10th and 90th centile) (n=822)	SGA (<10th centile) (n=30)	P values	Crude OR (95% CI)
Non-Caucasian race	269 (32.7)	9 (30.0)	0.463	1.13 (0.52 to 2.44)
Smoked during gestation	66 (8.1)	4 (13.3)	0.231	1.03 (0.97 to 1.09)
Smoked until gestation	173 (21.2)	7 (23.3)	0.465	1.01 (0.97 to 1.04)
GDM	157 (19.1)	12 (40.0)	0.008	2.82 (1.33 to 5.98)
Insulin-treated GDM	40 (4.9)	4 (13.3)	0.040	2.82 (1.03 to 7.74)
Pregnancy-induced hypertension	27 (3.3)	3 (10.0)	0.050	3.27 (0.94 to 11.45)
Urinary tract infection	72 (8.8)	8 (26.7)	0.005	3.79 (1.63 to 8.81)
Gestational age at birth (weeks)	39.7±1.2	37.6±1.8	0.001	
<37 GW	10 (1.2)	13 (43.3)	0.001	27.5 (15.2 to 49.8)
IWG	206 (25.1)	14 (46.6)	0.016	3.20 (1.40 to 7.33)
Control group versus intervention group	415 (49.2)/429 (50.8)	25 (83.3)/5 (16.7)	0.001	4.93 (1.91 to 12.77)

Data are mean±SD or number (%).

AGA, adequate for gestational age; GDM, gestational diabetes mellitus; GW, gestational week; IWG, insufficient weight gain; SGA, small for gestational age.

Most of the adverse pregnancy outcomes evaluated were similar between GDMw and NGTw. However, rates of NICU admissions, IWG, SGA newborns and urinary tract infections were higher in the GDMw. The higher rates of NICU admission are concurrent with results from a retrospective cohort.<sup>22</sup>

While the rates of excessive weight gain were lower in the GDMw than in NGTw, the rates of IWG were significantly higher. One possible explanation is that following GDM diagnosis, and consequently the care and advice provided, women reduce energy intake, substituting high energy-dense foods for healthier food options.<sup>7</sup> Another potential explanation is the fact that GDMw self-monitor blood glucose. Undoubtedly, it is an indispensable tool in improving glycemic control and permits the tailoring of MNT to each individual.<sup>33</sup> However, the downside of self-monitoring blood glucose is women's attitude toward not achieving tight glycemic control and concern that hyperglycemia could lead to insulin therapy.<sup>34,35</sup> Women could thus restrict the consumption of the foods associated with higher glucose levels and limit carbohydrate/caloric intake. In fact, when present, IWG occurred within the first weeks of self-monitoring of blood glucose, prior to insulin initiation, and therefore did not seem to be related to insulin therapy per se (data not shown).

Determining appropriate gestational weight gain in overweight and obese women is an ongoing debate.<sup>12,13,23,36–38</sup> There is rising evidence that a lower gestational weight gain than that recommended by the Institute of Medicine in overweight and obese women reduces the risk for LGA neonates, macrosomia, pre-eclampsia and cesarean sections.<sup>37</sup> A systematic review and meta-analysis reported higher rates of SGA and lower rates of LGA in overweight women who lost weight during pregnancy.<sup>23</sup> Similarly, a recent systematic review and meta-analysis associated IWG with higher rates of SGA and prematurity and with

lower rates of LGA and macrosomia.<sup>31</sup> These data agree with those reported in the present study. The effect of IWG on SGA is still controversial and needs to be further studied. In any case, given the higher rates of IWG and SGA newborns, we have found strategies should be designed to try to avoid the occurrence of both.

Rates of urinary tract infections were significantly higher in GDMw than in NGTw. Maternal urinary tract infections could have facilitated higher rates of SGA newborns, since they have been independently associated with prematurity and restricted intrauterine growth.<sup>39</sup> In addition, women who had urinary tract infections required antibiotic treatment, potentially leading to changes in the microbiota that could induce higher rates of SGA newborns.<sup>40</sup> Furthermore, *Escherichia coli* has been associated with SGA newborns secondary to placental insufficiency and a higher risk of prematurity.<sup>41,42</sup>

As compared with other studies, our rates of insulin therapy were the lowest. A low-carbohydrate diet, with a carbohydrate content of 40%, similar to ours, was not associated with lower rates on insulin treatments as compared with a control diet in women with GDM.<sup>27</sup> In addition, pregnancy outcomes were found to be similar between groups. Rates of SGA, macrosomia, cesarean sections and maternal hypertension were lower in our group of women with GDM as compared with women allocated to the low-carbohydrate diet.<sup>27</sup> This is so despite similarities in total caloric distribution of carbohydrates in our study and theirs. These differences could be attributed to the quality of fats consumed by our subjects, whose diet was rich in extra virgin olive oil and nuts. They could also be attributed to the high content in fruits and vegetables. In fact, a recent systematic review and meta-analysis revealed that using Dietary Approaches to Stop Hypertension (DASH) diets as MNT in GDM was associated with improvements in HOMA-IR, medication need and



macrosomia.<sup>18</sup> Moreover, low glycemic index diets have shown to reduce birth weight, risk of macrosomia and need for medication. However, the results from studies testing different dietary interventions in GDM treatment indicate that mean birth weight in their studied sample was found to be higher than the one found in our women with GDM, including those following a low-carbohydrate<sup>12</sup> and low glycemic index diet.<sup>17</sup> Yamamoto *et al*<sup>18</sup> concluded that neither a fat-modification nor low-carbohydrate diet modifies outcomes such as HbA<sub>1c</sub>, HOMA-IR, insulin need, or neonatal birth weight, macrosomia and LGA. However, our results show that the levels of HbA<sub>1c</sub> and HOMA-IR after GDM diagnosis and treatment are comparable with that of healthy women without GDM, and so were rates of birth weight, rates of macrosomia and LGA.

While our study does not compare one nutritional approach with another in GDM treatment, the maternal-fetal outcomes found in our study seem to be promising when compared with those found in other studies that used different types of MNT. It is important to consider that our results are being compared with studies whose population were mainly women of high risk—mostly high BMI and/or metabolic risk factors. This means that baseline characteristics between our group of women are not like those of others, and therefore making comparisons of our outcomes with that of others is not accurate enough.

This study seems to suggest that MNT based on a MedDiet enhanced with extra virgin olive oil and nuts, thus with a high fat content, is associated with glycemic control and with a reduction in GDM-related adverse perinatal outcomes. Further studies are needed to confirm our findings. It would be ideal to conduct a randomized controlled trial specifically designed to evaluate the effect of a MedDiet MNT on glycemic control and perinatal outcomes, in addition to assessing the cause of IWG in women with GDM.

### Limitations

Some limitations were found in this study. First, this was a post-hoc analysis, and therefore the original objective of the study was not to evaluate the efficacy of MNT in controlling glycemia in GDMw. Moreover, the data available of the diet of pregnant women give qualitative rather than quantitative information. Exact caloric and macronutrient intake is lacking because in GDM management women are not provided with a diet with a specific daily total caloric intake. They are given nutritional counseling on what foods to eat and the approximate quantity in which they should eat them, not a strict meal plan. Another limitation is that some of the GDMw had been allocated to the intervention group, prior to GDM diagnosis. The nutritional recommendations given to women of the intervention group were like the ones provided in GDM management. Therefore, women belonging to the intervention group who later developed GDM (77/177) had been following recommendations of MedDiet with

enhanced consumption of extra virgin olive oil and pistachios for a longer period than those belonging to the control group. Nevertheless, we observed no interaction in perinatal outcomes between women of the control and intervention group who later developed GDM.

### CONCLUSION

In summary, comprehensive management of GDM, using a MedDiet-based MNT, is associated with the achievement of similar HbA<sub>1c</sub> levels at 36–38 gestational weeks as that of women with NGT. Some GDM-related perinatal complications were not different between GDMw and NGTw. Notwithstanding the higher rates of SGA newborns and IWG, the fact that there were no differences in the rates of excessive weight gain, pregnancy-induced hypertension, type of delivery, perineal trauma, prematurity and LGA newborns is an important finding. This indicates the potential benefit of using this type of diet as MNT in women with GDM. However, strategies are needed to reduce the rates of SGA newborns and IWG and thus avoid their deleterious consequences.

### Author affiliations

<sup>1</sup>Endocrinology and Nutrition Department, Hospital Clínico San Carlos and Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain

<sup>2</sup>Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain

<sup>3</sup>Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain

<sup>4</sup>Preventive Medicine Department, Hospital Clínico Universitario San Carlos and Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain

<sup>5</sup>Gynecology and Obstetrics Department, Hospital Clínico Universitario San Carlos and Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain

<sup>6</sup>Clinical Laboratory Department, Hospital Clínico Universitario San Carlos and Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain

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**Contributors** Conceptualization: ALC-P, NGdIT, AD, EB, MAH, MJT, MC and MAR. Data curation and formal analysis: ALC-P, CA-B, NGdIT, AD, MF, LdV, JV, CF, IJ, NI, MJT, IR, IM, MCM, AB and MAR. Funding acquisition: ALC-P. Investigation: ALC-P, CA-B, NGdIT, AD, MF, EB, LdV, JV, CF, IJ, MAH, NI, MJT, IR, MPM, MCM, AB, MC and MAR. Methodology: ALC-P, CA-B, NGdIT, AD, MF, EB, LdV, JV, CF, IJ, MAH, NI, MJT, IR, MPM, MCM, AB, MC and MAR. Supervision: ALC-P, MF, MC and MAR. Validation and visualization: ALC-P and MF. Drafting and writing and review and editing of the original article: ALC-P, CA-B, NGdIT, AD and IR. All authors were involved in the critical revision of the manuscript for important intellectual content, material support and study supervision. All authors have seen and agreed with the content of the last version of the manuscript. ALC-P is the guarantor of this work and as such had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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