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Article

Early Mediterranean-Based Nutritional Intervention Reduces the Rate of Gestational Diabetes Mellitus in Overweight and Obese Pregnant Women: A Post-Hoc Analysis of the San Carlos Gestational Prevention Study

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Abstract: Obesity is a risk factor for the development of gestational diabetes mellitus (GDM). However, the most optimal type of nutritional intervention to prevent GDM in high-risk women is not clearly defined. This study investigates if nutritional treatment based on the Mediterranean diet (MedDiet) before 12th gestational week (GW) in women at high risk due to a body mass index (BMI)≥25kg/m², reduces the rate of GDM and metabolic syndrome (MetS) at 3 years postpartum. We performed a post-hoc analysis of the San Carlos Gestational Prevention Study. A total of 735 women with BMI≥25kg/m² were evaluated between 2015-2018, 246 in standard diet control group (CG) and 489 in MedDiet intervention group (IG). The rate of GDM was significantly lower in IG compared to CG (25.1%vs31.7%;p=0.037). Postnatal follow-up was completed by 141 women in CG (57%) and 312 women in IG (64%). At 3 years postpartum, we observed a reduction (relative risk 95% confidence interval) in the rates of impaired fasting glucose (IFG) (0.51 (0.28-0.92);p=0.019), obesity (0.51 (0.28-0.92),p=0.041), waist circumference (WC)≥89.5cm (0.54 (0.31-0.94);p=0.022) and MetS (0.56 (0.33-0.94);p=0.003). MedDiet reduces the rate of GDM and postpartum MetS in women with BMI≥25kg/m², suggesting that its implementation should be routinely recommended from the first GWs.

Keywords: obesity; overweight; metabolic syndrome; fasting blood glucose; mediterranean diet

1. Introduction

The prevalence of overweight and obesity is a growing public health problem worldwide (1,2). This pathophysiological condition is associated with metabolic disturbance and increased insulin resistance (3). Moreover, during mid-pregnancy, placental hormones change maternal physiology to achieve a state of insulin resistance to support fetal growth. Thus, starting pregnancy with pre-existing obesity-related insulin resistance poses an increased risk of developing GDM (4). It is well documented that both GDM and obesity are independently associated with adverse maternal and

infant outcomes such as pre-eclampsia, emergency caesarean delivery, fetal macrosomia and neonatal hypoglycemia (5–8). Previous studies in our health-care area have observed a significant increase in the risk of GDM, with its associated maternal and fetal adverse events (9,10). Consequently, the development of preventive strategies become a priority.

Numerous randomized controlled trials (RCTs) have been conducted to attempt a reduction in the incidence of GDM. These trials have explored the effect of dietary modifications, physical activity, combined interventions, and medication. However, the results remain controversial (11), and very few have demonstrated efficacy in high-risk populations (12–14). Heterogeneities of the population included, the types of intervention evaluated and the time of their initiation are some of the main causes that explain the inconsistencies observed (15). Treatment of GDM has focused on proper glycemic control and adequate weight gain during pregnancy using diet and exercise (4,15,16), and, if lifestyle approaches alone are not sufficient, insulin or other antihyperglycemic drug therapies may be prescribed (17). Nutritional intervention may include a wide range of possibilities. Although no specific diet has been described for the management of GDM, previous studies have shown that large amounts of carbohydrates (CHO), especially rapidly absorbed CHO, have a negative impact on glycemic control (18–21). Therefore, individualized moderation of CHO intake is reasonable, and the focus should turn to the type of CHO, prioritizing those high in fiber.

MedDiet is high in complex CHO and healthy fats. It has demonstrated many health benefits for people with obesity, including weight loss and reduction of associated comorbidities (22–24). In this regard, the San Carlos study has demonstrated a decrease in GDM in its cohort of pregnant women using a prompt (12th GW) nutritional intervention, based on a MedDiet, with free supply of extra virgin olive oil (EVOO) and nuts (10). However, prevention strategies in the specific setting of overweight and obesity has not been fully explored.

In this context, the main aim of this study is to investigate if early nutritional treatment in overweight or obese women reduces the incidence of GDM and its associated complications, including maternal-fetal adverse effects during pregnancy and at 3 years postpartum.

2. Materials and Methods

2.1. Study Design

The Hospital Clínico San Carlos is a recognized healthcare, education and research center in Madrid, Spain. Pregnant women have their first clinical visit between 8th and 12th GW, coinciding with the first ultrasound scan. At this visit, the first trimester's blood tests are reviewed, and general recommendations are given for a good pregnancy. The oral glucose tolerance test (OGTT) to detect GDM is performed between 24-28 weeks of gestation, using the IADPSG criteria. With the aim of preventing GDM, the San Carlos study, a single-center, prospective, RCT, was launched in 2015. It included all pregnant women attending their first gestational visit between 8th and 12th GW with FBG <92 mg/dL. This cohort encompasses three main research studies that we have used in our analysis, including only women with a BMI≥ 25 kg/m^2 from each of the three cohorts/studies:

The first study (Study 1) was a RCT (ISRCTN84389045, ethic code CI 13/296-E), in which women were randomly assigned before the 12th GW to either the CG or the IG. In this way, nutritional intervention could be ensured for at least 3 months. The IG was recommended a MedDiet guideline: insisting on increased consumption of EVOO (>40 ml/day) and pistachios (1 handful per day), with both foods provided free of charge. In contrast, women in the CG group were advised to limit their daily EVOO intake to less than 40 ml and to avoid eating nuts more than three times a week.

The second study (Study 2) (ISRCTN13389832, ethic code CI 16/442-E) assessed the effects of giving MedDiet-based recommendations in early pregnancy in a single group based on usual clinical practice, Real World (RW). These women were encouraged to follow the same nutritional guidelines as the RCT IG of Study 1, but without providing them with free EVOO and nuts.

And the last study (Study 3) was a RCT (ISRCTN16896947, ethic code CI 16/316) in which women with a body mass index (BMI) ≥ 25 kg/m2 were randomized into CG and IG. In this case, intervention

consisted in increasing the consumption of nuts and EVOO, but only pistachios were administered free of charge, not EVOO.

A post hoc analysis of this sample was performed for women with overweight or obesity (BMI≥ 25 kg/m²). IGs from both RCTs and the group participating in the practice-based study underwent the analysis as IGs. This was because they were all encouraged to follow a MedDiet guideline, including specific dietary advice related to nuts and EVOO. These IGs were compared with the two CGs in the RCTs. Women diagnosed with GDM were closely monitored by the Department of Endocrinology and received a consistent protocolized treatment, regardless of whether they were assigned to the control or intervention group.

During the study, pregnant women were followed-up uniformly to reinforce the nutritional intervention. Three visits were made during pregnancy, coinciding with the third, fifth and ninth month of gestation. At 3 months postpartum, another motivational interview was conducted to encourage all patients, regardless of the group they belonged to, to follow the previously proposed nutritional recommendations. After 3 years of the study, patients were invited again for a voluntary follow-up visit to evaluate the results. However, several women refused to participate for different reasons, such as being pregnant again or health problems, among others.

2.2. Patients

A total of 735 pregnant women: 246/CG (144/RCT + 102/pistachios) and 489/IG (120 RCT + 162 RW + 207 Pistachios) were included in the present study. All agreed to participate in the study and signed the informed consent. Women's demographic and clinical characteristics at baseline can be seen in Table 1.

Table 1. Characteristics of maternal population with pregnancy BMI≥25 kg/m² at baseline visit (8-10th GW) assessed in the clinical trial population by groups.

	CONTROL (N=246)	INTERVENTION (N=489)	p
Age (years)	31.8 + 5.6	32.9 + 5.1	0.067
Race/Ethnicity			
Caucasian	121 (49.6)	267 (54.7)	
Latin American	117 (48.0)	206 (42.2)	
Others	8 (2.5)	16 (3.1)	0.103
Family history of T2D	62 (25.3)	155 (31.3)	
MetS (>2 components)	56 (22.9)	114 (23.4)	0.330
Previous history of GDM	7 (2.8)	24 (4.7)	
Miscarriages	93 (37.9)	195 (39.9)	0.137
Educational status:			
Elementary education	32 (13.1)	37 (7.6)	
Secondary School	93 (38.)	162 (33.2)	
University Degree	117 (47.8)	278 (56.9)	
UNK	4 (1.2)	11 (2.2)	0.066
Employment	187 (76.3)	376 (77.0)	0.355
Number of pregnancies:			
Primiparous	90 (36.7)	171 (35.1)	
Second pregnancy	66 (26.9)	154 (31.6)	
>2 pregnancies	90 (36.8)	164 (33.4)	0.608
Smoker:			
Never	152 (62.0)	269 (55.1)	
Current	14 (5.7)	42 (8.6)	0.382
Body Weight (Kg):			
Pre pregnancy	72.7 + 12.1	71.8 + 11.2	0.336

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At baseline	75.5 + 11.6	74.8 + 10.4	0.365
BMI (kg/m²):			
Pre pregnancy	27.8 + 3.9	27.4 + 3.6	0.223
At baseline	28.9 + 3.7	28.6 + 3.3	0.209
Blood Pressure (mmHg):			
Systolic	113 + 9	113 + 11	0.438
Diastolic	69 + 9	70 + 9	0.484
FBG (mmol/L)	4.5 + 0.4	4.5 + 0.3	0.380
Insulin	22 + 26	23 + 26	0.567
HOMA-IR	1.4 + 1.8	1.5 + 1.7	0.587
Cholesterol (mg/dl)	175 + 33	179 + 33	0.330
Triglycerides	94 + 46	93 + 48	0.806
HbA1c %	5.1 + 0.2	5.1 + 0.3	
mmol/mol	32 + 0.8	32 + 0.9	0.928
TSH mcUI/mL	2.1 + 1.3	2.1 + 1.6	0.482
Med Score	4.7 + 1.7	4.9 + 1.7	0.221
Nutrition Score	0.2 + 3.2	0.2 + 3.1	0.859
Physical Activity	-1.8 + 0.9	-1.8 + 0.9	0.872

Data are Mean $\pm$ SD or number (%) Metabolic Syndrome (MetS). body mass index (BMI); Mediterranean Diet Score (Med Score); Type 2 Diabetes (T2D) Gestational Diabetes Mellitus (GDM) after PREDIMED Study.

2.3. Studied Variables:

2.3.1. Clinical and Demographic Characteristics:

At the first visit, a brief medical history was taken, including age, ethnicity (Caucasian, Latin American or others), family history of Type 2 diabetes mellitus (T2DM), having more than two components of the MetS (BMI≥30 kg/m², WC ≥89.5 cm, systolic blood pressure (SBP)≥ 130 mm Hg, diastolic blood pressure (DBP) ≥85 mmHg, triglycerides (TG) ≥150 mg, HDL-Chol <50 mg/dL, abnormal glucose regulation (AGR) and HOMA-IR ≥ 3.5), previous miscarriages, educational level (elementary education, secondary school, university degree), employment status, number of previous pregnancies and smoking habits (never or currently). Anthropometric data such as weight (kg) and BMI (kg/m²) were also collected, and blood pressure was measured using a digital sphygmomanometer (Omron 705IT, Omron Global, Kyoto, Japan). In patients who were followed up at 3 years postpartum, it was possible to analyze body composition by means of electrical bioimpedance (SECA mBCA 514), obtaining weight (kg), fat mass (FF) (kg) and BMI (kg/m²). WC was measured with a non-stretch tape measure using ISAK criteria.

2.3.2. Laboratory Parameters:

Blood and urine samples were obtained after an overnight fast of at least 8 hours. Fasting blood glucose (mmol/L) was measured in serum by the Glucose-Hexokinase method in an AU5800-Beckman Diagnostic. To measure HbA1c as a percentage, ion exchange high-performance liquid chromatography (HPLC) was used with a Tosoh G8 analyzer (Tosoh Co., Tokyo, Japan). The method is standardized against the International Federation of Clinical Chemistry and has an imprecision of 1.23% for values of 32.23 mmol/mol (5.1% NGSP) and 1.36% for values of 85.24 mmol/mol (10% NGSP). To measure fasting serum insulin (FSI), a chemiluminescence immunoassay on an IMMULITE 2000 Xpi (Siemens, Healthcare Diagnostics, Munich, Germany) was used, with an imprecision of 21 IUU/mL concentrations of 5.91%. Homeostasis for insulin resistance (HOMA) was calculated as glucose (mmol/L) × insulin (µIU/mL)/22.7. Total cholesterol was quantitatively assessed using the colorimetric enzymatic test method (CHOD-PAP). In a similar way, the colorimetric enzymatic method using glycerol phosphate oxidase p-amino phenazone (GPO-PAP) was used to determine serum TG. Fasting serum insulin (FSI) levels were determined using a chemiluminescence

immunoassay performed on an IMMULITE 2000 Xpi analyzer from Siemens Healthcare Diagnostics in Munich, Germany. The inter-assay accuracy was 6.3% for concentrations of 11 uIU/mL and 5.91% for insulin concentrations of 21uIU/mL. Thyroid-stimulating hormone (TSH) levels were assessed using a third-generation sandwich-chemiluminescence immunoassay with magnetic particles. This method employed human TSH mouse monoclonal antibodies and the DXI-800® analyzer from Beckman–Coulter. The manufacturer's specified reference range for TSH in non-pregnant adults is 0.38–5.33 µIU/mL, with a sensitivity of 0.01 µIU/mL. The intraassay coefficient of variation (CV) is less than 10%, and the TSH measurement range spans from 0.01 to 50.0 µIU/mL. Intra-assay CVs are 4.9% for a concentration of 0.69 µIU/mL, 5,8% for 5.47 µIU/mL, and 6.2% for 29 µIU/mL. In addition, to ensure the quality of the procedures, an External Quality Assurance Programme of the SEQC (Spanish Society of Clinical Chemistry) evaluates the methods monthly and performs a review of the methods.

2.3.3. Lifestyle and Data Collection:

The Mediterranean diet adherence screener (MEDAS), a validated semiquantitative questionnaire derived from the PREDIMED study, was used to evaluate the nutritional intervention and adherence to the MedDiet (25). A score above 5 indicated adequate adherence, although the aim was to achieve a minimum score of 7. The second questionnaire applied was the Nutrition and Diabetes Complications Trial (DNCT), which more precisely reflects the consumption of specific food groups per week, as well as the physical activity carried out on a regular basis. This questionnaire evaluates 15 items: three of them focused on physical activity and the remaining twelve on diet. Factors that prevent T2DM were given an A (+1 point); neutral factors were given a B, which do not prevent T2DM but do not increase the risk (+0 points); and a C was given when the factor increased the risk of developing T2DM (-1 point). Further details of the assessment are given in the pilot study (26).

2.4. Statistical Analysis

Categorical variables are represented as percentages, while continuous variables are expressed as median (standard deviation) and interquartile range (IQR). Differences between groups were compared using X2 tests, Student's t-test, or the Mann-Whitney U-test, depending on the type of variable and its normal or non-normal distribution. Logistic regression was used to assess the impact of nutritional treatment on adverse maternal, neonatal and delivery outcomes that showed significant differences in univariate analysis. The control group served as the reference group. Relative risk (RR) was adjusted, and the 95% confidence interval (95% CI) was calculated considering age, parity, and BMI. All p-values were two-tailed and were considered statistically significant if less than 0.05. These analyses were performed using SPSS software, version 21, based in Chicago, IL, USA.

3. Results

Table 2 shows maternal and fetal outcomes during pregnancy in the CG and IG. The rate of GDM was lower in the CG (31.7%) in comparison to the IG (25.1%) (p=0.037), which was associated with lower fasting basal glucose. HbA1c was also lower in both the second and third trimesters of pregnancy (5.1 vs 4.9; p=0.001 and 5.4 vs 5.2; p=0.001, respectively), although neither value conferred a diagnosis of pre-diabetes (HbA1c≥5.7%). No significant differences were observed in weight gain during pregnancy or adequate weight gain from baseline BMI. In terms of treatment, no significant changes were observed in the number of patients who had nutritional intervention or in total insulin doses between the two groups. However, there were differences in basal insulin requirements, with lower doses needed in IG versus CG (11,5% vs 0,1%; p=0,030), probably due to lower fasting basal glucose levels. IG women had lower rates of other associated comorbidities such as diastolic blood pressure (DBP) between 36-38th GW, and urinary tract infection (UTI) and albuminuria. There were no differences in blood pressure between 24-28th GW, in the diagnosis of hypertension or preeclampsia, or in bacteriuria. Regarding neonatal outcomes, there was an increase in small-for-

gestational-age (SGA) neonates in the IG relative to the CG (6,1 vs 2,8%; p=0,036). However, there were no differences in other anthropometric variables, such as weight and length, nor in large-for-gestational-age (LGA) infants. There were also no differences in rates of prematurity or dystocia, umbilical cord pH, APGAR, or other adverse effects in the newborn (hypoglycemia, respiratory problems, fever).

Table 2. Maternal, pregnancy and neonatal outcomes.

MATERNAL OUTCOMES	**CONTROL** **(N=246)**	**INTERVENTION** **(N=489)**	*p*
GDM n (%)	78 (31.7)	123 (25.1)	0.037
75g-OGTT 24-28 GW			
FBG (mmol/L)	4.9 ± 0.4	4.7 ± 0.4	0.014
1 h Blood Glucose mmol/L	7.1 ± 1.7	7.0 ± 1.7	0.839
2 h Blood Glucose mmol/L	6.1 ± 1.5	6.1 ± 1.3	0.885
HbA1c			
24-28 GW %	5.1 ± 0.3	4.9 ± 0.3	0.001
mmol/mol	32 ± 0.9	30 ± 0.9	
36-38 GW %	5.4 ± 0.4	5.2 ± 0.3	0.001
mmol/mol	34 ± 0.9	33 ± 0.8	
FBG 36-38 GW (mmol/L)	4.5 ± 0.4	4.4 ± 0.4	0.046
FSI (mcUI/mL)			
24-28 GW	13 ± 5.7	10 ± 6	0.040
36-38 GW	17 ± 12	14 ± 13	0.037
HOMA-IR			
24-28 GW	$2.8 \pm 1,9$	2.4 ± 1.5	0.037
36-38 GW	4.0 ± 2.7	3.7 ± 5.3	0.085
Nutritional treatment	41 (52.6)	66 (53.7)	
Insulin requirements (total)	37 (47.4)	57 (46.3)	0.192
Bolus	6 (7.7)	4 (3.2)	
Basal	22 (28.2)	52 (42.2)	
Basal/Bolus	9 (11.5)	1 (0.1)	0.030
Weight gain (Kg)			
to Baseline (8-10 GW)	2.9 ± 4.3	2.8 ± 4.6	0.817
to 24-28 GW	7.7 ± 5.4	7.3 ± 5.8	0.479
to 36-38 GW	11.1 ± 8.5	11.6 ± 7.9	0.549
Adequate weight gain			
To 24-28 GW (<5 kg)	78 (31.7)	162 (33.1)	0.273
To 36-38 GW (< 9kg)	66 (26.8)	118 (24.1)	0.798
BP (mm Hg)			
24-28 GW Systolic	110 ± 10	110 ± 10	0.782
Diastolic	66 ± 8	66 ± 8	0.939
36-38 GW Systolic	119 ± 12	117 ± 11	0.069

Diastolic	75 ± 9	72 ± 9	0.046
Pregnancy-induced			
Hypertension	13 (5.2)	28 (5.7)	0.902
Preeclampsia	5 (2.0)	13 (2.7)	0.698
Albuminuria	8 (3.3)	4 (0.1)	0.019
Bacteriuria	63 (25.6)	105 (21.5)	0.119
Urinary Tract Infection	33 (13.4)	27 (5.5)	0.001
Delivery			
Vaginal eutocic	142 (58.1)	277 (56.7)	
Instrumental	45 (18.5)	75 (15.9)	
Cesarean section	59 (23.4)	137 (27.2)	0.579
Emergency	32 (54.3)	59 (43.1)	0.051
NEONATAL OUTCOMES			
GW at birth	39.7 ± 1.3	39.4 ± 1.7	0.032
≤ 37 weeks	7 (2.9)	23 (4.7)	0.415
≤ 34 weeks	1 (0.5)	3 (0.6)	0.108
Birthweight (g)	3302 ± 442	3283 ± 568	0.666
Centile	51 ± 29	54 ± 29	0.303
Height (cm)	49.4 ± 2.0	49.4 ± 2.2	0.970
Centile	43 ± 30	45 ± 28	0.388
LGA >90 centile	12 (4.9)	37 (7.6)	0.109
SGA <10 centile	7 (2.8)	30 (6.1)	0.036
Ph	7.27 ± 0.06	7.28 ± 0.08	0.161
≤7	12 (0.5)	36 (0.7)	0.783
1 min Apgar	8.8 ± 0.8	8.7 ± 1.2	0.070
<7	4 (1.6)	19 (3.9)	0.669
5 min Apgar	9.9 ± 0.4	9.7 ± 0.8	0.074
<7	3 (1.2)	14 (2.8)	0.496
Neonatal			
Hypoglycemia	6 (2.4)	7 (1.4)	0.384
Respiratory distress	4 (1.6)	7 (1.4)	0.570
Hyperbilirubinemia	7 (2.8)	17 (3.5)	0.422
NICU	12 (4.9)	12 (2.5)	0.108

Gestational Diabetes Mellitus (GDM); Fasting Blood Glucose (FBG); Fasting Serum Insulin (FSI); Blood Pressure (BP); Gestational Week (GW); Large for Gestational Age (LGA); Small for Gestational Age (SGA); Neonatal intensive care unit (NICU).

Table 3 shows biochemical, anthropometric, and clinical data of women at postnatal, 3-month and 3-year follow-up. This follow-up was completed by a total of 141 women of the CG women (57%) and 312 of the IG women (64%). We found a higher weight gain at 3 years postpartum in the CG compared to the IG (5.1±10.4 vs 3.6±6.5; p=0.045). There were no significant differences in other anthropometric measures. In analytical parameters, no differences were seen except for higher LDL-Chol in CG against IG at 3 months postpartum (128±29 vs 118±31; p=0.007). In terms of lifestyle,

differences in MedDiet adherence were observed, with higher scores in IG than in CG at both 3 months and 3 years postpartum (6.4±1.7 vs 5.9±1.9; p=0.042 and 6.9±2.0 vs 6.5±1.9; p=0.013). However, no differences were found in the level of physical activity.

Table 3. Postnatal biochemical, anthropometric, and clinical data of women during postnatal follow-up, at 3 months and 3 years post-delivery by groups.

	CG (N=141; 57%)		IG (312; 64%)		p (CG vs IG)	
	3-M PD	**3-year PD**	**3-M PD**	**3-year PD**	**3-M PD**	**3-yearPD**
BW (Kg)	77.2 + 11.1	77.7 + 16.2	77.1 + 10.9	75.0 + 12.9	0.978	0.770
BMI(Kg/m²)	29.7 + 3.9	29.3 + 5.0	29.6 + 3.8	28.3 + 3.7	0.840	0.491
BW-Change (Kg)	5.8 + 6.4	5.1 + 10.4	5.2 + 7.1	3.6 + 6.5	0.528	0.045
WC (cm)	93 + 8	93 + 11	93 + 9	92 + 10	0.718	0.903
FM (Kg)	Na	30.4 + 12.3	Na	29.4 + 6.2	---	0.652
sBP(mmHg)	116 + 15	117 + 13	115 + 13	114 + 12	0.752	0.282
dBP(mmHg)	75 + 11	75 + 10	74 + 10	73 + 8	0.672	0.336
T-Chol (mg/dL)	203 + 38	184 + 29	199 + 40	179 + 34	0.312	0.284
HDL-Chol	59 + 12	54 + 15	60 + 17	55 + 11	0.811	0.449
LDL-Chol	128 + 29	112 + 25	118 + 31	107 + 28	0.007	0.116
TG (g/L)	97 + 50	96 + 48	95 + 53	93 + 45	0.781	0.602
Apo-B (mg/dL)	96 + 23	90 + 24	91 + 25	86 + 24	0.228	0.496
FSI (µIU/mL)	9.1 + 8.1	13.2 + 16.2	8.4 + 8.3	10.6 + 7.8	0.485	0.255
HOMA-IR	2.1 + 1.8	3.9 + 2.8	2.2 + 2.8	3.4 + 4.4	0.634	0.760
FSG (mmol/L)	4.8 + 0.5	5.1 + 0.6	4.8 + 0.4	5.0 + 0.5	0.623	0.140
2hOGTT(mmol/L)	Na	5.8 + 1.7	Na	5.4 + 0.9	----	0.191
HbA1c-IFCC %	5.3 + 0.2	5.4 + 0.3	5.3 + 0.3	5.4 + 0.3	0.915	0.728
cPR (mg/dL)	0.42 +0.49	0.65 + 1.01	0.62 + 0.82	0.63+1.04	0.381	0.932
PA Score	-1.6 + 0.7	-1.8 + 1.0	-1.7 + 0.9	-1.6 + 1.0	0.462	0.305
Nutrition Score	3.5 + 2.9	1.6 + 3.1	3.8 + 3.5	1.8 + 3.6	0.558	0.710
MEDAS Score	5.9 + 1.9	6.5 + 1.9	6.4 + 1.7	6.9 + 2.0	0.042	0.013

Data are Mean (SD). Months (M); Post Delivery (PD); Body weight (BW); Body Mass Index (BMI); Waist Circumference (WC); Fat Mass (FT); No available (Na); systolic blood pressure (sBP); diastolic blood pressure (dBP); total-cholesterol (T-chol.); High-Density Lipoprotein (HDL); Low-Density Lipoprotein (LDL); Triglyceride (TG); Fasting Serum Insulin (FSI); lipoprotein B (APO-B); fasting serum glucose (FSG); Homeostasis assessment model for insulin resistance (HOMA-IR); C reactive protein (CPR); Mediterranean Diet Adherence Screener (MEDAS). Physical Activity (PA) Score, (Walking daily (>5 days∕week) Score 0: At least 30 min. Score +1, if >60 min. Score -1, if <30 min. Climbing stairs (floors∕day, >5 days a week): Score 0, between 4 and 16; Score +1, >16; Score -1: <4).

A detailed comparison of the postpartum rate of MetS components between overweight and obese women separated by IG vs CG and woman with GDM vs NGT is shown in Table 4. We compared the relative risk (RR) of developing MetS and its components according to the nutritional intervention at 3 months (panel A) and 3 years (panel B) after delivery. No significant differences were found at 3 months postpartum between IG and CG in any of the MetS components. However, as expected, at 3 months postpartum there was a reduction in RR (95% CI) in the GDM group versus the NGT group in the rates of IFG, prediabetes, and all MetS components (WC ≥89.5 cm, SBP of ≥130 mmHg, DBP ≥85 mmHg, and AGR), except for HOMA-IR in which there were no different between groups.

In contrast, at 3 years postpartum (panel B) there was a reduction in the RR (95% CI) of the IFG rate (0.51 (0.28-0.92); p=0.019). Also, there were significant differences in the risk of developing MetS between both groups. This would imply that the nutritional intervention could be a protective factor against long-term MetS, as there was a higher rate of women with obesity in the CG (0.51 (0.28-0.92); p=0.041), as well as a higher rate of women with a WC ≥89.5 cm (0.54 (0.31-0.94); p=0.022). There were no significant differences for the other components of the MetS or in the RR of developing prediabetes.

Finally, comparing the GDM group with the group of women with GTN at 3 years postpartum, a decrease in the RR of both IFG (1.84 (1.34-2.53); p=0.000) and prediabetes (1.73 (1.15-2.60); p=0.001) was observed. Regarding the components of MetS, a higher risk of developing MetS for having more than 2 components was found in the GDM group vs. women with NGT (1.62 (1.01-2.65); p=0.008). This was due to the increased rate of women with WC ≥89.5 cm and AGR. In contrary, there was no significant difference in the rate of women with BMI >30 kg/m2, nor with HOMA-IR≥3.5, nor elevated blood pressure (SBP ≥130 mmHg, nor DBP≥85 mmHg), nor in a dysregulated lipid profile (TG ≥150 mg/dL and HDL<50 mg/dL) between both groups.

Table 4. Comparison of post-delivery rate of metabolic syndrome (MetS) components between obese/overweight women from IG vs CG and women with GDM vs normal glucose tolerance (NGT).

	CG (141) VS IG (312)			GDM (146) VS NGT (307)		
	% (N)	RR (95% CI) IG	p	% (n)	RR (95% CI) GDM	p
PANEL A. (3 MONTHS)						
GLYCEMIC STATUS						
IFG	5.0 (7) VS 4.5 (14)	0.90 (0.36-2.28)	0.496	7.5 (11) vs 3.3 (10)	1.44 (1.09-2.27)	0.040
PREDIABETES (HBA1C ≥ 5.7%)	5.0 (7) VS 6.7 (21)	1.43 (0.59-3.46)	0.289	13.0 (19) vs 2.9 (9)	1.47 (1.01-2.13)	0.008
METS COMPONENTS						
RAISED (WC ≥ 89.5 cm)	71.3 (100) VS 68.9 (215)	1.04 (0.87-1.23)	0.332	75.8 (111) vs 66,5(204)	1.36 (1.19-1.56)	0.000
RAISED SBP ≥ 130 mm Hg	8.5 (12) VS 10.5 (33)	1.27 (0.62-2.60)	0.316	19.2 (28) vs 5.5 (17)	1.22 (1.01-1.56)	0.041
RAISED DBP ≥ 85 mm Hg	17.0 (24) VS 14.2 (44)	0.81 (0.41-1.60)	0.326	28.8 (42) vs 8.5 (26)	1.44 (1.08-1.94)	0.002
RAISED TRIG. ≥150 mg/dL	11.6 (16) VS 11.1 (34)	0.96 (0.51-1.79)	0.503	13.8 (20) vs 9.8 (30)	1.22 (1.00-1.54)	0.032
REDUCED HDL-C <50 mg/dL	21.8 (22) VS 21.7 (43)	1.00 (0.56-1.78)	0.550	22.3% (21) vs 21.5 %(44)	1.02 (0.84-1.23)	0.217
AGR	7.8 (11) VS 9.3 (29)	1.25 (0.60-2.61)	0.345	15.1 (22) VS 5.9 (18)	1.48 (1.11-2.01)	0.001
RAISED HOMA-IR ≥3.5	12.2 (17) VS 10.2 (31)	0.81 (0.39-1.71)	0.355	11.6 (17) VS 10.1 (31)	1.22 (0.93-1.60)	0.069
>2 COMPONENTS OF METS	11.4 (16) VS 13.2 (41)	1.19 (0.55-2.58)	0.413	17.8 (26) VS 10.1 (31)	1.37 (1.00-1.96)	0.035
PANEL B. (3 YEARS)						
GLYCEMIC STATUS						
IFG	17.7 (25) VS 9.6 (30)	0.51 (0.28-0.92)	0.019	21.9 (32) vs 7.5 (23)	1.84 (1.34-2.53)	0.000
PREDIABETES (HBA1C ≥ 5.7%)	8.5 (12) VS 8.0 (25)	1.23 (0.57-2.65)	0.370	15.1 (22) vs 4.9 (15)	1.73 (1.15-2.60)	0.001
IGT	9.5 (14) VS 0	n. a		9.6 (14) vs 0 (0)	n. a	

METS COMPONENTS

BMI ≥ 30 (Kg/m²)	41.1 (58) vs 24.0 (75)	0.45 (0.19-0.96)	0.041	34.2 (50) vs 27.0 (83)	1.02 (0.76-2.32)	0.547
RAISED (WC ≥ 89.5 cm)	62.5 (88) vs 44.6 (139)	0.54 (0.31-0.94)	0.022	75.0 (102) vs 40.7 (125)	1.22 (1.07-1.52)	0.031
RAISED SBP ≥ 130 mm Hg	13.5 (19) vs 11.2 (35)	0.90 (0.30-2.73)	0.530	18.5 (27) vs 8.8 (27)	1.20 (0.75-1.93)	0.298
RAISED DBP ≥ 85 mm Hg	17.0 (24) vs 5.1 (16)	0.75 (0.51-1.12)	0.227	9.6 (14) vs 8.5 (26)	1.00 (0.61-1.63)	0.632
RAISED TRIG. ≥150 MG/dL	11.3 (16) vs 10.6 (33)	0.94 (0.45-1.98)	0.507	15.8 (23) vs 8.5 (26)	1.22 (0.93-1.61)	0.069
REDUCED HDL-C <50 mg/dL	26.2 (37) vs 23.4 (73)	0.99 (0.65-1.52)	0.524	43.8 (64) vs 15.0 (46)	1.12 (0.96-1.31)	0.074
AGR	21.9 (31) vs 14.1 (44)	0.69 (0.42-1.11)	0.083	28.8 (42) vs 10.7 (33)	1.72 (1.33-2.23)	0.000
RAISED HOMA-IR ≥ 3.5	12.8 (18) vs 6.4 (20)	1.00 (0.46-2.18)	0.578	11.6 (17) vs 6.8 (21)	1.17 (0.84-1.63)	0.227
>2 COMPONETS OF METS	24.1 (34) vs 8.0 (25)	0.56 (0.33-0.94)	0.003	22.6 (33) vs 8.5 (26)	1.62 (1.01-2.65)	0.008

Data are % (number). Impaired Fasting Glucose (IFG); Metabolic syndrome (MetS); High-Density. Lipoprotein (HDL); Waist Circumference (WC); Systolic Blood pressure (sBP); diastolic blood pressure (dBP); Triglycerides (TRG); abnormal glucose regulation (AGR); Impaired Glucose Tolerance (IGT); Body Mass Index (BMI); GDM: Gestational Diabetes Mellitus, NGT: Normal Glucose Tolerance; Control group (CG). RR, relative risk. p denotes differences between groups.

4. Discussion

This study shows that a nutritional intervention based on MedDiet significantly reduces the rate of GDM and the RR of developing MetS at 3 years postpartum, when implemented at the beginning of pregnancy (before 12 weeks of gestation) in women with BMI≥25kg/m². In fact, this is because FBG and HBA1c levels were significantly lower in the IG group.

A recent systematic review suggested that nutritional intervention during pregnancy and postpartum may improve glucose regulation in patients with GDM (27). However, nutritional intervention covers a wide range of possibilities. This is why many studies insist on focusing on the type of nutritional intervention recommended, and aim to develop specific guidelines for a standardized approach (4,28,29). Our study has provided evidence for using a nutritional intervention with MedDiet based on vegetables, fruits, legumes, whole grains, lean meats instead of processed meats, oily fish, EVOO and nuts, as well as reducing consumption of processed and sugary foods as early as possible in pregnant women to reduce the likelihood of developing GDM and the long-term negative postnatal metabolic impact. In addition, the dietary recommendations given are specific, measurable, and assessed through validated semi-quantitative questionnaires. This allows not only to reproduce the study, but also to establish specific food consumption frequencies for dietary recommendations.

We found no significant differences in the rate of maternal-fetal adverse events. This may be because the total sample included women who are already at high prior risk of developing adverse events in pregnancy due to their own excess weight. In fact, all patients studied presented a BMI≥25 kg/m² both at baseline and after intervention. A recent RCT in pregnant women at risk of hyperglycemia (29) showed a significant, but modestly smaller, decrease in adverse neonatal events. This study performed the intervention later, before 20 weeks' gestation, and has the limitation of non-standardized treatment of GDM. Perhaps these differences are explained by the fact that this study included overweight patients with additional risk factors for developing GDM, such as previous diagnosis of GDM, high gestational age, first-degree relatives with diabetes, polycystic ovarian syndrome, and non-European ancestry. In addition, the sample included a limited number of Hispanic women.

Previous studies have focused on the beneficial effects of the prevention of GDM on the control of total weight gain during pregnancy (4,28,30,31). However, in this study, we observed a reduction in the rate of GDM, even in the setting of no significant differences in total weight gain between women in the GC and the IG. This could be because of the influence of the complex interrelationship between weight, fat distribution and diet. In fact, we did observe a higher rate of women with WC≥89.5 cm at 3 years postpartum in the CG, drawing the attention to the importance of body composition and distribution in the follow-up of weight gain during pregnancy. Thus, our study reinforces what other large studies such as PREDIMED have shown: MedDiet prevents the development of MetS in the long-term follow-up due to a lower central distribution of adipose tissue. It would be interesting to validate methods for the assessment of body composition in pregnant women, in order to develop more personalized nutritional recommendations in the specific setting of pregnancy (32).

A topic of great interest concerns the timing of initiation and duration of the nutritional intervention set for pregnant women for the prevention of GDM. Many studies argue in favor of its implementation as soon as possible, especially in high-risk patients (31,33). In this regard, previous reports suggest the need for initiating the intervention in the 20th GW to achieve a relevant reduction of GDM (29), but not all reports have observed a clear benefit when implementing it at this time (12). There is no doubt that appropriately designed and targeted interventions can be effective tools for the management of pregnancies which are complicated by overweight and obesity. However, demonstration of its efficacy is somehow blurred because of lack of resources and failure of previous studies to establish the appropriate time at which this personalized nutritional care should be provided to effectively prove benefit.

Our study entails some limitations. Firstly, this is a post-hoc study, meaning that the initial main objective was not to evaluate women with overweight or obesity. This limits the sample size; however, we have managed to group enough patients to obtain significant data. On the other hand, postnatal follow-up was performed in approximately 60% of women, mainly due to the difficulty of attendance because of the recent delivery, having other small children, and unavailability to attend medical follow-ups. Other causes were a change of community, follow-up in a private hospital or not wishing to continue participating in the study. However, this proportion is still considered acceptable and is descriptive of our population, representing more than half of the total sample. This highlights the challenge of adhering to the recommended postnatal follow-up by all scientific guidelines. Another limitation is that diet is a subjective, complex, and changing parameter and questionnaire responses could be biased. However, semi-quantitative questionnaires are a standardized, quick, and non-invasive tool to adequately represent food intake, and are always administered by specialized professionals to minimize bias. Therefore, the use of validated questionnaires allows us to overcome this limitation, and provides a genuine character to our study, by objectively quantifying and measuring the nutritional intervention carried out.

5. Conclusions

In conclusion, our research demonstrates that an early nutritional intervention using MedDiet, along with supplementation of EVOO and nuts, in women with a BMI≥25kg/m² and initiated during early pregnancy, decreases the rate of GDM and positively influences the risk of developing MetS over a three-year period after delivery. Therefore, indicating MedDiet-based dietary patterns in women with excess weight from early pregnancy can be considered a preventive strategy for the development of postnatal GDM and MetS. Future studies with a defined and measurable nutritional intervention in high-risk women are needed to further confirm our findings.

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