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Keywords: Pregnancy; Prediabetic State; Abnormal Glucose Regulation; Postpartum; Glucose Intolerance

Article

Modifiable Risk Factors and Trends in Changes in Glucose Regulation during the 1st Three Years Postdelivery. The St Carlos Gestational Diabetes Mellitus Prevention Cohort

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Abstract: Objective: To identify risk factors(RF) related to abnormal glucose regulation(AGR) 3 years postpartum according to 3-month-postpartum glucose status. Research design: Normoglycemic pregnant women of the St. Carlos Gestational Study included before gestational week 12, during 2015-2017. Of 3,036 eligible women, 2529 were followed-up until delivery: 1400 participated in postpartum follow-up. AGR defined as fasting serum glucose (FSG)>5.6 mmol/L and/or HbA1c >5.7% (39 mmol/mol) and/or 2h-SG ≥140/mg/dL after 75-g OGTT. 12-modifiable and 3-unmodifiable RF were analyzed for associations with glycemic changes. Reinforcement of Mediterranean Diet adherence was provided to all women at the postpartum visit by a dietitian Results: 137/1400(9.8%) women presented AGR 3 years postpartum, 27/137(19.7%) also had at 3 months, whereas 110/137(80.2%) had not. The remaining 1,263(90.2%) women were normoglycemic 3 years postpartum, 1180/1263(84.3%) were at 3 months, while 83/1263(6.08%) had AGR and became normoglycemic. Women with GDM were more likely to progress to AGR 3 years postpartum (OR:1.60[1.33-1.92]) and less likely to remain normoglycemic (OR:0.22[0.15-0.33]) versus non-GDM women. Having >2/3 unmodifiable RF was associated with a reduced rate of maintained normoglycemia (OR:0.56[0.39-0.80]) and an increased risk of progression to AGR (OR:1.90[1.28-2.83]). Having >5/12 modifiable RF was associated with a reduced rate of maintained normoglycemic (OR:0.74[0.51-0.99]) and reversion of AGR (OR:0.49[0.25-0.97]), an increased progression to AGR (OR:1.40[1.00-2.09]), and persistence of AGR (OR:2.57[1.05-6.31]). Pre-gestational BMI≥25kg/m2 (OR:1.80[1.19-2.71]), post-delivery weight gain (OR:2.22[1.10-4.48]), and waist circumference >89.5cm (OR:0.54[0.36-0.79]), (all p<0.05) were the main modifiable RF. Conclusions: RF related to an increased probability for 3-year-postpartum AGR despite 3-month normoglycemia were identified, potentially useful when designing personalized strategies for pregnant women, directed towards minimizing unfavorable outcomes.

Keywords: Pregnancy; Prediabetic State; Abnormal Glucose Regulation; Postpartum; Glucose Intolerance

1. Introduction

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Gestational Diabetes Mellitus (GDM) is defined as an abnormal glucose tolerance with onset or initial detection during pregnancy. The prevalence of GDM is increasing [1], and it represents one of the most common medical complications of pregnancy [2]. In addition to its well-known obstetric and neonatal complications [3], GDM is a recognized risk factor (RF) for future maternal and offspring obesity [4], abnormal glucose regulation (AGR), T2DM [4,5], and cardiovascular disease [6,7]. Different RF have been identified for GDM, including maternal overweight/obesity, delayed childbearing, a prior history of GDM, a family history of T2DM, and ethnicity [1,2,8,9]. Appropriate screening, diagnosis, and treatment [6] have been related to improved pregnancy outcomes. However, there is a lack of consensus for long-term follow-up management and preventive strategies in women with a prior history of GDM as well as for their offspring [2].

For short-term follow-up, scientific societies recommend postnatal assessment of glycemic status at 3 months postpartum in women diagnosed with GDM, to detect current AGR, as well as to determine the future risk for developing T2DM and cardiovascular disease [1,6,10,11]. Remarkably, abnormal glucose regulation (AGR) at 3 months postpartum has also been observed in women without a history of GDM, suggesting that pregnancy might be a pro-diabetogenic state [12–15]. In neither women with prior AGR nor those with NGT have risk factors for subsequent AGR been fully established. Thus, both progression to AGR from normoglycemia as well as reversion to normal glucose regulation (NGR) from AGR may be possible. In fact, both reversion to NGT and progression to T2DM and the metabolic syndrome (MetS) have been described in populations with prediabetes [16,17]. Nevertheless, detection and optimal management may be crucial for return to a normoglycemic state.

The San Carlos GDM Prevention Cohort comprises different studies for the prevention of GDM with a Mediterranean Diet(MedDiet)-based early nutritional intervention, enhanced with extra virgin olive oil (EVOO) and nuts [18,19] initiated before gestational week (GW) 12. Women from this cohort were evaluated during pregnancy, as well as in short and long-term follow-up, thereby representing a unique sample to assess postnatal glucose changes as well as to determine risk factors and potential target populations in whom preventive strategies should be intensified.

The aim of this study was to assess rates of reversion to NGR, persistence of AGR, progression to AGR, or persistence of normoglycemia at 3 years postpartum, according to data collected at 3 months postpartum in participants included in the San Carlos GDM Prevention Cohort as well as to evaluate potential RF that could affect changes in glucose regulation.

2. RESEARCH DESIGN AND METHODS.

2.1. Study design

The study population originated from the San Carlos GDM Prevention Cohort which includes several studies:

The San Carlos GDM Prevention Study a randomized controlled trial (ISRCTN84389045; https://doi.org/10.1186/ISRCTN84389045) directed towards evaluating the effect of an intervention based on a MedDiet enriched with EVOO and nuts on the incidence of GDM. The results indicated the intervention reduced the incidence of GDM and adverse pregnancy outcomes [18].To translate these beneficial effects, these recommendations were adopted as standard nutritional management in a real-world study in clinical practice (ISRCTN13389832; https://doi.org/10.1186/ISRCTN13389832) [19]. This study was a prospective, clinical-based, interventional study with a single group. Women received a motivational lifestyle interview with emphasis on daily consumption of EVOO and nuts. Finally, a prospective, clinical-based randomized intervention study was carried out to test whether different components of MedDiet, in particular EVOO and nuts, had a different effect on the likelihood of developing GDM in pregnant women with a BMI ≥ 25 and < 35 kg/m^2 (ISRCTN16896947; https://doi.org/10.1186/ISRCTN16896947).

The Institutional Review Board and The Clinical Ethics Committee of the Hospital Clínico San Carlos approved the aforementioned studies (CI 13/296-E, CI 16/442-E and CI 16/316). Written informed consents were provided and signed by all participants.

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2.2. Study population

Universal screening for GDM is performed in all pregnant women in our setting. Eligible participants were recruited by the Endocrinology and Nutrition Department of the Hospital Clínico San Carlos, a tertiary hospital in Madrid, Spain, with a reference healthcare population of approximately 445,000 patients, between January 2015 and November 2017, and followed-up a median of 3 years after delivery.

Inclusion criteria were: pregnancy in women ≥18 years of age, normoglycemia at 8-12 GW (FSG <92 mg/dL, 5.1 mmol/L) and a single gestation. Exclusion criteria included: gestational age at entry ≥14 GW, pre-gestational diabetes or FSG ≥92 mg/dL (≥5.1 mmol/L), multiple pregnancy, intolerance to nuts or EVOO, new pregnancy during the 3-year follow-up, and medical conditions or pharmacological therapy that could compromise the effect of the intervention and/or the follow-up program.

A total of 3,026 women attending their first gestational visit at 8-12 GW were assessed for inclusion. From these, 2,529 were followed until delivery. Finally, 1,400 women (55.4 %) participated in the 3-years-postpartum follow-up program.

2.3. Study timeline and intervention

The gestational protocol has been previously reported [18,19].

Postpartum Follow-up protocol:

Visit 1, 3 months postpartum: Clinical evaluation, dietary questionnaire, blood and urine sample, and a motivational lifestyle interview. This meeting was held with all women regardless of whether they belonged to the control or intervention group, or whether they had had GDM or not. It consisted in guidance from dieticians in a 1-hour group session. The recommendations were similar for all women in both the control group and intervention group: reinforcement of MedDiet adherence and ≥40 mL daily EVOO consumption (raw and for cooking), and at least 25–30 g of pistachios ≥3 days/week.

Visit 2, 3 years postpartum: Clinical evaluation, dietary questionnaire, blood and urine sample, with a 2-hour 75-g OGTT.

2.4. Data collection

Clinical and anthropometric data were collected: maternal age; ethnicity; education; employment; smoking status; personal history (hypertension, dyslipidemia, obesity, other diseases); obstetric history (number or pregnancies, prior GDM, miscarriages); family history (diabetes, hypertension, dyslipidemia, obesity and MetS, the latter considered when >2 components of the MetS were present in at least one first-degree family member). Pre-gestational body weight (BW), gestational BW, height, body mass index (BMI), blood pressure.

Laboratory tests: Blood samples were drawn after an overnight 8-10 hour fast. Fasting serum glucose (FSG) was determined by the glucose oxidase method, serum triglycerides with a colorimetric enzymatic method using glycerol phosphate oxidase p-amino phenazone (GPO-PAP). HbA1c levels were standardized by the International Federation of Clinical Chemistry and Laboratory Medicine using ion-exchange high-performance liquid chromatography in gradient, with a Tosoh G8 analyzer (Tosoh Co., Tokyo, Japan). Serum insulin was determined by a chemiluminescence immunoassay in an Inmmulite 2000 Xpi (Siemens, Healthcare Diagnostics, Munich, Germany). The homeostatic model assessment-insulin resistance (HOMA-IR) was calculated as FSG (mmol/L) x fasting serum insulin (FBI) (μU/mL) / 22.5. Serum levels of high-density lipoprotein cholesterol (HDL-c) were measured in an Olympus 5800 (Beckman-Coulter, Brea, CA, USA).

Dietary and lifestyle assessment: The Diabetes Nutrition and Complication Trial (DNCT) questionnaire was used to assess physical activity and eating habits, as previously described [21]. The 14-point Mediterranean Diet Adherence Screener (MEDAS) was used to evaluate the adherence to a MedDiet pattern [22]. These were filled out at each visit by a dietician in a personal interview.

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2.5. Categorization of glucose testing at 3 months and 3 years postpartum

Categories based on FSG and/or HbA1c at 3 months after delivery: we defined women with a FSG <100 mg/dL (< 5.6 mmol/L) and HbA1c <5.7% (<39 mmol/mol) as NGR, and ≥100 mg/dL (5.6 mmol/L) and/or HbA1c ≥5.7% (39 mmol/mol) as AGR. At 3 years postpartum, a 2-hour serum glucose during 75-g OGTT ≥140/mg/dL was considered abnormal, while <140 was considered normal [23].

2.6. Unmodifiable and modifiable RF

-Three non-modifiable RF have been considered in this study: -A family history of T2DM and/or >2 components of the MetS (categorized as 0: if none, 1: ≥1 presented). -Parity (0: primiparous, 1: multiparous), and -Age (0: <35, 1: ≥35 years). Women were classified as being in an unfavorable category when 2 or 3 unmodifiable risk factors coexisted.

Twelve modifiable RF have been considered: -Pre-pregnancy and – 3-month postpartum BMI (0: <25, 1: ≥25 kg/m^2. -Weight change, defined as the difference between BW at 3 months postpartum and pre-pregnancy BW (0: ≤0, 1: >0 kg). -Waist circumference adapted for the Spanish population (0: <89.5 cm, 1: ≥89.5 cm). -Hypertension (0: systolic blood pressure (SBP) <130 and diastolic blood pressure (DBP) <85 mmHg, 1: SBP ≥130 and/or DBP ≥85 mmHg). -Dyslipidemia (0: HDL-c ≥50 mg/dL and triglycerides <150 mg/dL, 1: HDL-c <50 mg/dL and/or triglycerides ≥150 mg/dL). -Alcohol consumption in the post-natal period (0: between15 and 30 g alcohol/day, 1: <15 or ≥30 g alcohol/day). Smoking habits (0: no or former, 1: smokers). The eating pattern was evaluated using -the Nutrition questionnaire (0: ≥4, 1: <4 score) and -MEDAS (0: ≥6, 1: <6 score). Physical activity was evaluated with the -activity score (PAS) (0: ≥0, 1: <0 score) and - daily minutes of sport activity of at least moderate intensity (0: ≥15, 1: <15 min/day). Women were classified in the unfavorable group when >5 modifiable risk factors coexisted.

2.7. Study outcomes

The primary endpoint was to evaluate glycemic status at 3 years postpartum based on the 3-month-postpartum glycemic state. Specifically, the 3-year reversion or persistence of AGR and the 3-year progression or persistence of (NGR) rates were considered.

The secondary endpoint was to identify different pre-gestational, gestational and 3-month post-delivery risks factors that could impact on glycemic changes.

2.8. Statistical analysis

Variables are presented with their number and frequency distribution or the median and interquartile range (IQR). Continuous variables are given by their mean and standard deviation (±SD) and were compared using 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. Comparison between group characteristics for categorical variables was evaluated by the χ^2 test.

The magnitude of association between 3-year-postpartum glucose regulation status (persistence or reversion of normoglycemia, and progression or persistence of abnormal glucose regulation) and modifiable or unmodifiable risk factors were evaluated using the crude odds ratio (OR) and 95% confidence interval (95%CI).

All p values are 2-tailed at <0.05. Analyses were performed using SPSS, version 21 (Chicago, Illinois).

3. RESULTS

Women participants were older than non-participants, were more frequently non-smokers, held university degrees, and were qualified workers. Additionally, they showed higher scores in the Nutrition and MEDAS questionnaires when compared to non-participants. However, the rate of GDM (20.6% vs 15.2%), pre-term deliveries, and small for gestational age babies, was higher in participants. No differences in anthropometric, blood pressure, glycemic and lipid parameters were found between the two groups (Table 1).

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Table 1. Prepregnancy and pregnancy characteristics of women included in the San Carlos GDM Prevention Cohort eligible for the postdelivery program.

	Non-participants (n=1129)	Participants (n=1400)	*P*
			Sociodemographic features
Age (years)	32.1 ± 5.5	33.1 ± 4.9	0.001
Ethnicity			
Caucasian	724 (64.1)	935 (66.8)	
Hispanic	364 (32.2)	430 (30.7)	
Others	41 (3.6)	35 (2.5)	0.040
University Degree	683 (60.5)	964 (68.9)	0.001
Workers	839 (74.3)	1134 (81.0)	0.001
Smoking status			
Never smokers	604 (53.5)	801 (57.2)	
Current smokers	113 (10.0)	95 (6.8)	0.001
Pregnancies			
First	458 (40.6)	625 (44.6)	
Second	347 (30.7)	415 (29.6)	
Third or above	324 (28.7)	360 (25.7)	0.251
Prior			
GDM	37 (3.3)	48 (3.4)	0.535
Miscarriage	417 (36.9)	458 (32.7)	0.018
Family history of some components of the MetS	463 (41.0)	603 (43.1)	0.130
			Pre-pregnancy features
Body weight (kg)	61.9 ± 11.4	61.7 ± 11.2	0.655
BMI (kg/m^2)	23.4 ± 4.0	23.4 ± 4.0	0.896
Questionnaires (scores)			
Nutrition	0.1 ± 3.2	0.5 ± 3.1	0.003
MEDAS	4.8 ± 1.7	5.0 ± 1.8	0.016
Physical activity	-1.8 ± 1.0	-1.9 ± 1.0	0.441
			Pregnancy and delivery features
SBP (mmHg) (8-12GW)	109 ± 10	109 ± 10	0.167
DBP (mmHg) (8-12GW)	67 ± 9	67 ± 9	0.613
FSG (mg/dL) (8-12GW)	80 ± 6	80 ± 6	0.056
HbA1c (%)(8-12GW)	5.1 ± 0.3	5.2 ± 0.2	0.181
HOMA-IR (8-12GW)	1.2 ± 1.4	1.1 ± 1.3	0.126
Triglycerides (mg/dL) (8-12GW)	80 ± 33	82 ± 41	0.901
GDM (24-28w)	172 (15.2)	289 (20.6)	<0.001
Body weight gain (24GW)	7.4 ± 4.8	7.1 ± 4.1	0.176
Body weight gain (38GW)	11.7 ± 6.7	11.8 ± 6.3	0.863
Insulin treatment	40 (23.3)	70 (24.2)	0.432
High BP or preeclampsia	45 (4.0)	53 (3.8)	0.960
Prematurity (< 37GW)	40 (3.5)	90 (6.4)	0.001
Cesarean section	244 (21.6)	296 (21.2)	0.740
LGA (> 90 percentile)	42 (3.7)	50 (3.6)	0.471
SGA (< 10 percentile)	34 (3.0)	80 (5.7)	0.001

Data are shown as mean ± standard deviation for quantitative variables or number (%) for qualitative variables. Statistical significance at the P < 0.05 level. BMI; body mass index; BP, blood pressure; DBP, diastolic blood pressure; FSG, fasting serum glucose; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; LGA, large

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for gestational age; MEDAS, Mediterranean Diet Adherence Screener; MetS, metabolic syndrome; SBP, systolic blood pressure; SGA, small for gestational age; GW, gestational weeks.

A total of 110 women (7.9%) presented AGR at 3 months postpartum. They were more frequently of Hispanic origin, and had a lower rate of college-level studies compared to women with NGR. They also had a higher pregestational BW and BMI, and during pregnancy presented a higher rate of GDM (44% vs 19%; p<0.001), preeclampsia, and newborn SGA, and a more unfavorable 3-month-postpartum metabolic profile (Table 2).

Table 2. Comparison between women with abnormal glucose regulation (AGR) and normal glucose regulation (NGR) at 3 months postdelivery.

	Participants (n=1400)		
	NGR (n=1290)	AGR (n=110)	*P*
Sociodemographic features			
Age (years)	33.1 ± 4.9	33.3 ± 4.6	0.724
Ethnicity			
Caucasian	878 (68.1)	57 (51.8)	
Hispanic	383 (29.7)	47 (42.7)	
Others	29 (2.2)	6 (5.5)	0.002
University Degree	903 (70.0)	61 (55.5)	0.001
Workers	1051 (81.5)	83 (75.5)	0.231
Smoking status			
Never smokers	734 (56.9)	67 (60.9)	
Current smokers	85 (6.6)	10 (9.1)	0.505
First pregnancy	585 (45.3)	40 (36.4)	0.422
Prior			
GDM	42 (3.3)	6 (5.5)	
Miscarriage	411 (31.9)	47 (42.7)	0.347
Family history MetS (>2 components)	257 (19.9)	25 (22.7)	0.893
Pre-pregnancy features			
Body weight (kg)	61.0 ± 11.0	64.0 ± 14.0	0.012
BMI (kg/m^2)	23.3 ± 3.9	24.6 ± 4.8	0.001
Questionnaires (scores)			
Nutrition	0.5 ± 3.1	0.1 ± 3.1	0.095
MEDAS	5.0 ± 1.8	4.7 ± 1.7	0.166
Physical activity	-1.9 ± 1.0	-1.8 ± 0.9	0.784
Pregnancy and delivery features			
SBP (mmHg) (8-12GW)	108 ± 10	110 ± 11	0.021
DBP (mmHg) (8-12GW)	67 ± 9	68 ± 9	0.396
FSG (mg/dL) (8-12GW)	80.3 ± 6.0	82.8 ± 5.6	<0.001
HbA1c (%)(8-12GW)	5.1 ± 0.2	5.3 ± 0.4	0.045
HOMA-IR (8-12GW)	1.1 ± 1.3	1.4 ± 1.5	0.007
Triglycerides (mg/dL) (8-12GW)	80 ± 37	104 ± 73	<0.001
GDM (24-28w)	245 (19.0)	44 (40.0)	<0.001
Body weight gain (24w)	7.2 ± 4.2	6.7 ± 3.7	0.343
Body weight gain (38w)	11.8 ± 6.4	11.3 ± 5.4	0.407
Insulin treatment	55 (4.3)	15 (13.6)	0.204
High BP or preeclampsia	43 (3.3)	10 (9.1)	0.036
Prematurity (< 37w)	79 (6.1)	11 (10.0)	0.088
Cesarean section	267 (20.7)	29 (26.4)	0.567

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LGA (> 90 percentile)	43 (3.3)	7 (6.4)	0.091
SGA (< 10 percentile)	67 (5.2)	13 (11.8)	0.007
3 months postpartum			
Body weight (kg)	66.3 ± 11.6	69.7 ± 12.8	0.015
BMI (kg/m²)	25.1 ± 4.3	26.6 ± 4.8	0.005
Weight change (3-m - pregestational)	4.7 ± 5.5	6.0 ± 7.1	0.052
Waist circumference (cm)	85.4 ± 9.5	90.0 ± 9.9	<0.001
SBP (mmHg)	111 ± 12	113 ± 11	0.142
DBP (mmHg)	71 ± 9	72 ± 9	0.583
FSG (mg/dL)	83.6 ± 7.0	94.9 ± 12.1	<0.001
HbA1c (%)	5.2 ± 0.3	5.6 ± 0.3	<0.001
HOMA-IR	1.8 ± 2.4	3.4 ±4.9	<0.001
Triglycerides (mg/dL)	80 ± 43	95 ± 65	0.006
HDL-cholesterol (mg/dL)	64 ± 17	60 ± 13	0.027
Questionnaires (scores)			
Nutrition	3.9 ± 3.5	3.5 ± 3.5	0.071
MEDAS	6.2 ± 1.9	5.9 ± 1.8	0.377
Physical activity	-1.6 ± 0.9	-1.7 ± 0.8	0.618
Sport activity (min/d)	16 ± 90	3 ± 16	0.065

Data are shown as mean ± standard deviation for quantitative variables or number (%) for qualitative variables. Statistical significance at the P < 0.05 level. BMI; body mass index; BP, blood pressure; DBP, diastolic blood pressure; FSG, fasting blood glucose; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; FSG, fasting serum glucose; LGA, large for gestational age; m, months; MEDAS, Mediterranean Diet Adherence Screener; MetS, metabolic syndrome; AGR, abnormal glucose regulation; NGR, normal glucose regulation; SBP, systolic blood pressure; SGA, small for gestational age; W, weeks.

Of 137 (9.8%) women exhibiting AGR 3 years postpartum, 27 (1.9%) had it at 3 months while 110 (7.9%) were NGT at 3 months. Of the 1,263 (90.2%) women with NGT at 3 years postpartum, 1,180 (84.3%) maintained it from the beginning, while 83 (5.9%) normalized glucose regulation from 3-month-postpartum (Table 3).

Table 3. Glycemic status change at 3 years (3-y) postdelivery according to metabolic characteristics at 3 months (3-m) postdelivery.

	3-m AGR (110)			3-m NGR (n=1290)		
	3-y NGR Reversion (n=83)	3-y AGR Persistence (n=27)	*P*	3-y AGR Progression (n=110)	3-y NGR Persistence (n=1180)	*P*
Age (years)	32.7 ± 4.6	34.9 ± 4.5	0.031	34.8 ± 4.5	32.9 ± 4.9	0.001
GDM (24-28 GW)	30 (36.1)	14 (51.2)	0.001	50 (45.5)	195 (16.5)	0.001
3-m body weight (kg)	69.5 ± 11.8	69.8 ± 12.3	0.008	69.0 ± 11.8	66.0 ± 11.5	0.031
3-m BMI (kg/m²)	26.2 ± 4.6	27.6 ± 5.1	0.014	26.3 ± 4.9	25.0 ± 4.2	0.014
< 25	57 (68.7)	15 (55.6)		69 (62.7)	859 (72.8)	
25- 29.9	16 (19.3)	6 (22.2)		25 (22.7)	232 (19.7)	
≥ 30	10 (12.0)	6 (22.2)	0.138	16 (14.5)	89 (7.5)	0.034
Pre-gestational obesity	11 (13.3)	3 (11.1)	0.907	13 (11.8)	63 (5.3)	0.005
3-y weight (kg)	64.0 ± 13.4	67.6 ± 10.8	0.023	67.3 ± 11.1	63.0 ± 10.8	0.023
Body weight change						
3-m minus pregestational	4.2 ± 6.5	6.6 ± 7.1	0.056	6.6 ± 6.9	4.7 ± 5.5	0.011
3-y minus 3-m	-4.1 ± 3.9	-2.1 ± 5.1	0.026	-0.7 ± 5.0	-2.0 ± 5.6	0.014
3-y minus pregestational	0.8 ± 0.5	0.9 ± 0.6	0.917	4.8 ± 5.6	1.2 ± 2.5	0.033

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3-m waist (cm)	88.9 ± 8.9	90.3 ± 10.2	0.036	87.6 ± 8.9	85.2 ± 9.6	0.036
3-m SBP (mmHg)	110 ± 10	113 ± 12	0.071	113 ± 14	110 ± 12	0.071
3-m DBP (mmHg)	68 ± 6	73 ± 9	0.175	73 ± 12	71 ± 9	0.175
3-m FSG (mg/dL)	92 ± 11	96 ± 12	0.021	86 ± 7	83 ± 7	0.001
3-m HbA1c (%)	5.6 ± 0.3	5.7 ± 0.3	0.042	5.3 ± 0.2	5.2 ± 0.3	0.001
3-m HOMA-IR	2.6 ± 2.2	3.5 ± 5.5	0.907	1.8 ± 1.2	1.7 ± 2.4	0.907
3-m HDL-c (mg/dL)	62 ± 13	52 ± 12	0.016	62 ± 19	64 ± 16	0.627
3-m Triglycerides (mg/dL)	90 ± 51	109 ± 94	0.399	82 ± 34	80 ± 43	0.006
3-m Questionnaires (scores)						
Nutrition	3.7 ± 3.6	2.9 ± 3.3	0.429	4.0 ± 3.5	4.1 ± 3.5	0.282
MEDAS	6.1 ± 1.8	5.6 ± 1.6	0.366	6.0 ± 2.1	6.2 ± 1.8	0.377
Physical activity	-1.6 ± 0.9	-1.8 ± 0.6	0.499	-1.5 ± 0.9	-1.6 ± 0.9	0.339
3-m sport activity (min/d)	32 ± 18	0 ± 6	0.415	14 ± 69	34 ± 96	0.065

Data are shown as mean ± standard deviation for quantitative variables or number (%) for qualitative variables. Statistical significance at the $P < 0.005$ level. AGR, abnormal glucose regulation; NGR, normal glucose regulation; BMI; body mass index; DBP, diastolic blood pressure; FSG, fasting serum glucose; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; FBG, fasting blood glucose; m, months; MEDAS, Mediterranean Diet Adherence Screener; NGR, normal glucose regulation; SBP, systolic blood pressure; w, weeks.

Women were classified into groups according to their 3-month-postpartum glucose regulation status:

Persistence of AGR: At 3 years postpartum, 27/110 women (24.5%) maintained AGR. These women were older, presented a higher BMI, waist circumference and lower HDL-cholesterol levels at 3 months postpartum. Furthermore, their BW was higher at 3-year follow-up and they had lost less weight from 3 months to 3 years, compared to those women who reverted to normoglycemia.

-AGR reversion to normoglycemia: Of a total of 83/110 (75.5%) women with AGR at 3 months postpartum, 83 (75.5%) normalized their glucose parameters at 3 years postpartum. Women who reverted their altered glycemic state were younger and presented a lower body mass index and waist circumference measure and higher HDL levels at 3 years postdelivery than women with persistence of AGR. No differences were found in the rest of the anthropometric, metabolic and clinical variables studied in both groups, including the pre-gestational body weight

-AGR progression: Of the 1290 women with normoglycemia at 3 months postdelivery, 110 women (8.5%) progressed to AGR at 3 years postdelivery. Compared to women with NGR persistence, women with AGR progression were older and presented a higher BMI, waist circumference and triglyceride levels at 3 months postpartum. In this latter group, pre-gestational obesity was more prevalent, and they showed more weight gain at 3 months and 3 years postdelivery compared to their pre-gestational weight and thus, lose less weight during follow-up, from 3 months to 3 years.

-NGR persistence: 1180/1290 (91.5%) women with NGR at 3 months postpartum maintained normal glucose regulation at 3 years postpartum. These women had a more favorable body weight evolution, losing more weight and/or gaining less weight that those women who did not maintain normoglycemia. These women also had a lower rate of pre-gestational obesity, and a lower age at pregnancy.

Analysis of modifiable and unmodifiable risk factors

Logistic regression analysis was used to identify independent predictors of the glycemic changes. Women with GDM were more likely to progress to AGR at 3 years postpartum, and less likely to remain normoglycemic compared with NGT women. Having at least 2 unmodifiable risk factors was associated with a reduction in the rate of persistence of normoglycemia and an increased risk of progression to AGR. Similarly, being overweight/obese pregestation, having regained pregestational weight at 3 months and having a central distribution of fat reduced the rate of

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persistence of NGR at 3 years postpartum, and increased the probability of progression to AGR. Having >5 unfavorable modifiable risk factors was associated with a reduction in the rate of persistence of NGR (0.74:0.51-0.99) and reversion of AGR (0.49:0.25-0.97), and was also associated with an increased risk of progression to AGR (1.40:1.00-2.09) and persistence of AGR (2.57:1.05-6.31), all p<0.05), respectively. Data are shown in Table 4.

Table 4. Associations between unmodifiable and modifiable risk factors and glycemic status at follow-up.

	NORMAL GLUCOSE REGULATION (NGR)				ABNORMAL GLUCOSE REGULATION (AGR)			
	Persistence (n=1180)		Reversion (n=83)		Progression (n=110)		Persistence (n=27)	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
GDM (24-28w)	195 (78.9)	**0.22(0.15-0.33)**	30 (68.2)	0.51 (0.21-1,23)	50 (20.4)	**1.60 (1.33-1.92)**	14 (31.2)	1.34 (0.88-2.05)
Unmodifiable risk factors								
Family history MetS	225 (19.1)	**0.64 (0.43-0.96)**	21 (25.3)	0.87 (0.70-1.08)	32 (29.1)	**1.63 (1.04-2.54)**	4 (14.8)	0.51 (0.16-1.66)
Parity	634 (53.7)	0.79 (0.55-1.14)	49 (59.0)	0.50 (0.22-1.14)	67 (60.9)	1.29 (0.87-1.93)	21 (77.8)	2.49 (0.89-6.65)
Age ≥ 35 years	577 (48.9)	**0.63 (0.44-0.92)**	41 (49.4)	1.06 (0.86-1.32)	66 (60.0)	**1.64 (1.10-2.46)**	15 (55.6)	1.28 (0.54-3.06)
Unfavorable group≥2	435 (36.9)	**0.56 (0.39-0.80)**	34 (41.0)	0.80 (0.42-1.55)	59 (53.6)	**1.90 (1.28-2.83)**	13 (48.1)	1.34 (0.56-3.20)
Modifiable risk factors								
Preg-BMI ≥ 25kg/m^2	307 (26.0)	**0.59 (0.41-0.85)**	27 (32.5)	**0.45 (0.22-0.92)**	43 (39.1)	**1.80 (1.19-2.71)**	14 (51.9)	**2.85 (1.12-7.25)**
Del-BMI ≥ 25kg/m^2	321 (27.2)	0.69 (0.48-1.01)	26 (31.1)	0.66 (0.35-1.26)	41 (37.3)	**1.50 (1.00-2.27)**	12 (44.4)	1.75 (0.72-4.27)
Weight change > 0kg	833 (70.6)	**0.53 (0.29-0.94)**	51 (61.4)	**0.43 (0.20-0.93)**	93 (84.5)	**2.22 (1.10-4.48)**	7 (25.9)	3.64 (0.93-14.39)
WC ≥ 89.5cm	205 (17.4)	**0.54 (0.36-0.79)**	24 (28.9)	0.76 (0.39-1.48)	32 (29.1)	**2.02 (1.29-3.12)**	10 (37.0)	1.45 (0.58-3.61)
Hypertension	55 (4.7)	0.61 (0.35-1.08)	3 (3.6)	0.84 (0.65-1.08)	12 (10.9)	**1.94 (1.04-4.04)**	6 (22.2)	2.31 (0.35-15.14)
Dyslipidemia	164 (13.9)	0.98 (0.94-1.02)	13 (15.7)	0.64 (0.31-1.29)	12 (10.9)	1.28 (0.72-2.29)	7 (25.9)	1.89 (0.66-5.36)
Alcohol consumption	69 (5.8)	0.99 (0.92-1.05)	2 (2.4)	0.47 (0.17-1.33)	7 (6.4)	0.25 (0.53-2.98)	2 (7.4)	3.24 (0.43-24.20)
Smoking	7 (0.6)	na	0	na	0	na	0	na
Nutrition score < 4	636 (53.9)	0.68 (0.45-1.04)	32 (38.6)	0.79 (0.33-1.85)	71 (64.5)	1.42 (0.97-2.07)	12 (44.4)	1.38 (0.45-4.22)
MEDAS score < 6	683 (57.9)	0.99 (0.95-1.02)	52 (62.7)	0.87 (0.36-2.11)	68 (61.8)	1.19 (0.79-1.66)	16 (59.3)	1.11 (0.57-2.16)
Physical Activity < 0	906 (76.8)	0.66 (0.32-1.37)	77 (92.8)	0.57 (0.09-3.58)	99 (90.0)	1.45 (0.76-2.76)	26 (96.3)	2.03 (0.23-17.62)
Sport Activity < 15min	1026 (86.9)	0.93 (0.84-1.03)	81 (97.6)	na	100 (90.9)	**1.83 (1.00-3.35)**	27 (100)	**1.33 (1.19-1.49)**
Unfavorable group >5	387 (32.8)	**0.74 (0.51-0.99)**	33 (39.8)	**0.49 (0.25-0.97)**	46 (41.8)	**1.40 (1.00-2.09)**	17 (63.0)	**2.57 (1.05-6.31)**

Odds ratios in bold denote statistical significance at P <0.05 level. Unfavorable group: the presence of 2-3 unmodifiable risk factors or > 5 modifiable risk factors. BMI, body mass index; Del, delivery; MEDAS, Mediterranean Diet Adherence Screener; P-preg, pre-pregnancy; WC, waist circumference.

4. DISCUSSION

Gestational diabetes mellitus markedly increases the risk for later development of T2DM [5,24-26] and cardiovascular disease [26]. While most studies focus on GDM detection and the risk of developing diabetes later in life, there is limited evidence of glycemic dysregulation after a normal

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gestation or of NGT at 3 months postpartum. Yet, optimal detection and management might be crucial to avoid detrimental long-term outcomes.

The present prospective 3-year follow-up study of women with AGR (7.9%) or NGR (92.1%) at 3 months postpartum with or without prior GDM diagnosis showed that 24.5% of those with AGR maintained AGR at 3-year postpartum, while 75.5% reverted to NGR. Furthermore, AGR at 3-year-follow-up was observed in 8.5% of women with NGR 3 months postpartum. Therefore, a normal glucose profile during pregnancy or 3 months postdelivery does not guarantee normoglycemia in young women post-pregnancy, even in the absence of a prior GDM diagnosis. Women with GDM were less likely to remain normoglycemic than NGT women during gestation, and more likely to progress to AGR at 3 years postpartum.

Previous studies deal primarily with follow-up of patients with prior GDM. Furthermore, they focus on the risk for development of T2DM following delivery [27–29]. However, Retnakaran et al [30], reported that 17.1% of women with recent GDM followed by NGT at 3 months postpartum progressed to AGR when reassessed 9 months later. Furthermore, these authors found that even in women with milder degrees of gestational glucose intolerance, the incidence of prediabetes/diabetes at 1-year post-partum was around 10%, despite a normal 3-month OGTT [30].

The current study broadens the scope of evaluation of post-pregnancy disorders, by focusing on glycemic changes following pregnancy regardless of glycemic status during gestation. AGR 3 months postpartum was observed in 7.9% of the women, 40% of them with a prior diagnosis of GDM. This figure represents a lower prevalence than previously reported, with AGR rates ranging from 11 to 36% [31–34]. However, study heterogeneity hinders an adequate comparison of results, as GDM diagnostic criteria were not uniform. Nor was there homogeneity in the timing and criteria of postpartum tests. Furthermore, the lower prevalence observed in our sample could be explained by a predominant Caucasian race of participants, and a more generalized MedDiet pattern in Spain.

Importantly, fully 60% of the women exhibiting AGR at 3 months postpartum did not have prior GDM. Although pregnancy is known to deteriorate glucose tolerance [35], a majority of post-gestation studies have focused on women who had developed GDM [31–34]. Yet not studying non-GDR women prevents detection of postpartum AGR in a majority of women, according to our findings, excluding them from the early implementation of potentially beneficial clinical interventions.

In the current study, older women with a family history of type 2 diabetes and/or metabolic syndrome were less likely to present a normoglycemic status at 3-year follow-up. Furthermore, the risk for progressing from normoglycemia to abnormal glucose regulation at 3-year follow-up was higher in women exhibiting a combination of 2-3 unmodifiable risk factors. Within the modifiable risk factors, a higher pre-gestational and delivery BMI, greater gain weight during follow-up, central obesity, hypertension and less than 15 minutes per day of moderate physical activity were associated with a higher probability of progression to abnormal glucose regulation. In fact, the combination of >5 modifiable risk factors was linked to abnormal glucose regulation persistence.

Some of these factors have previously been related to later onset of diabetes in women with prior GDM, such as an older age, waist circumference ≥ 88 cm [28], higher BMI [30]. However, we did not find independent associations between insulin treatment during pregnancy and later onset of AGR or dyslipemia, as other studies have reported [28,29].

Out of the 2,529 women completed the gestation period study and 55.4% completed follow-up, a relatively high percentage given that women with new pregnancies were excluded. The high response rate could be related to the fact that long-term adherence to a MEdDiet enriched in EVOO and nuts together with physical activity was feasible for the women involved, thus promoting long-term adherence. However, other factors could have been decisive in the commitment of the women studied to compliance with the recommendations, such as a high educational status, and a better lifestyle habits.

The strengths of the current study include a complete assessment of a cohort of women, not limited to patient self-reference, but including a clinical and laboratory evaluation. In addition, to the best of our knowledge, this study provides one of the most comprehensive evaluations of different

modifiable and non-modifiable risk factors to date, not only during pregnancy but also at pre-gestational and early post-partum stages, permitting identification of women more prone to abnormal glycemic changes. Another strength is that early screening at 3 months postpartum was universal for all women, regardless of their risk for glycemic disorders through follow-up of a MedDiet pattern enhanced with EVOO and nuts. This MedDiet pattern is feasible for all women to follow and could limit the rate of progression to AGR.

The study is not exempt from limitations. Firstly, the diagnostic criteria for AGR at 3 months postpartum were based on the use of HbA1c and FSG. The OGTT was not performed at 3 months but rather at 3 years postpartum. This could underestimate the rate of women with early AGR. However, >90% of participants were breastfeeding at that moment, and many women find the OGTT inconvenient. In fact, the rate of screening process attendance when the OGTT was in use was <60%. Additionally, we previously found that the combination of A1c-FSG may identify a similar number of women with prediabetes while assuring a higher rate of attendance to tests. Secondly, the rate of alcohol consumption was low in our population. This may be because alcohol consumption was not recommended during the breastfeeding period, and maintenance of lactation is encouraged. Thirdly, the time dedicated to exercise was quite limited in our population, with an average of 15 minutes daily in > 50% of women. We therefore cannot exclude the obtention of further benefits in women more physically active, beyond what we have observed in the current study. However, 15 minutes daily could be sufficient to obtain positive metabolic effects, and is not in the realm of the unattainable, even in the postpartum period.

In conclusion, according to the data obtained in the current study, only 40% of the women with AGR in the early postpartum evaluation had had GDM while the rest had been normoglycemic during pregnancy, suggesting that all women should be tested after delivery, with at least a FSG and A1c.

Women should be individually monitored after the pregnancy to detect early glycemic changes, in an attempt to avoid the long-term development of T2DM and cardiovascular complications. This is particularly important for those women who are over 35 years of age and have a family history of MetS. Our data indicate that a 3-year follow-up could be of particular benefit for women with pre-pregnancy overweight/obesity, and those who have not recovered their pre-pregnancy weight, and who also have a central distribution of body fat. Efforts must be made to ensure that at least 50% of the modifiable risk factors of the 12 evaluated in this study are favourable. These findings should be contemplated in the practical-clinical guidelines and applied in the settings in which these women are treated.

Author Contributions: MAR, AB, ALC-P, ADu, PMM, MAR, PdM, JAD, LdV, VM, JV, IR, MP, RMO were involved in Conceptualization and design, data curation, analysis and interpretation of data. AlC-P is responsible of funding acquisition. ALC-P, CF, IM, IJ, MAR, MJT, MMN, MP, Adu, PdM, AB, LdV, VM, JV; RMO. were involved in Supervision, Validation and Visualization Researched data, contributed to discussion, and investigation. MC, MP, PMM, MAR, MAR were involved in researched data and reviewed and edited the manuscript. Writing – original draft: ALC-P, MAR, VM, IR, PMM wrote the first draft of the manuscript Writing – review & editing: MAR, ALC-P, PMM, VM, IR. All authors have seen and agree with the content of the full last version of manuscript. AL C-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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Data and Resource Availability: The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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