Can J Diabetes 43 (2019) 621–626

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Gestational Glycemic Parameters and Future Cardiometabolic Risk at Medium-Term Follow Up

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Key Messages

- This study presents follow-up data at 8 years in a cohort of female subjects who had been previously investigated for gestational diabetes mellitus.
- Baseline intrapregnancy glycemic parameters were shown to be independently associated with current lipid parameters; the area under the curve$_{glucose}$ of the oral glucose tolerance test performed during pregnancy showed the strongest association.
- The area under the curve$_{glucose}$ of the oral glucose tolerance test performed during pregnancy was also found to be independently associated with the presence of metabolic syndrome at 8 years of follow up.
- A high prevalence of subclinical atherosclerosis, as assessed by carotid intima-media thickness, was found in the study population (83%).
- None of the intrapregnancy glycemic parameters were shown to be associated with the presence of increased carotid intima-media thickness. This might merit longer follow-up periods.

ARTICLE INFO

Article history:
Received 28 September 2018
Received in revised form
17 February 2019
Accepted 20 March 2019

Keywords:
cardiometabolic risk
gestational diabetes
pregnancy-associated dysglycemia

ABSTRACT

Objectives: Gestational diabetes is known to be associated with increased risk for future maternal cardiovascular disease. However, it is not known which gestational glycemic parameters mediate this risk. The study's aim was to assess the relationship between gestational glycemic parameters and gestational diabetes with future cardiometabolic status.
Methods: This cohort study comprised subjects who underwent assessment for gestational diabetes by means of a 75 g oral glucose tolerance test at Mater Dei Hospital, Malta, during 2009. These patients were consequently followed up through January 2018. Carotid intima-media thickness was assessed as a marker of subclinical atherosclerosis in both common carotid arteries.
Results: The mean age of the study population was 38.3±5.4 years. Of the 203 participants, 43 (21.2%) had gestational diabetes. Gestational diabetes and individual glycemic parameters of intrapregnancy oral glucose tolerance tests were associated with higher glycated hemoglobin, fasting plasma glucose, low-density-cholesterol and lower high-density-cholesterol levels and with the presence of the metabolic syndrome in both univariate and multivariate analyses after a median follow up of 8 years. Neither gestational diabetes nor individual glycemic parameters of intrapregnancy oral glucose tolerance tests was associated with current carotid intima-media thickness.
Conclusions: Our results suggest that there is no threshold of glycemic parameters for predicting future cardiometabolic status. Our data also suggest that the known association between gestational diabetes and cardiovascular disease is mediated, at least in part, by higher postpregnancy glycemia and worse lipid profiles, even though these metabolic parameters often remain within the normal range.

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1499-2671/
https://doi.org/10.1016/j.jcjd.2019.03.007

Mots Clés:
risque cardiométabolique
diabète gestationnel
dysglycémie associée à la grossesse

RÉSUMÉ

Objectifs : Il est connu que le diabète gestationnel est associé à un risque accru de maladies cardiovasculaires ultérieures chez la mère. Toutefois, on ne connaît pas les paramètres glycémiques gestationnels qui entraînent ce risque. L'objectif de l'étude était d'évaluer la relation entre les paramètres glycémiques gestationnels et le diabète gestationnel, et le risque cardiométabolique futur.
Méthodes : L'étude de cohorte regroupait des sujets qui avaient subi une épreuve d'hyperglycémie provoquée par voie orale après l'ingestion de 75 grammes de glucose au Mater Dei Hospital, à Malte, en 2009, pour évaluer le diabète gestationnel. Ces patients ont par conséquent eu un suivi jusqu'en janvier 2018. L'épaisseur de l'intima-média carotidienne a servi de marqueur d'athérosclérose subclinique des deux artères carotides communes.
Résultats : L'âge moyen de la population étudiée était de 38,3 ± 5,4 ans. Parmi les 203 participantes, 43 (21,2 %) avaient un diabète gestationnel. Dans les analyses univariées et multivariées après un suivi médian de 8 ans, le diabète gestationnel et les paramètres glycémiques individuels de l'épreuve d'hyperglycémie provoquée par voie orale durant la grossesse ont été associés à des concentrations plus élevées d'hémoglobine glyquée, des concentrations plasmatiques de la glycémie à jeun plus élevées, des concentrations de cholestérol de faible densité plus élevées et à des concentrations de cholestérol de haute densité plus faibles ainsi qu'à la présence du syndrome métabolique. Ni le diabète gestationnel ni les paramètres glycémiques individuels des épreuves d'hyperglycémie provoquée par voie orale durant la grossesse n'ont été associés à l'épaisseur présente de l'intima-média carotidienne.
Conclusions : Nos résultats montrent que les seuils de paramètres glycémiques ne permettent pas de prédire le risque cardiométabolique futur. Nos données suggèrent également que l'association connue entre le diabète gestationnel et les maladies cardiovasculaires est médiée, du moins en partie, par une glycémie plus élevée après la grossesse et de plus mauvais profils lipidiques, même si ces paramètres métaboliques demeurent souvent dans les valeurs normales.

Introduction

The International Diabetes Federation estimates that 20.9 million, or 16.2%, of live births in 2015 occurred in women who had had some form of hyperglycemia during pregnancy (1). Gestational diabetes mellitus (GDM) is known to be associated with increased risk for future maternal cardiovascular disease. The evidence comes primarily from a large record-linkage study in Canada that had a median follow up of 11.5 years and that showed that previous GDM was associated with increased risk for cardiovascular events (2). The Nurses' Health Study, likewise, reported that GDM was associated with cardiovascular disease (3); however, GDM was self-reported in this study. Neither study provides data about whether the association is mediated through dysglycemia or other factors such as dyslipidemia.

Both high fasting and high postprandial glucose levels have been linked to cardiovascular disease and increased mortality rates, not only in patients with type 2 diabetes (4–8) but also in subjects without diabetes (9,10). Interestingly, low fasting blood glucose levels have also been shown to be associated with increased rates of mortality in the general population (11), while isolated postload hyperglycemia has been demonstrated to be associated with higher mortality rates than combined fasting and postload hyperglycemia (12), suggesting that postprandial glucose excursions and glucose fluctuations might also be important in cardiovascular risk.

We hypothesized that dysglycemia during pregnancy is a marker of dysglycemia of a similar pattern but of lesser magnitude following pregnancy. The aim of this study was, therefore, to investigate whether various glycemic indexes observed during oral glucose tolerance tests (OGTTs) performed during pregnancy are associated with future metabolic parameters and carotid intima-media thickness (CIMT); the latter has been well validated as a marker of atherosclerosis and cardiovascular risk (13). We investigated a number of intrapregnancy glycemic parameters, including fasting plasma glucose levels, 2-h and 3-h postload plasma glucose levels, measures of glucose excursions and total postload glucose exposure, represented by the area under the curve for glucose ($AUC_{glucose}$), in order to explore which best predicted future cardiometabolic risk. We also investigated the association of GDM with future metabolic parameters and CIMT.

Methods

Study population

Eligible participants were subjects who had undergone assessment for GDM at Mater Dei Hospital, Malta, during 2009, by means of OGTTs. The list of eligible participants was obtained from the clinic where OGTTs are routinely performed. They are performed between the 24th and 28th weeks of pregnancy in our institution, and they include fasting plasma glucose (G_0), 2-h postload plasma glucose (G_2) and 3-h postload plasma glucose (G_3). These were noted together with G_2-G_0, G_3-G_0 and G_3-G_2. $AUC_{glucose}$ was also calculated according to the following formula: $G_0+1.5G_2+1.5G_3$. Assessment for GDM is performed in our institution in pregnant females who are deemed to be at high risk for developing gestational diabetes.

Consequently, the participants were followed up till 2018, when they were assessed for the presence of subclinical atherosclerosis by measurements of CIMT.

The study protocol was approved by the University of Malta Research Ethics Committee. All participants gave written informed consent.

Clinical and laboratory measurements

At follow up, in 2018, full medical and drug histories were noted for all participants. The weights of the neonates born in 2009 or 2010 were also noted. Clinical examinations were performed. Heights and weights were measured using a calibrated balance with stadiometer and with the participants wearing light clothes and without shoes. Body mass indexes were calculated as weight (in kg) divided by height (in meters) squared (kg/m^2). Waist circumferences were measured to the nearest 0.5 cm in the horizontal plane at the midpoint between the lowest rib and the iliac crest (14). Waist indexes were calculated as waist circumference (cm)

divided by 80 (15). Office blood pressures were measured with patients in the supine position after 5 min of rest.

All participants underwent routine blood investigations in the fasting state on the day of the clinical examination. The blood investigations included fasting lipid profiles and fasting plasma glucose, glycated hemoglobin (A1C) and serum creatinine levels. Estimated glomerular filtration rates were calculated using the Modified Diet in Renal Disease formula (16). A1C levels were measured by high-performance liquid chromatography.

Carotid intima-media thickness measurement

CIMT was assessed in both common carotid arteries in each participant using the Esaote (Genoa, Italy) quality intima-media thickness (QIMT) radio frequency device; the higher value was taken as the reference QIMT for each participant. The common carotid artery was utilized because, according to the Mannheim consensus, it increases the accuracy and reproducibility of the measurements obtained. The Esaote QIMT uses radio frequency signals to enable measurement of the CIMT with high spatial resolution. The QIMT tool automatically provides accurate measurements of all of the parameters that are independent of both the investigator's and the device's settings. In addition, reports generated using QIMT include a table that shows the expected QIMT values table and gives a clear indication of whether the CIMT is abnormal according to the patient's age; these tables have been validated using large worldwide databases (17). The Howard table, which was derived from the Atherosclerosis Risk in Communities study and represents the QIMT values in micrometers, was used in the study population. For each participant, the percentage of difference in QIMT was defined as ([Reference QIMT−Expected QIMT] / Expected QIMT) × 100.

Clinical definitions

GDM was defined according to the recommendations provided by the International Association of Diabetes and Pregnancy Study Groups (18) and the World Health Organization (19) with regard to fasting and 2-h postprandial glucose levels. Thus, the International Association of Diabetes and Pregnancy Study Groups recommend the following values as diagnostic thresholds: 5.1 mmol/L for fasting plasma glucose, 10 mmol/L for 1-h plasma glucose and 8.5 mmol/L for 2-h plasma glucose; however, according to the 2006 World Health Organization criteria, GDM is diagnosed if 1 or more of the following criteria is met:

1) fasting plasma glucose ≥7.0 mmol/l (126 mg/dL)
2) 2-h plasma glucose ≥11.1 mmol/L (200 mg/dL) following a 75 g oral glucose load
3) random plasma glucose ≥11.1 mmol/L (200 mg/dL) in the presence of diabetes symptoms.

Metabolic syndrome was defined according to the current International Diabetes Federation definition (20).

Statistical analysis

Results are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]). Continuous variables were checked for normal distribution using the Kolmogorov-Smirnov statistics. Comparisons of continuous variables between 2 groups were made using independent-sample t tests for normally distributed variables. For nonparametric variables, the Mann-Whitney U test was used for comparison of 2 groups. Categorical variables were compared using the chi square test. The Pearson test was used to test correlation of normally distributed variables, and the Spearman test was used for correlation of non-normally distributed variables.

Multivariate analysis was performed to identify independent associations between the individual glycemic parameters of the baseline OGTT and current metabolic status. In view of the gamma distribution of the data, the generalized linear model was the statistical test utilized. Consequently, binary logistic regression analysis was performed to identify independent determinants of the occurrence of metabolic syndrome at follow up. Variables were entered into the regression model if their p values were <0.1 in univariate analysis. Predictors were removed from the model if their p values exceeded 0.05.

All tests were 2-sided, and a p value of <0.05 was considered to be statistically significant.

Results

In 2009, 240 pregnant females had undergone assessment for possible GDM in Mater Dei Hospital. Of these, 203 females agreed to participate in the study. Thus, approximately 85% of the eligible participants participated. There was no significant difference in the baseline characteristics of the subjects who accepted when compared to those who did not want to participate. Thus, the study population comprised 203 Caucasian premenopausal females with a mean current age of 38.3±5.4 years. Of the 203 participants, 43 (21.2%) had been diagnosed with GDM in 2009. The average birth weight of those children was 3.4 kg in the participants with GDM compared to 3.5 kg in participants without gestational diabetes (p=0.41). The median (IQR) fasting plasma glucose during the OGTTs performed during the index pregnancy in 2009 was 4.48 (4.17 to 4.84) mmol/L, the median (IQR) 2-h postload plasma glucose was 6.25 (5.38 to 7.5) mmol/L and the median (IQR) 3-h postload plasma glucose was 4.01 (3.36 to 5.09) mmol/L.

The characteristics of the participants with and without GDM are outlined in Table 1. Participants with previous GDM had higher average levels of fasting plasma glucose, A1C, low-density lipoprotein (LDL) cholesterol, total:high-density lipoprotein (HDL) cholesterol ratio and non-HDL cholesterol but lower HDL cholesterol levels, even if the levels were still within the normal range. However, there were no significant differences between the 2 groups in systolic blood pressure, diastolic blood pressure, triglycerides, CIMT, red blood cell distribution width and mean platelet volume levels; the latter 2 have been associated with adverse cardiovascular outcomes. There was a nonsignificant trend for body mass index to be higher in women with previous gestational diabetes.

Correlation analysis was performed to assess for any possible associations between the individual glycemic parameters of the baseline OGTTs with current lipid profiles, current waist indexes, body mass indexes, blood pressures and CIMT. There were significant associations among many of the baseline intrapregnancy glycemic parameters and current lipid parameters, as shown in Table 2. No associations were shown between lipid profiles and waist index vs 3-h postprandial glucose levels and the G_3-G_0 levels. Consequently, multivariate analysis was performed to identify independent associations between the baseline individual glycemic parameters and the current metabolic statuses; adjustment for age was performed. Baseline fasting plasma glucose levels were shown to be independently associated with HDL-C (p=0.001; beta=−0.36; 95% CI −0.56 to −0.15); G_2 was shown to be independently associated with LDL-C (p=0.016; beta=0.33; 95% CI 0.06 to 0.6); whereas $AUC_{glucose}$ was shown to be independently associated with both HDL-C (p= 0.04; beta=−1.1; 95% CI −2.15 to −0.04) and LDL-C (p=0.002; beta=0.96; 95% CI 0.34 to 1.58).

Subgroup analyses were consequently performed to assess for differences between participants with vs those without metabolic

Table 1
Comparison of current clinical parameters in those with and without previous gestational diabetes

Factor	Gestational diabetes (n=43)	No gestational diabetes (n=160)	p value
Age, years*	38.65±4.72	38.19±5.64	0.59
BMI (kg/m^2)†	31.02 (27.45–35.95)	28.78 (24.52–36.62)	0.06
Waist index†	1.23 (1.1–1.33)	1.15 (1.05–1.35)	0.09
Metabolic syndrome, n (%)	20 (46.5%)	33 (20.6%)	0.001
Office systolic pressure, mmHg†	125 (114–144)	126 (116–135)	0.62
Office diastolic pressure, mmHg†	76 (70–85)	76.5 (69–82)	0.45
Hemoglobin, g/dL†	13.2 (12.2–14)	13.1 (12.3–13.78)	0.59
Red cell distribution width, %†	12.9 (12.2–13.8)	13.1 (12.4–13.8)	0.58
Mean platelet volume, fL†	10.7 (9.9–11.3)	10.6 (10–11.3)	0.81
Estimated glomerular filtration rate, mL/min/1.73 m^2†	109 (101–119)	103 (93–118)	0.07
Total cholesterol, mmol/L†	5.15 (4.52–6.03)	4.92 (4.41–5.55)	0.14
HDL cholesterol, mmol/L†	1.35 (1.16–1.63)	1.57 (1.25–1.85)	0.01
Total:HDL cholesterol, mmol/L†	3.79 (3.04–4.77)	3.19 (2.61–4.07)	0.006
LDL cholesterol, mmol/L†	3.19 (2.75–3.95)	2.81 (2.4–3.4)	0.01
Non-HDL cholesterol, mmol/L†	3.7 (3.1–4.52)	3.36 (2.76–3.9)	0.02
Triglycerides, mmol/L†	1.0 (0.66–1.52)	0.9 (0.66–1.33)	0.36
Albumin-creatinine ratio, mg/g†	4.48 (1–13.06)	4.4 (1–10.06)	0.65
Fasting plasma glucose, mmol/L†	5.05 (4.79–5.59)	4.9 (4.56–5.14)	0.005
Glycated hemoglobin, %†	5.4 (5.1–5.7)	5.2 (5–5.5)	0.02
% Difference in CIMT, %*	23.92±21.65	19.05±17.38	0.18

BMI, body mass index; *CIMT,* carotid intima-media thickness; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein.
* Data mean ± standard deviation.
† Data are median (interquartile range).

syndrome and increased CIMT. Table 3 compares the baseline OGTT glycemic parameters, histories of GDM and birth weights in those currently with metabolic syndrome and those without. Fasting plasma glucose, 2-h postload plasma glucose and $AUC_{glucose}$ of the OGTT performed during pregnancy showed the strongest associations with both current lipid profiles and with the presence or otherwise of the metabolic syndrome after 8 years. Binary logistic analysis was consequently performed to identify independent associations with metabolic status at follow up; adjustment for age was again performed. Consequently, $AUC_{glucose}$ (p=0.04; OR 1.11; 95% CI 1.006 to 1.23) and age (p=0.04; OR 1.1; 95% CI 1.005 to 1.14) were shown to be independent determinants of the occurrence of metabolic syndrome at follow up.

No significant associations were demonstrated between glycemic parameters and current abnormal CIMT status, as outlined in Table 4. None of the baseline glycemic indexes derived from the OGTT performed in 2009 nor past histories of GDM were shown to be correlated with the occurrence of atherosclerosis as assessed by CIMT.

Discussion

Our data show that glycemic parameters of the OGTT performed during pregnancy were independently associated with lower current HDL cholesterol and higher current LDL cholesterol at 8 years of follow up (Table 2). Independent associations were shown between current lipid status and fasting plasma glucose levels or the 2-h postload plasma glucose and the $AUC_{glucose}$; the latter demonstrated the strongest association with both the HDL and LDL cholesterol levels. No significant associations were shown, either with the 2-h postload glucose excursion (G_2-G_0) or the 3-h postload plasma glucose (G_3) levels, which were, on average, lower than both the fasting and 2-h postload plasma glucose levels. These results suggest that the total glycemic exposure is more important than glucose fluctuations. Fasting plasma glucose levels are markers of interprandial glycemia, whereas the 2-h postload plasma glucose and the $AUC_{glucose}$ levels are markers of postprandial glycemia.

Table 2
Significant associations between baseline glycemic parameters and current metabolic status; univariate and multivariate analysis

Glycemic parameter	Metabolic parameter, univariate analysis						Multivariate analysis	
	HDL-C	Total:HDL	LDL-C	Non-HDL-C	Trigl	WI	HDL-C	LDL-C
Fasting PG	p<0.001, r=−0.248	p<0.001, r=0.25		p=0.016, r=0.17	p=0.025, r=0.159	p<0.001 r=0.25	p=0.001 β=−0.36	
G_2	p=0.002, r=−0.22	p=0.001, r=0.24	p=0.003, r=0.206	p=0.004, r=0.204		p=0.13 r=0.11		p=0.016 β=0.33
G_3						p=0.06 r=0.42		
$AUC_{glucose}$	p=0.002, r=−0.22	p<0.001, r=0.247	p=0.001, r=0.232	p=0.001, r=0.227		p=0.05 r=0.14	p=0.04 β=−1.1	p=0.002 β=0.96
G_2-G_0		p=0.029, r=0.154	p=0.029, r=0.154	p=0.039, r=0.146		p=0.67 r=0.03		
G_3-G_0						p=0.21 r=−0.09		
G_3-G_2		p=0.038, r=−0.147				p=0.39 r=−0.06		

$AUC_{glucose}$, area under the glucose curve; *β,* gradient; C, cholesterol; *G_0,* fasting plasma glucose; *G_2,* 2-h postload plasma glucose; *G_3,* 3-h postload plasma glucose; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *PG,* plasma glucose; *WI,* waist index.

Table 3
Association between glycemic parameters of OGTT during pregnancy and birth weight with current presence of metabolic syndrome

Covariate	Metabolic syndrome absent (n=149)	Metabolic syndrome present (n=53)	p value
G_0, mmol/L*	4.36 (4.09–4.75)	4.79 (4.46–5.25)	<0.001
G_2, mmol/L*	6.12 (5.34–7.39)	7.12 (5.77–7.72)	0.01
G_3†	3.94 (3.28–5.01)	4.2 (3.5–5.24)	0.12
$AUC_{glucose}$, mmol/L*	19.65 (17.94–22.06)	21.74 (18.97–24.45)	0.002
G_2-G_0, mmol/L*	1.71 (0.94–3.00)	2.13 (1.08–2.93)	0.29
G_3-G_0, mmol/L*	−0.49 (−1.14–0.61)	−0.43 (−1.4–0.22)	0.38
G_3-G_2, mmol/L†	−2.15±1.76	−2.34±1.57	0.45
GDM, n (%)	23 (15.4%)	20 (37.7%)	0.001
Weight of baby, kg*	3.49 (3.06–3.77)	3.5 (3.1–3.77)	0.95

$AUC_{glucose}$, area under the glucose curve; *CIMT*, carotid intima-media thickness; *G_0*, fasting plasma glucose; *G_2*, 2-h postload plasma glucose; *G_3*, 3-h postload plasma glucose; *GDM*, gestational diabetes mellitus; *OGTT*, oral glucose tolerance test.
* Data are median (interquartile range).
† Data mean ± standard deviation.

Table 4
Relationship between glycemic parameters of OGTT during pregnancy, gestational diabetes mellitus and birth weight with current presence of abnormal CIMT

Variable	Normal CIMT (n=34)	Increased CIMT (n=169)	p value
G_0, mmol/L*	4.29 (4.11–4.75)	4.48 (4.18–4.86)	0.22
G_2, mmol/L*	6.23 (5.43–8.02)	6.28 (5.38–7.48)	0.69
G_3, mmol/L*	4.20 (3.66–4.92)	4.00 (3.29–5.13)	0.44
AUC, mmol/L*	20.74 (17.69–24.02)	20.11 (18.17–22.37)	0.78
G_2-G_0, mmol/L*	1.95 (1.06–3.52)	1.81 (1.00–2.78)	0.31
G_3-G_0, mmol/L*	0.01 (−0.9–0.58)	−0.6 (−1.26–0.42)	0.1
G_3-G_2, mmol/L†	−2.32±1.72	−2.16±1.72	0.62
GDM, n (%)	8 (23.5%)	35 (20.7%)	0.45
Weight of baby, kg*	3.35 (3.13–3.67)	3.5 (3.08–3.8)	0.49

$AUC_{glucose}$, area under the glucose curve; *CIMT*, carotid intima-media thickness; *G_0*, fasting plasma glucose; *G_2*, 2-h postload plasma glucose; *G_3*, 3-h postload plasma glucose; *GDM*, gestational diabetes mellitus; *OGTT*, oral glucose tolerance test.
* Data are median (interquartile range).
† Data mean ± standard deviation.

Our data also provide further evidence that previous gestational diabetes, as diagnosed by World Health Organization criteria, predicts future metabolic syndrome after a median follow up of 8 years. Furthermore, women with previous gestational diabetes had worse metabolic status, including lower HDL cholesterol and higher LDL cholesterol, non-HDL cholesterol, total:HDL cholesterol ratio, A1C and fasting plasma glucose levels, even though in most instances these parameters were still within the normal range. The lipid changes found in our study are similar to those previously described at 3 months postpartum (21). Our data show that these changes are still present after a median of 8 years. It should be noted that elevations in total and LDL cholesterol and a reduction in HDL cholesterol have all been linked to worse outcomes, with no threshold effect (22–26). Fasting plasma glucose (27) and A1C levels (28) have, likewise, been linked to adverse cardiovascular outcomes, even within the normal range. Therefore, our results suggest that the association between gestational diabetes and adverse cardiovascular events is at least partly mediated through persistent mild metabolic derangements.

The fact that we found similar associations, both when we categorized participants as being with or without gestational diabetes as well as when we treated the various glycemic parameters as continuous variables, makes our results internally consistent and strengthens the validity of our findings. Our data are consistent with those of Retnakaran and Shah (29), who reported that women who received an antepartum OGTT but who did not have GDM had higher cardiovascular event rates than women who did not undergo OGTTs during pregnancy. The authors interpret the fact that women received antepartum OGTTs as indirect evidence of a mild degree of dysglycemia, but they have no data on the glucose levels during the OGTTs.

Our data did not show a relationship between GDM or gestational glycemic parameters to CIMT; this is likely to require a longer follow up to become manifest. The differences in the metabolic parameters at 8 years of follow up are likely to result in accelerated atherosclerosis and increased lifetime risk for cardiovascular events at a longer follow-up period.

Our data suggest that the known association between GDM and cardiovascular disease is mediated, at least in part, by higher postpregnancy glycemia and worse lipid profiles, even though these metabolic parameters often remain within the normal range. The link between dysglycemia during pregnancy and most of the lipid abnormalities is most likely to be mediated through insulin resistance, namely, that insulin resistance is the common antecedent to both pregnancy-associated dysglycemia and future lipid abnormalities (30). However, there is also some evidence that hyperglycemia itself can induce insulin resistance (31). The possible role of insulin resistance is strengthened by the fact that previous gestational diabetes, higher fasting, 2-h postload plasma glucose and $AUC_{glucose}$ levels were all associated with future metabolic syndrome. The most plausible explanation for the association between the glycemic parameters and LDL cholesterol is that the former are markers of unhealthy lifestyles (32–34). Mild, persistent postpregnancy dysglycemia is also likely to contribute to increased cardiovascular risk through other mechanisms, including endothelial dysfunction, subclinical inflammation, oxidative stress and generation of advanced glycation endproducts.

The major strengths of our study are that we had access to the glucose results of the OGTTs performed during pregnancy and that we had a reasonably long follow up of 8 years. Another strength is that we had a high follow-up rate. One limitation is that we do not have 1-h postload plasma glucose levels, which are used in the new International Association of Diabetes and Pregnancy Study Groups criteria (17). These criteria were, however, generated to predict obstetric rather than cardiovascular outcomes. Our patients had undergone OGTTs, so they must have been deemed by their attending physicians to be at higher risk for having dysglycemia. This is reflected in the relatively high proportion (21.2%) of our patients' having GDM. Our cohort, therefore, consisted of a population that was enriched for pregnancy-associated dysglycemia. Nonetheless, we were able to include patients with a wide range of OGTT glycemic parameters, enabling us to study their relationships with future cardiometabolic status.

Another important limitation is the fact that the decision to perform OGTTs during pregnancy was left to the discretion of the caring obstetrician. While we do appreciate that this can be a potential confounding variable, the data provided is registry data and, thus, provides useful information that is more likely to represent the real-world situation rather than specific recruitment of subjects. There is also lack of information with regard to multiparity and the metabolic status of the participants at the time the OGTTs were performed; such missing data is inherent in many registry data. Nonetheless, it is known that lipid levels during gestation are not truly indicative of the underlying lipid status. Ideally, the metabolic status of the participants would have been recorded prior to the commencement of pregnancy. Another limitation was the inability to account for multiple testing.

In this study, we managed to assess cardiovascular risk profiles in a specific middle-aged female population. Nonetheless, it would be highly relevant to assess cardiovascular risk in middle-aged females in different cohorts, mainly previously pregnant females who did not require assessment by OGTTs during pregnancy as well as another cohort of similarly aged females who had never been pregnant. These would serve as useful controls and would help to

elucidate the underlying prevalence and pathophysiology of subclinical atherosclerosis in middle-aged females.

Conclusions

We report that gestational diabetes and individual glycemic parameters of intrapregnancy OGTTs are associated with future lipid abnormalities, dysglycemia and the metabolic syndrome up to 8 years after pregnancy. We observed linear relationships between glycemic parameters and cardiovascular risk. Therefore, we suggest that rather than categorizing women as having or not having gestational diabetes, creation of novel risk engines based on glycemic parameters of intrapregnancy OGTTs might be more appropriate for predicting future cardiovascular risk. This merits further study in view of the relatively short follow-up period of 8 years. Our data also suggest that the known association between gestational diabetes and cardiovascular disease is mediated, at least in part, by higher postpregnancy glycemia and worse lipid profiles, even though these metabolic parameters often remain within the normal range. Longer follow up of the study cohort might help to elucidate further the relation between gestational dysglycemia and the occurrence of subclinical atherosclerosis and microvascular disease.

Author Disclosures

Conflicts of interest: None.

Author Contributions

Sara Xuereb and Rachel Xuereb were involved in the collection of data; Caroline Jane Magri was involved in data collection as well as in as statistical analysis. Stephen Fava conceived the study and contributed to the statistical analysis. Robert G Xuereb and Joseph Galea were involved in the interpretation of the results obtained. All authors were additionally involved in writing and revising of manuscript.

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