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Research paper

Subtypes of gestational diabetes and future risk of pre-diabetes or diabetes

Ravi Retnakaran[a,b,c,*], Chang Ye[a], Anthony J. Hanley[a,b,d], Philip W. Connelly[b,e,f], Mathew Sermer[g], Bernard Zinman[a,b,c]

[a] Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, Canada
[b] Division of Endocrinology, University of Toronto, Toronto, Canada
[c] Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada
[d] Department of Nutritional Sciences, University of Toronto, Toronto, Canada
[e] Keenan Research Centre for Biomedical Science of St. Michael's Hospital, Toronto, Canada
[f] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada
[g] Department of Obstetrics and Gynecology, Mount Sinai Hospital, Toronto, Canada

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ABSTRACT

Background: Recent studies have suggested that gestational diabetes (GDM) is a heterogeneous condition with distinct subtypes determined by whether the predominant metabolic abnormality is impaired insulin sensitivity or deficient insulin secretion. However, it is not known if the elevated future risk of pre-diabetes/diabetes associated with GDM varies according to these subtypes. Thus, we sought to evaluate maternal metabolic function in the 1st year postpartum in relation to GDM subtypes.

Methods: In this prospective cohort study conducted in Toronto, Canada, 613 women underwent GDM screening by oral glucose tolerance test (OGTT) in pregnancy, followed by repeat OGTT at both 3-months and 12-months postpartum between 09/2003 and 03/2016. The antepartum OGTT identified 3 groups of women: GDM with predominant sensitivity defect (GDM-sensitivity), GDM with predominant secretion defect (GDM-secretion), and non-GDM.

Findings: Antepartum findings persisted after pregnancy, with lower insulin sensitivity in GDM-sensitivity (Matsuda index; HOMA-IR) and lower insulin secretion in GDM-secretion (Stumvoll first-phase; insulinogenic index (IGI)) at both 3-months and 12-months (all $p<0.005$). Beta-cell compensation (Insulin Secretion-Sensitivity Index-2; IGI/HOMA-IR) was lower in both GDM subtypes compared to non-GDM (all $p<0.0005$) but did not differ between GDM-sensitivity and GDM-secretion. Similarly, both subtypes exhibited higher post-challenge glycemia on OGTT at 3-months and 12-months than non-GDM (all $p<0.0005$) but did not differ from one another. The prevalence of pre-diabetes/diabetes was higher in both GDM-sensitivity (30.9%; 95%CI: 21.7−41.2) and GDM-secretion (27.6%; 16.7−40.9) than in non-GDM (10.4%; 7.7−13.6) at 12-months (both $p<0.005$), with no difference between GDM subtypes ($p = 0.75$).

Interpretation: Beta-cell dysfunction, glycemia and incident pre-diabetes/diabetes do not vary between GDM subtypes in the 1st year postpartum.

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1. Introduction

`The diagnosis of gestational diabetes mellitus (GDM) carries both (i) short-term obstetrical implications related to fetal overgrowth and resultant adverse outcomes at delivery, and (ii) longer-term risk of maternal progression to pre-diabetes and type 2 diabetes in the years thereafter [1,2]. Accordingly, in clinical practice, general goals of GDM management focus on (i) antepartum glycemic control to reduce the likelihood of fetal overgrowth and (ii) postpartum surveillance for early detection of worsening glucose tolerance. However, the

Abbreviations: GCT, glucose challenge test; GDM, gestational diabetes mellitus; HOMA-IR, Homeostasis Model Assessment of insulin resistance; IGI/HOMA-IR, insulinogenic index divided by HOMA-IR; ISSI-2, Insulin Secretion-Sensitivity Index-2; OGTT, oral glucose challenge test

* Corresponding author at: Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, Canada
E-mail address: Ravi.Retnakaran@sinaihealthsystem.ca (R. Retnakaran).

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Research in context

Evidence before this study

Recent publications have described distinct subtypes of gestational diabetes mellitus (GDM) defined by whether the predominant metabolic abnormality is impaired insulin sensitivity or deficient insulin secretion. While these studies have suggested that GDM subtypes confer differential risks of obstetrical/neonatal outcomes, an outstanding question that has been raised in these reports is whether the elevated future risk of pre-diabetes/diabetes associated with GDM might also vary according to these subtypes. Thus, we searched PubMed for studies published between Jan/1/1950 and June/7/2021 that evaluated heterogeneity or subtypes of GDM after pregnancy.

Added value of this study

In this prospective cohort study, we highlight the problem with this approach of defining a subtype of GDM based on an insulin secretion measure in isolation, without considering ambient insulin sensitivity. Specifically, when beta-cell compensation is assessed, the GDM-sensitivity and GDM-secretion subtypes both exhibit similar beta-cell dysfunction across the first year after delivery. Accordingly, while GDM-sensitivity and GDM-secretion each predict higher rates of pre-diabetes/diabetes at 3-months and 12-months postpartum (compared to women without GDM), the respective prevalence rates are similar in both GDM subtypes.

Implications of all the available evidence

GDM subtypes defined by insulin sensitivity and insulin secretion in pregnancy share similar underlying beta-cell dysfunction and hence similar future risks of pre-diabetes/diabetes. For subtyping GDM based on the presumed predominant metabolic defect, the insulin secretory response needs to be evaluated in relation to ambient insulin sensitivity to provide insight into the pathophysiologic process (beta-cell dysfunction) that would reflect a secretory defect.

appropriateness of this uniform approach to management has recently been drawn into question owing to the suggestion that GDM may be a heterogeneous condition comprised of distinct phenotypic subtypes depending on whether the predominant maternal metabolic defect is impaired insulin sensitivity or deficient insulin secretion [3]. Indeed, in 2016, Powe and colleagues defined subtypes of GDM in this way (based on the Matsuda index of insulin sensitivity and the Stumvoll 1st phase index of insulin secretion) and reported that women with GDM who had a predominant insulin sensitivity defect had larger neonates and a greater likelihood of adverse pregnancy outcomes (including large-for-gestational-age and Caesarean delivery) than those with a predominant secretion defect [4]. Subsequent reports in other populations have supported the concept of heterogeneity of GDM yielding differential obstetrical/neonatal risks [5-8], thereby raising the possibility of potentially tailoring the antepartum management of GDM based on the subtype. While all of these studies have focused on pregnancy outcomes, a recurrent question raised in these reports has been whether the elevated future risk of pre-diabetes/diabetes associated with GDM might also vary according to the subtypes [4,5,7,8], If so, such insight could inform the targeting of postpartum surveillance efforts to the subtype(s) of GDM that confer the highest risk of developing type 2 diabetes. However, little is known about the relationship between GDM subtypes and future risk of pre-diabetes/diabetes. Thus, in this context, we sought to evaluate metabolic function and glucose tolerance in the 1st year postpartum in relation to GDM subtypes.

2. Methods

2.1. Study population

The study population consisted of women participating in a prospective observational cohort study in which we are characterizing the relationship between glucose tolerance in pregnancy and subsequent metabolic function after delivery. The study protocol has been previously described in detail [9,10]. In brief, women were recruited at the time of antepartum screening for GDM in late 2nd/early 3rd trimester and returned for metabolic characterization at 3-months and 1-year postpartum. The study protocol has been approved by the Mount Sinai Hospital Research Ethics Board and all women have provided written informed consent for their participation.

2.2. Study visits

At our institution, pregnant women are screened for GDM by 50 g glucose challenge test (GCT), followed by referral for diagnostic oral glucose tolerance test (OGTT) if the GCT is abnormal (plasma glucose $\geq$7.8 mmol/L at 1-h after ingestion of 50 g glucose load). For this study, women were recruited either before or after the screening GCT and all participants then completed a 3-h 100 g OGTT, irrespective of the GCT result (i.e. even if it was normal). The recruitment of women after an abnormal GCT served to enrich the prevalence of GDM in the study population [9,10]. This antepartum OGTT was performed with the baseline study visit. Any women diagnosed with GDM on this OGTT (defined by National Diabetes Data Group (NDDG) criteria) [11] were then referred for clinical care to the specialized diabetes in pregnancy clinic, where glucose-lowering management was implemented consisting of dietary and lifestyle counseling, followed by antepartum insulin therapy (if glycemic targets were not achieved).

As previously described [9,10], study participants (both those with GDM and those without GDM) returned to the clinical investigation unit at 3-months and 12-months postpartum for serial metabolic characterization, including 2-h 75 g OGTT on both occasions. On each OGTT, pre-diabetes and diabetes were defined according to Diabetes Canada clinical practice guidelines [12]. Pre-diabetes refers to impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or combined IFG and IGT. In addition, as described previously [9,10], participants underwent measurement of weight, waist and blood pressure at both postpartum visits and completed questionnaires, including the Baecke questionnaire at 1-year postpartum, which assessed physical activity in the previous year [13,14].

2.3. Physiologic indices assessed on OGTT at each study visit

The OGTTs at baseline in pregnancy and at 3- and 12-months postpartum were all performed in the morning after overnight fast. For these multi-sample OGTTs, venous blood samples were drawn for measurement of glucose and specific insulin at fasting and at 30-, 60-, and 120-minutes (and 180-min in pregnancy) following ingestion of the glucose load. Specific insulin was measured with the Roche-Elecsys-1010 immunoassay analyzer and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, Canada). With this system, the coefficient of variation of insulin measurement has been 2.8%, 3.9% and 3.3% at levels of 130, 556 and 1208 pmoL/L, respectively.

The multi-sample OGTTs with serial measurement of glucose and insulin enabled evaluation of insulin sensitivity/resistance, insulin secretion, and beta-cell function, as follows:

(A) *Insulin Sensitivity / Insulin Resistance:* Whole-body insulin sensitivity was assessed with the Matsuda index [15]. Insulin resistance (primarily hepatic) was measured by Homeostasis Model Assessment of insulin resistance (HOMA-IR) [16].

(B) *Insulin Secretion:* Insulin secretion was assessed by two established indices: (i) Stumvoll 1st phase index, using the equation

Table 1
Antepartum and postpartum characteristics of the study population, stratified into the following 3 groups: (Group I) non-GDM; (Group II) GDM-sensitivity; and (Group III) GDM-secretion.

	Group I Non-GDM (n = 434)	Group II GDM-Sensitivity (n = 94)	Group III GDM-Secretion (n = 58)	Overall P-value	Pairwise Comparisons between Groups I vs II P-value	I vs III P-value	II vs III P-value
At OGTT in Pregnancy							
Age (yrs)	34.6 ± 4.2	34.9 ± 3.9	35.7 ± 4.8	0.17	>0.99	0.19	0.79
Ethnicity:				0.02			
White (%)	311 (71.7)	57 (60.6)	45 (77.6)				
Asian (%)	50 (11.5)	10 (10.6)	8 (13.8)				
Other (%)	73 (16.8)	27 (28.7)	5 (8.6)				
Pre-pregnancy BMI (kg/m^2)	24.6 ± 4.5	28.7 ± 6.9	22.7 ± 3.2	<0.0001	<0.0001	0.01	<0.0001
Family history of DM (%)	245 (57.5)	62 (68.1)	41 (71.9)	0.03	0.18	0.12	>0.99
Parity				0.65			
Nulliparous (%)	229 (52.8)	48 (51.1)	33 (56.9)				
One (%)	154 (35.5)	36 (38.3)	22 (37.9)				
> One (%)	51 (11.8)	10 (10.6)	3 (5.2)				
Insulin Sensitivity/Resistance:							
Matsuda index	4.8 (3.2 - 7.1)	2.1 (1.6 - 2.6)	5.2 (4.3 - 6.6)	<0.0001	<0.0001	0.23	<0.0001
HOMA-IR	1.7 (1.0 - 2.5)	3.3 (2.5 - 4.5)	1.3 (0.9 - 1.6)	<0.0001	<0.0001	0.0004	<0.0001
Insulin Secretion:							
Stumvoll 1st phase	1330 ± 623	1756 ± 672	566 ± 177	<0.0001	<0.0001	<0.0001	<0.0001
Insulinogenic index	17.9 (12.4 - 26.9)	16.4 (13.1 - 24.2)	8.3 (6.2 - 10.8)	<0.0001	<0.0001	<0.0001	<0.0001
Beta-cell Function:							
ISSI-2	813 ± 257	516 ± 139	560 ± 148	<0.0001	<0.0001	<0.0001	0.76
IGI/HOMA-IR	11.2 (7.8 - 17.4)	5.6 (3.0 - 7.5)	6.6 (4.1 - 9.8)	<0.0001	<0.0001	<0.0001	0.01
At 3-months Postpartum							
Breastfeeding (months)	3.2 ± 1.1	2.7 ± 1.1	2.9 ± 1.0	0.0004	0.0005	0.26	0.69
BMI (kg/m^2)	26.4 ± 4.8	29.8 ± 6.5	23.8 ± 3.5	<0.0001	<0.0001	0.0006	<0.0001
Waist circumference (cm)	89.4 ± 11.6	96.7 ± 12.8	84.5 ± 9.1	<0.0001	<0.0001	0.009	<0.0001
Systolic BP (mm Hg)	107.9 ± 10.5	113.1 ± 11.1	104.5 ± 11.1	<0.0001	<0.0001	0.08	<0.0001
Diastolic BP (mm Hg)	64.6 ± 8.2	68.7 ± 8.9	61.3 ± 8.5	<0.0001	<0.0001	0.01	<0.0001
At-12-months Postpartum							
Breastfeeding (months)	9.4 ± 4.1	7.6 ± 4.4	10.6 ± 5.6	0.0002	0.002	0.16	0.0003
BMI (kg/m^2)	25.5 ± 5.0	29.7 ± 7.4	23.1 ± 3.6	<0.0001	<0.0001	0.004	<0.0001
Waist circumference (cm)	86.8 ± 12.0	96.3 ± 14.5	82.3 ± 8.2	<0.0001	<0.0001	0.03	<0.0001
Systolic BP (mm Hg)	108.6 ± 10.8	111.9 ± 11.6	104.8 ± 12.5	0.0007	0.03	0.04	0.0005
Diastolic BP (mm Hg)	64.9 ± 8.4	68.3 ± 9.2	63.5 ± 7.9	0.0005	0.002	0.68	0.002
Total physical activity:							
Sport index	2.3 ± 0.8	2.2 ± 0.8	2.3 ± 0.7	0.62	>0.99	>0.99	>0.99
Leisure-time index	3.1 ± 0.6	3.0 ± 0.6	3.1 ± 0.5	0.25	0.48	>0.99	0.39
Work index	2.9 ± 0.6	2.9 ± 0.6	3.0 ± 0.6	0.73	>0.99	>0.99	>0.99

Overall P-values refer to comparison across the 3 groups using analysis of variance or Kruskal-Wallis test for continuous variables, and χ^2 test or Fisher exact test for categorical variables. For pairwise comparisons of continuous variables, two-sample t-test was performed. For pairwise comparisons of 2-level categorical variables, $\chi 2$ test or Fisher exact test was performed. P values for pairwise comparisons were adjusted using Bonferroni correction.
Abbreviations: BMI – body mass index; DM – diabetes mellitus; HOMA-IR – Homeostasis Model Assessment of insulin resistance; ISSI-2 – Insulin Secretion-Sensitivity Index-2; IGI/HOMA-IR – insulinogenic index/HOMA-IR; BP – blood pressure.

generated by Stumvoll et al. (which was based on stepwise linear regression analysis of insulin and glucose values at 0-, 60-, and 120-minutes and age and BMI in nondiabetic subjects) [17] and (ii) insulinogenic index (defined as the incremental change in serum insulin over the first 30 min of the OGTT divided by the incremental change in glucose during the same time span) [18].

(C) *Beta-cell Function:* The assessment of beta-cell compensation requires the evaluation of insulin secretion in relation to ambient insulin secretion. Beta-cell compensation was assessed by two established indices: (i) Insulin Secretion-Sensitivity Index-2 (ISSI-2), which is an OGTT-based measure that is analogous to the disposition index obtained from the intravenous glucose tolerance test against which it has been directly validated [19,20], and (ii) insulinogenic index/HOMA-IR [18].

2.4. Subtypes of GDM

The study population (n = 613) consisted of 434 women who did not have GDM (non-GDM) and 179 women with GDM. The women with GDM were then classified into subtypes according to the classification system proposed by Powe et al., [4] wherein the predominant metabolic defect was defined according to the distributions of insulin sensitivity (measured by Matsuda index) and insulin secretion (measured by Stumvoll 1st phase index) in the women without GDM. The GDM subtypes were defined as follows:

(A) GDM with predominant insulin sensitivity defect (GDM-sensitivity) (n = 94): women with GDM in whom Matsuda index in pregnancy was below the 25th percentile of the distribution of Matsuda index in pregnancy in the non-GDM women;

(B) GDM with predominant insulin secretion defect (GDM-secretion) (n = 58): women with GDM in whom the Stumvoll 1st phase index in pregnancy was below the 25th percentile of the distribution of the Stumvoll 1st phase index in pregnancy in the non-GDM women;

(C) GDM with both insulin sensitivity and secretion defects (GDM-mixed) (n = 7): women with GDM who met the criteria for both the insulin sensitivity and insulin secretion defects as defined above;

(D) GDM with neither defect (GDM-neither) (n = 20): women with GDM who met neither of the above criteria for insulin sensitivity defect or insulin secretion defect.

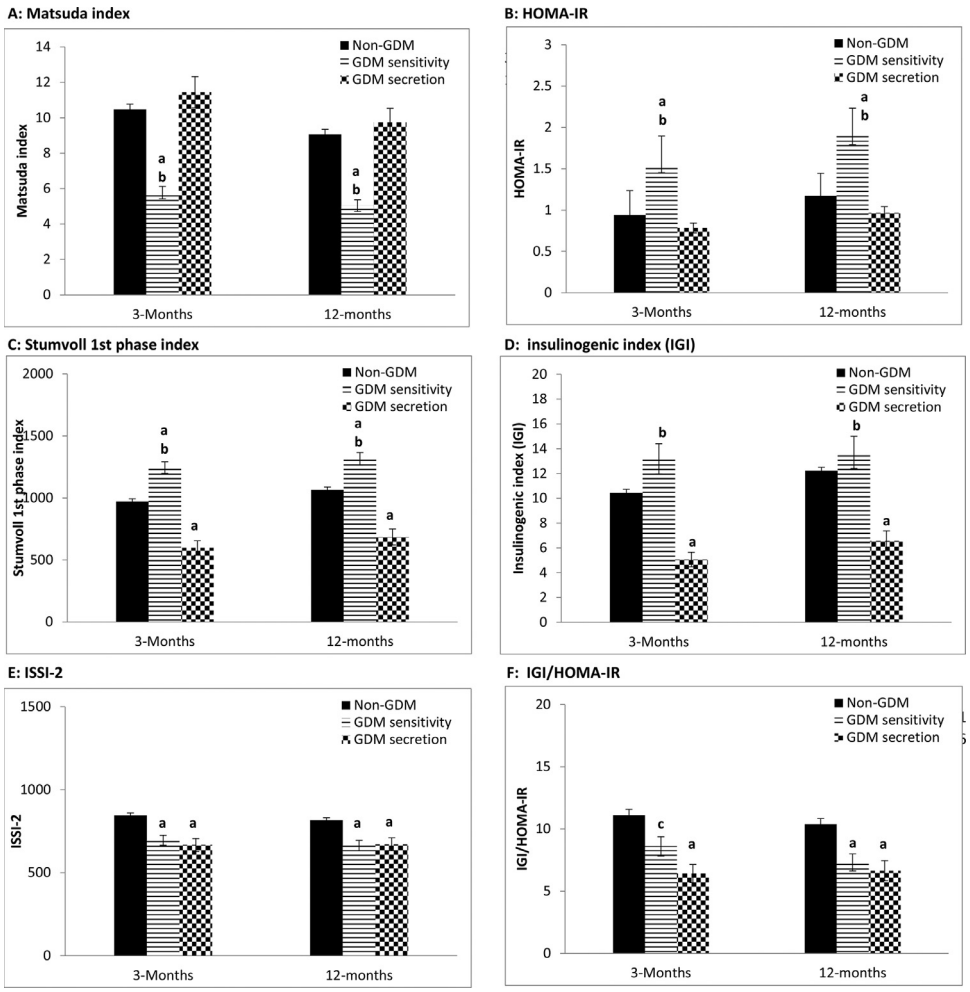

Fig. 1. Comparison of (A) Matsuda index, (B) Homeostasis Model Assessment of insulin resistance (HOMA-IR), (C) Stumvoll 1st phase index, (D) insulinogenic index (IGI), (E) Insulin Secretion-Sensitivity Index-2 (ISSI-2), and (F) IGI/HOMA-IR between the non-GDM, GDM-sensitivity, and GDM-secretion groups at 3-months and 12-months postpartum, respectively.

Solid black bar is non-GDM; horizontal lines bar is GDM-sensitivity; checkered bar is GDM-secretion Error bars show standard error of the sample mean [a]denotes $P<0.0005$ vs non-GDM; [b] denotes $P<0.005$ vs GDM-secretion; [c] denotes $P<0.05$ vs non-GDM.

2.5. Statistical analysis

Since there were few women with GDM-mixed (n = 7) or GDM-neither (n = 20), the main analyses were performed in the (613−27=) 586 women comprising the three main groups: non-GDM, GDM-sensitivity, and GDM-secretion. We compared antepartum and postpartum characteristics across these 3 groups using analysis of variance or Kruskal-Wallis test for continuous variables, and χ^2 test or Fisher exact test for categorical variables (Table 1). For each continuous variable, two-sample t-test was performed for pairwise comparisons amongst the 3 groups. For each 2-level categorical variable, χ^2 test or Fisher exact test was performed for pairwise comparisons amongst the 3 groups. At each of the 3-month and 12-month postpartum visits, we compared the unadjusted mean levels of measures of insulin sensitivity/resistance (Matsuda index and HOMA-IR), insulin secretion (Stumvoll 1st phase and insulinogenic index), and beta-cell function (ISSI-2 and IGI/HOMA-IR), across the 3 groups and within each pair of groups, using analysis of variance (Fig. 1). Furthermore, multiple linear regression analysis was performed at each visit to evaluate adjusted mean levels of these six indices, after adjustment for age, ethnicity, family history of diabetes, duration of breastfeeding, and current BMI (Online Fig. 1). To investigate the glycemic response to the OGTT at 3- and 12-months postpartum, we plotted the glucose response curve for each group at fasting, 30-, 60- and 120-minutes during the OGTT (Fig. 2). At each time point, we compared mean glucose level within each pair of groups, using two-sample t-test. We also evaluated the prevalence of pre-diabetes and diabetes at each of the postpartum visits and compared within each pair of groups using χ^2 test (Fig. 3). In all of the above analyses, P values for pairwise comparisons were adjusted using Bonferroni correction. In light of the small sample sizes in the GDM-mixed and GDM-neither groups, we also performed exploratory analyses comparing insulin sensitivity/resistance, insulin secretion, beta-cell function and glycemia on the OGTT across the 4 GDM subtypes by Kruskal-Wallis test (Online Table 1). All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Continuous variables were tested for normality of distribution both visually and with the Shapiro-Wilk test, and natural log transformations of skewed variables were used, where necessary, in subsequent analyses. Two-tailed P values < 0.05 were considered significant.

2.6. Role of funding source

The funding bodies (Canadian Institutes of Health Research; Diabetes Canada) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and final responsibility to submit for publication.

3. Results

Table 1 shows the antepartum and postpartum characteristics of the study population of 586 women, stratified into the following 3 groups: (i) non-GDM (n = 434), (ii) GDM-sensitivity (n = 94), and (iii) GDM-secretion (n = 58). These participants completed the OGTT in pregnancy at mean 29.5 ± 3.0 weeks gestation. As anticipated, the GDM-sensitivity group had the lowest whole-body insulin sensitivity (Matsuda index) and highest insulin resistance (HOMA-IR) on the antepartum OGTT, coupled with the highest pre-pregnancy BMI (all $p<0.0001$) (Table 1). Similarly, the GDM-secretion group had the lowest insulin secretion, as measured by Stumvoll 1st phase index and insulinogenic index (IGI) (both $p<0.0001$). We next evaluated beta-cell compensation by considering insulin secretion in relation to ambient insulin resistance [18]. This analysis revealed that beta-cell function in pregnancy (measured by ISSI-2 and IGI/HOMA-IR) was lower in both GDM subtypes compared to non-GDM (all $p<0.0001$) but, importantly, was not lower in the GDM-secretion group compared to the GDM-sensitivity group (Table 1).

At both 3- and 12-months postpartum, the GDM-sensitivity group had the highest BMI and waist circumference, followed in turn by the non-GDM and GDM-secretion groups (all $p<0.0001$). Systolic blood pressure and diastolic blood pressure followed the same pattern of differences (all $p \leq 0.0005$). Duration of breastfeeding was lowest in GDM-sensitivity and there were no differences between the 3 groups in physical activity at 12-months.

3.1. Glucose metabolism at 3-months and 12-months after delivery

The metabolic defects pertaining to insulin sensitivity and insulin secretion that were noted on the antepartum OGTT persisted after pregnancy. Specifically, at both 3-months and 12-months postpartum, the GDM-sensitivity group had lower Matsuda index and higher HOMA-IR than both non-GDM (all $p<0.0005$) and GDM-secretion (all $p<0.005$), respectively (Fig. 1A and 1B). Similarly, the GDM-secretion group had lower insulin secretion (measured by either Stumvoll 1st phase or IGI) compared to both non-GDM (all $p<0.0005$) and GDM-sensitivity (all $p<0.005$), respectively (Fig. 1C and 1D). Importantly, both GDM subtypes exhibited poorer beta-cell compensation (measured by ISSI-2 and IGI/HOMA-IR) than non-GDM at 3- and 12-months postpartum (all $p<0.05$), with no differences between the GDM-secretion and GDM-sensitivity groups (Fig. 1E and 1F). These differences in insulin sensitivity (Matsuda, HOMA-IR), insulin secretion (Stumvoll 1st phase, IGI) and beta-cell function (ISSI-2, IGI/HOMA-IR) at both 3- and 12-months were unchanged upon adjustment for age, ethnicity, family history of diabetes, duration of breastfeeding, and current BMI (Online Fig. 1). It thus emerges that, although antepartum differences in insulin sensitivity and secretion persist between GDM subtypes across the first year postpartum, beta-cell function is similar in GDM-sensitivity and GDM-secretion during this time.

To assess whether average beta-cell function over time differed between the two GDM subtypes, we also performed repeated measures Analysis of Variance (ANOVA) and pairwise comparisons with Bonferroni correction in two datasets (i) from antepartum, 3-months postpartum and 12-months postpartum, and (ii) from 3-months and 12-months postpartum. These analyses showed that, with both approaches, there was no significant difference in beta-cell function over time between the GDM subtypes. Specifically, from pregnancy to 12-months postpartum, there were no significant differences between GDM-secretion and GDM-sensitivity in ISSI-2 (mean difference 8.4 (95%CI −55.8 − 72.5) or IGI/HOMA-IR (mean difference −0.02 (95%CI −0.21 − 0.17). Similarly, from 3-months to 12-months postpartum, there were also no significant differences between GDM-secretion and GDM-sensitivity in ISSI-2 (mean difference −10.3 (95%CI −94.2 − 73.5) or IGI/HOMA-IR (mean difference −0.20 (95%CI −0.45 − 0.06).

We next evaluated the glucose response curves on the OGTT at 3- and 12-months. As shown in Fig. 2A and 2B, the pattern of differences in glycemic response mirrored that of beta-cell function. Specifically, post-challenge blood glucose levels were higher in both GDM subtypes than in non-GDM at each timepoint on the OGTTs (all $p<0.0005$) but did not differ between the GDM subtypes. Of note, the glycemic responses of the GDM-sensitivity and GDM-secretion groups were nearly identical, with their glucose response curves super-imposed upon one another at 12-months postpartum.

We next evaluated glucose tolerance status. As shown in Fig. 3A, the prevalence of pre-diabetes/diabetes was much higher in both GDM-sensitivity and GDM-secretion compared to non-GDM at 3-months (both $p<0.005$), with no difference between GDM subtypes (difference 4.7%; 95%CI: −10.4 − 19.9%). The same pattern persisted at 12-months (Fig. 3B), with the prevalence rates of pre-diabetes/diabetes being much higher in both GDM-sensitivity (30.9%; 95%CI: 21.7 - 41.2%) and GDM-secretion (27.6%; 95%CI: 16.7 - 40.9%) than in non-GDM (10.4%; 95%CI: 7.7 - 13.6%) (both $p<0.005$). Again, there was no difference between the GDM subtypes (3.3%; 95%CI: −11.6 − 18.1%). It thus emerges that the GDM-sensitivity and GDM-secretion groups exhibit similar beta-cell dysfunction, glycemia and rates of pre-diabetes/diabetes at both 3- and 12-months postpartum.

Lastly, having demonstrated that the two main GDM subtypes confer similar future risk of pre-diabetes/diabetes, we performed exploratory analyses to evaluate the less common subtypes of GDM-mixed defect (n = 7) and GDM-neither defect (n = 20). As anticipated, there was a potential signal of lower beta-cell function and higher glycemia in the GDM-mixed group, though the relative rarity of this subtype in only 7 women (out of 179 with GDM) precluded reliable statistical comparison (Online Table 1). With that caveat noted, there were no significant differences across the 4 GDM subtypes in either beta-cell function or glycemia on the OGTT at 12-months (Online Table 1).

4. Discussion

In this study, we demonstrate that the insulin sensitivity and insulin secretion defects that have been suggested as defining the main subtypes of GDM persist across the first year postpartum. However, while the GDM-sensitivity and GDM-secretion subtypes both exhibit postpartum beta-cell dysfunction (as compared to women without GDM), their beta-cell compensation does not differ from one another. Indeed, their post-challenge glycemic responses to the OGTT were nearly identical at both 3-months and 12-months postpartum, respectively. Accordingly, while GDM-sensitivity and GDM-secretion each predict higher rates of pre-diabetes/diabetes at 3-months and 12-months (compared to non-GDM), the respective prevalence rates are similar in both GDM subtypes. It thus emerges that these subtypes of GDM do not differ in their identification of future risk of diabetes.

There is currently considerable interest in elucidating the heterogeneity of diabetes, with the recognition that such understanding may enable precision medicine, as recently highlighted in a consensus report from the American Diabetes Association and the European Association for the Study of Diabetes [21]. In this context, the initial report of GDM heterogeneity by Powe et al. [4] has led to a series of recent studies evaluating GDM subtypes in relation to pregnancy outcomes [5-8]. These observational studies have been fairly comparable in the maternal phenotypes identified by their subtypes but less consistent in their obstetrical/neonatal findings [4-8], likely reflecting the confounding effect of the clinical management of GDM on the latter associations and some differences between studies in the diagnostic criteria by which defects in insulin sensitivity and insulin secretion were defined. In the current study, the subtypes were defined in precisely the same manner as in the initial report by Powe et al. [4] Interestingly, our prevalence rates of the dominant subtypes

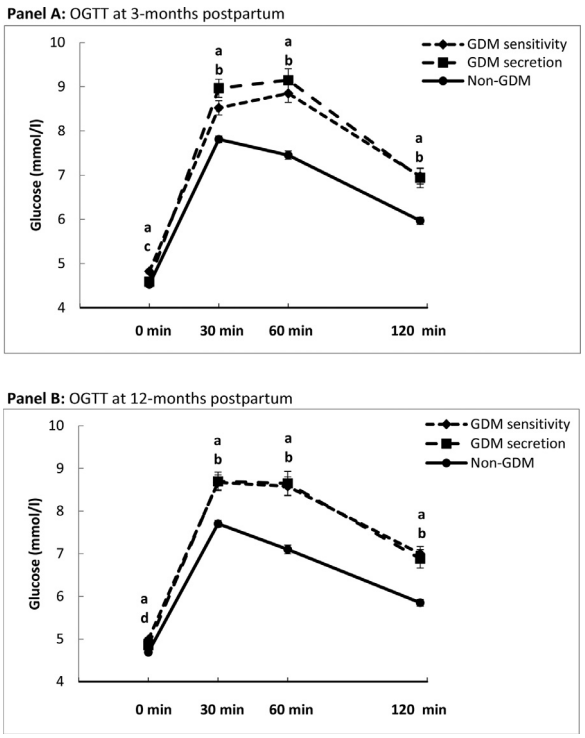

Fig. 2. Glucose response on the oral glucose tolerance test in each group (A) at 3-months postpartum and (B) at 12-months postpartum

Error bars show standard error of the sample mean

[a] denotes $P<0.0005$ for GDM-sensitivity vs non-GDM; [b] denotes $P<0.0005$ for GDM-secretion vs non-GDM; [c] denotes $P<0.01$ for GDM-sensitivity vs GDM-secretion; [d] denotes $P<0.05$ for GDM-secretion vs non-GDM.

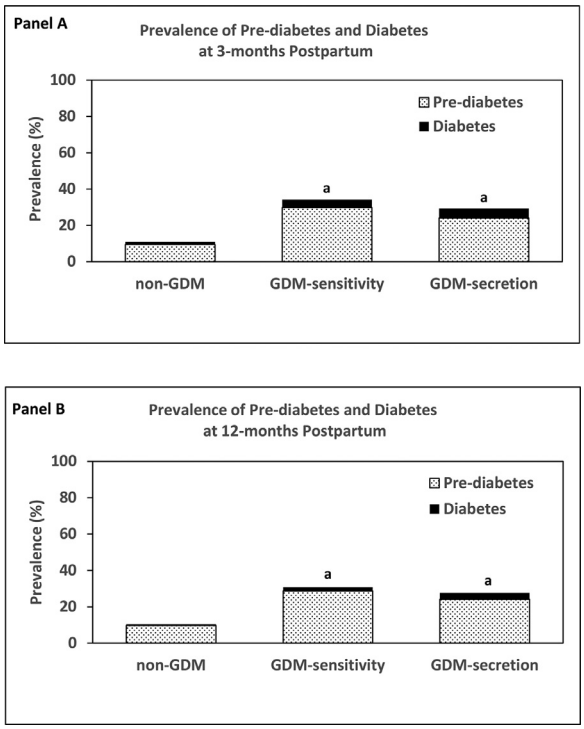

Fig. 3. Prevalence of pre-diabetes and diabetes in each group (A) at 3-months postpartum and (B) at 12-months postpartum

Spotted component of bar indicates pre-diabetes; solid black component of bar indicates diabetes

[a] denotes $P<0.005$ vs non-GDM.

of GDM-sensitivity (52.5% of all GDM) and GDM-secretion (32.4%) were quite comparable to those reported by Powe et al. (50.7% and 29.9%, respectively). Moreover, the antepartum phenotypic features of our GDM subtypes were consistent with those of the studies to date, which have noted greater adiposity in GDM-sensitivity and poorer beta-cell compensation in pregnancy in all GDM subtypes (including demonstrations with ISSI-2 and IGI/HOMA-IR) [4,5,7,8]. While they all focused on pregnancy outcomes, these previous studies repeatedly posed the question of whether GDM subtypes may identify women with differential future risks of dysglycemia [4,5,7,8].

The current study was thus designed to address this outstanding question with OGTTs at both 3- and 12-months postpartum in 179 women who had GDM and 434 who did not. Indeed, this sample size made it possible to not only compare GDM subtypes to non-GDM but to also compare the subtypes with each other. With this approach, we show that the antepartum differences in insulin sensitivity and secretion by which the subtypes were defined persist across both OGTTs and continue to distinguish the subtypes from one another across the first year after delivery. Importantly, however, the assessment of beta-cell function (which requires the integration of insulin secretion and insulin sensitivity) [18] shows a different pattern during this time, wherein the GDM subtypes clearly differ from non-GDM but not from each other (Fig. 1 Panels E-F).

This persistent beta-cell dysfunction in both of the dominant GDM subtypes provides a mechanistic basis for their similar future risks of pre-diabetes/diabetes, as becomes apparent upon consideration of the pathophysiology underlying the elevated risk of type 2 diabetes in women with a history of GDM [22]. GDM arises in women in whom there exists a chronic beta-cell defect such that their insulin secretion in response to the physiologic insulin resistance of pregnancy is insufficient to maintain glucose homeostasis (resulting in the hyperglycemia by which GDM is diagnosed) [1]. In an individual patient, the sufficiency of insulin secretion will be dependent upon her degree of insulin sensitivity, which exists along a physiologic spectrum [22]. Hence, in the population, there will be range for both insulin secretion and insulin sensitivity as reflected in the GDM subtypes described herein. However, irrespective of these ranges and these subtypes, insufficient beta-cell compensation remains the essential underlying requirement for the antepartum hyperglycemia by which GDM is identified. That is why, despite differences in insulin sensitivity and insulin secretion, beta-cell function does not differ between the GDM subtypes either in pregnancy or in the postpartum. After pregnancy, it is known that chronic beta-cell dysfunction and the worsening thereof over time is the pathophysiologic basis for the development of pre-diabetes and diabetes in women with previous GDM [23,24]. Thus, with our demonstration that beta-cell dysfunction does not differ between the GDM subtypes at either 3-months or 12-month postpartum, it is not surprising that glycemia and the risks of pre-diabetes/diabetes are similar as well. Indeed, the nearly identical glycemic responses to the OGTT at both 3-months and 12-months underscore this point.

These findings highlight the problem with trying to define a subtype of GDM based on an insulin secretion measure alone. Specifically, whereas low Matsuda index can be interpreted as reflecting insulin resistance, the interpretation of an insulin secretion measure (Stumvoll 1st phase) in isolation is more precarious. Indeed, in two women with different degrees of insulin sensitivity, lower insulin secretion may be an appropriate response in the more insulin-sensitive woman for maintaining glucose homeostasis. Accordingly, the insulin secretory response needs to be evaluated in relation to ambient insulin sensitivity to provide insight into the pathophysiologic process (beta-cell dysfunction) that would reflect a secretory defect. As noted above, all women with GDM have such a defect, as evidenced by the poorer beta-cell compensation in pregnancy in all subtypes when compared to non-GDM, as shown in the current report

and in previous studies [4,5,7,8]. Moreover, we further demonstrate that, when secretion is considered in relation to sensitivity (with measures of beta-cell compensation such as ISSI-2 and IGI/HOMA-IR), it becomes apparent that beta-cell function does not differ between GDM subtypes. This similar degree of beta-cell dysfunction between the subtypes is the basis of their comparable glycemia and glucose tolerance at both 3-months and 12-months postpartum. Similarly, in an earlier study in which GDM subtypes were defined based only on Matsuda index and 83% of participants completed an OGTT at 6−16 weeks after delivery, the resultant insulin sensitivity subtypes of GDM did not differ in their postpartum glucose tolerance [5]. Thus, while their insulin sensitivity and insulin secretion exist along spectra, women comprising GDM subtypes ultimately share similar underlying beta-cell dysfunction and hence similar future risks of pre-diabetes/diabetes.

In this study, the prevalence of GDM-mixed (i.e. both sensitivity and secretion defects meeting the thresholds of predominance) was quite low at 3.9% (reflecting only 7 out of 179 women with GDM), thereby precluding reliable assessment of future diabetic risk in this group. The prevalence of this subtype was lower than that in Powe et al., [4] although the 17.9% rate in that study reflected only 12 women (out of 67 with GDM). While it remains possible that GDM-mixed may identify a higher risk of pre-diabetes/diabetes, its prevalence suggests that this subtype represents a small minority of women with GDM. Another limitation of this study is that, since GDM was diagnosed based on NDDG criteria, it is uncertain if the current findings would extend to GDM diagnosed by International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria. Similarly, given the potential effects of genetic factors on beta-cell function, the current findings may not extend beyond this study population and its ethnic composition. An additional limitation (and in previous studies of GDM subtypes) is that insulin sensitivity, insulin secretion, and beta-cell function were assessed with OGTT-based surrogate indices rather than clamp measures. However, theses indices (Matsuda, HOMA-IR, Stumvoll 1st phase, IGI, ISSI-2, and IGI/HOMA-IR) are all validated measures that have been widely used in previous studies [15-20]. Moreover, in contrast to the more demanding and invasive nature of clamp studies, the OGTT-based measurements facilitated the assessment of 613 women on 3 occasions between late 2nd trimester and 1-year postpartum (of which 586 women were included in the main analyses), thereby yielding robust findings for the dominant GDM subtypes coupled with the evaluation of glucose tolerance status.

The key clinical implication of understanding heterogeneity in diabetes rests in the possibility of delivering precision medicine [21]. The studies linking GDM subtypes with obstetrical/neonatal outcomes have raised the possibility of such targeted therapy [3-8], although it was recently suggested that the coupling of clinical variables with continuous measures of insulin sensitivity and insulin secretion might provide better prediction of these outcomes [25]. Irrespective of their value for predicting obstetrical/neonatal outcomes, the current study suggests that these GDM subtypes will not markedly improve the identification of future diabetic risk. Given that women with a history of GDM have a 7-fold higher risk of developing type 2 diabetes as compared to their peers [26], our findings suggest that ongoing surveillance of glucose tolerance in the years after pregnancy is warranted in all women with GDM, irrespective of the subtype. Indeed, the postpartum beta-cell dysfunction that we have shown is shared across GDM subtypes ultimately confers the risk of progression to pre-diabetes and type 2 diabetes in this patient population [23,24].

In summary, the antepartum defects in insulin sensitivity and insulin secretion that have been suggested to define the main subtypes of GDM persist across the first year postpartum. However, irrespective of whether their predominant defect in pregnancy is considered to be deficient insulin sensitivity or deficient insulin secretion, women with these GDM subtypes exhibit comparable beta-cell dysfunction. Accordingly, the GDM-sensitivity and GDM-secretion subtypes exhibit similarly elevated glycemic responses and rates of pre-diabetes/diabetes at both 3- and 12-months postpartum. Thus, these subtypes of GDM do not differ in their identification of future risk of diabetes.

Declaration of Competing Interest

RR reports grants from Boehringer Ingelheim, grants and personal fees from Novo Nordisk, personal fees from Sanofi, personal fees from Eli Lilly, outside the submitted work. RR holds the Boehringer Ingelheim Chair in Beta-cell Preservation, Function and Regeneration at Mount Sinai Hospital and his research program is supported by the Sun Life Financial Program to Prevent Diabetes in Women. BZ reports personal fees from Eli Lilly, personal fees from NovoNordisk Advisory Board, personal fees from Merck, personal fees from Boehringer Ingelheim, outside the submitted work. CY, AJH, PWC, and MS have nothing to disclose.

Contributions

RR, AJH, PWC, MS and BZ designed and implemented the study. CY performed the statistical analyses. RR wrote the manuscript. RR and CY verified the data. All authors contributed to interpretation of the data and critical revision of the manuscript for important intellectual content. All authors approved the manuscript.

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Data sharing

De-identified data can be made available from the corresponding author after submission and institutional approval of a detailed proposal and completion of a signed data access agreement

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101087.

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