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Cardiometabolic Risk in Chinese Women with Prior Gestational Diabetes: A 15-Year Follow-Up Study

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Key Words
Gestational diabetes · Hypertension · Metabolic syndrome · Insulin sensitivity · Beta cell function

Abstract
Aims: The progression to type 2 diabetes mellitus (DM) and other long-term cardiometabolic risks in Chinese women with prior history of gestational diabetes (GD) was studied at 15 years postpartum. ***Methods:*** 139 Chinese women (45 with GD and 94 with normal glucose tolerance (NGT) at the index pregnancy) who had their insulin sensitivity and β-cell functions examined at 8 years postpartum were again followed up at 15 years for the investigation of the rate of type 2 DM, hypertension and metabolic syndrome. ***Results:*** Women with prior history of GD had a significantly higher rate of hypertension (35.6% vs. 16.0%, $p = 0.01$), type 2 DM (24.4% vs. 5.3%, $p < 0.001$) and impaired glucose regulation (26.6% vs. 14.9%, $p < 0.001$) than women with NGT during the index pregnancy. The Matsuda insulin sensitivity index and the quantitative insulin sensitivity check index at 8 years postpartum were independent predictors of both DM and metabolic syndrome at 15 years postpartum. ***Conclusions:*** The conversion rate of type 2 DM increased at an average rate of 1.6% per year after a pregnancy affected by GD. Insulin resistance at 8 years postpartum could refine a future diabetic risk in women with prior history of GD.

Introduction

The prevalence of diabetes mellitus (DM) for all age groups worldwide is estimated to be 4.4% by 2030; the total population affected is projected to rise from 171 million in 2000 to 366 million in 2030, with the majority of new patients from Asia and Africa [1]. Despite its prevalence being similar between men and women for most age groups, it is more prevalent in women after the age of 65 [1]. DM is estimated to have accounted for 3 million deaths globally in 2000. Again, DM was responsible for a higher proportion of deaths in women than in men in all regions and age groups [2]. In South East Asia, at least 1 in 5 deaths in women between the age of 35 and 64 is due to DM [2].

Owing to the silent nature of DM, diagnosis is often delayed until complications such as myocardial infarction occur [3, 4]. From large epidemiology studies, DM is

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a much stronger risk factor for coronary heart disease mortality in women than in men [5–7]. It has been reported that the risk of coronary heart disease mortality was 50% higher in women than in men with DM [8]. Despite a decline in the overall DM-related death in the last 30 years, the mortality rate of women with DM remained static and the risk of death was more than double in women with DM than those without [9]. From a women's health perspective, it would be most cost-effective to identify women at high risk of developing DM and intervene early with lifestyle modification followed by pharmacological treatment if necessary.

There is now much evidence to support a history of gestational diabetes (GD) being a strong risk factor for DM. In a systematic review of 28 studies, the cumulative incidence of type 2 DM in women with prior history of GD ranged from 2.6% at 6 weeks to 70% at 28 years postdelivery [10]. Recent meta-analyses of controlled studies also showed that GD conferred a 6- to 7.5-fold increased risk of DM and that 10–30% of women with DM also had a prior history of GD [11, 12]. However, the conversion rate to DM with the length of follow-up appeared to be conflicting in the literature. Kim et al. [10] showed that the progression to type 2 DM increased steeply in the first 5 years after delivery and the conversion rate plateaued beyond 5 years. In contrast, Bellamy et al. [12] have shown that the relative risk of DM increased from 4.7 within 5 years of a pregnancy complicated by GD to 9.3 at more than 5 years postpartum. Although the latter study did not demonstrate any heterogeneity in the subgroup analysis, they did suspect a possibility of variation amongst different ethnic groups.

In a prospective study of 801 Chinese women with GD during pregnancy, 23% and 13%, respectively, were found to have impaired glucose tolerance (IGT) or DM at 6 weeks postpartum [13]. Women with GD also had higher frequencies of other cardiovascular risk factors such as hypertension, obesity and dyslipidemia than their age-matched controls without GD [13]. In a cohort of Chinese pregnant women diagnosed with GD through a universal oral glucose tolerance test (OGTT) screening at midgestation, GD status increased the odds of future abnormal glucose tolerance (AGT) by 3.8 at 8 years after delivery [14]. In the present study, we continued to assess the long-term cardiometabolic risk in Chinese women with a prior history of GD at 15 years postpartum. Our objective was to define the long-term progression into DM, hypertension and metabolism syndrome (MetS) amongst Chinese women with a history of GD. We also studied whether insulin sensitivity and pancreatic cell function measured at an intermediate follow-up at 8 years postpartum are independent predictors of future DM and MetS at 15 years.

Patients and Methods

The subjects were 203 Chinese women (67 with GD and 136 with normal glucose tolerance; NGT) who had previously been followed up for the progression to AGT at 8 years postpartum [14]. As described earlier, all subjects had been recruited consecutively between 1992 and 1994 from the antenatal clinic of a tertiary referral hospital in a study to define the optimal screening and diagnostic criteria for GD [15]. All recruited subjects underwent a universal 75-gram OGTT administered between 24 and 28 weeks of gestation. The mothers were classified into NGT (i.e. fasting plasma glucose (PG) level <7.0 mmol/l and 2-hour PG level <7.8 mmol/l) and GD which included both IGT (i.e. fasting PG level <7.0 mmol/l and 2-hour PG level ≥7.8–11.1 mmol/l) and gestational diabetes mellitus (i.e. fasting PG level ≥7.0 mmol/l and/or 2-hour PG level ≥11.1 mmol/l) according to the 1999 World Health Organisation criteria.

At the 8-year follow-up, all subjects underwent a 75-gram OGTT at 0, 15, 30, 60 and 120 min with 5-point plasma glucose and insulin levels. Insulin sensitivity was calculated using the homeostasis model assessment insulin resistance index [HOMA-IR = I^0 (μU/ml) × G^0 (mmol/l)/22.5] [16], Matsuda insulin sensitivity index [Matsuda-ISI = $10{,}000/\sqrt{(G^0 \text{ (mg/dl)} \times I^0 \text{ (μU/ml)}) \times (\overline{G} \text{ (mg/dl)} \times \overline{I} \text{ (μU/ml)})}$] [17] and modified quantitative insulin sensitivity check index [QUICKI = $10/(\log I^0$ (μU/ml) + $\log G^0$ (mg/dl))] [18]; whereas pancreatic β-cell function was determined as AUC (I) (pmol/l)/AUC (G) (mmol/l) [19], homeostasis model assessment of β-cell function [HOMA-BCF = I^0 (μU/ml) × $20/(G^0$ (mmol/l) – 3.5)] [16] and insulinogenic indices at 15 min [$(I^{15} - I^0)$ (pmol/l)/$(G^{15} - G^0)$ (mmol/l)] and 30 min [$(I^{30} - I^0)$ (pmol/l)/$(G^{30} - G^0)$ (mmol/l)] [19] of the OGTT, respectively, where G^0, G^{15}, G^{30}, $\overline{G}$ and AUC (G) = fasting, 15, 30 min, mean PG levels and the area under the PG level-time curve from 0 to 120 min in the OGTT, and I^0, I^{15}, I^{30}, $\overline{I}$ and AUC (I) = fasting, 15, 30 min, mean insulin levels and the area under the plasma insulin level-time curve from 0 to 120 min in the OGTT, respectively.

All subjects diagnosed with hypertension or DM at the 8-year follow-up had been referred to an outpatient specialist clinic for further management. Women diagnosed with impaired glucose regulation (IGR) were provided with health education and advised on diet and lifestyle modification as well as the suggestion to seek regular medical follow-up. The women's cardiometabolic status at the 8-year follow-up including the number of future pregnancies has been presented in detail in an earlier publication [14].

Women consenting to the current study underwent an OGTT again 15 years after their index pregnancy after an overnight fast of ≥8 h. If the subjects who had been diagnosed with DM received pharmacological treatment, a fasting glucose test was performed together with HbA1c instead. Body weight, height, hip and waist circumferences were measured in light clothing while the percentage of body fat was assessed using a body composition analyzer (Model TBF 410, Tanita, Tokyo, Japan). Blood pressure (BP) was measured in the nondominant arm using an automated vital

signs monitor (Model 53000, Welch Allyn Inc., Oreg., USA,) with cuffs of appropriate bladder size which covered at least two thirds of the arm circumference. Measurements were performed thrice, at 1-min intervals, after ≥5 min of rest. The mean BP reading was used for analysis. Women with a known diagnosis of hypertension on medication or with a mean BP reading ≥140/90 mm Hg were defined as being hypertensive. All other significant medical conditions were recorded.

Advanced maternal age was defined as ≥35 years at delivery of the index pregnancy. Maternally overweight was defined as BMI ≥23 at booking according to the Asian criteria [20]. A family history of DM was defined as having at least one affected first-degree relative. The latest American Diabetes Association diagnostic criterion were used to define glycemic status, that is, DM was defined as a fasting PG level ≥7.0 mmol/l or a 2-hour PG level ≥11.1 mmol/l; IGT was defined as a fasting PG level <7.0 mmol/l and a 2-hour PG level ≥7.8 and <11.1 mmol/l, and impaired fasting glucose (IFG) as a fasting PG level ≥5.6 mmol/l and < 7.0 mmol/l. IFG and IGT were classified as IGR according to World Health Organisation 1999 recommendations. AGT was defined as IGR (IFG and/or IGT) and/or DM.

Using the International Diabetes Federation definition [21] modified from the latest American Diabetes Association criteria for IFG [22] and the Asian-specific definition of central obesity, MetS was defined as three or more of five risk factors: (1) waist circumference ≥80 cm; (2) FPG ≥5.6 mmol/l; (3) systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg; (4) fasting plasma triglyceride ≥1.7 mmol/l, and (5) high-density lipoprotein cholesterol <1.3 mmol/l.

Serum insulin was measured by DAKO insulin ELISA (DAKO Diagnostics, Ely, UK). Plasma triglycerides and high-density lipoprotein cholesterol were measured by enzymatic methods while PG was measured by hexokinase method (DP Modular Analytics, Roche Diagnostics, Indianapolis, Ind., USA). The study was approved by the Chinese University of Hong Kong Clinical Research Ethics Committee. Written informed consent was obtained from all participants.

Statistical Analyses

All data are expressed as median and range, mean ± SD or proportion. Between-group differences were compared by Student's t, Mann-Whitney U and ANOVA tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables as appropriate. Multivariable logistic regression analysis was used to obtain adjusted odds ratios with 95% CI, with forced entry of maternal age, BMI ≥23 at booking, family history of DM and GD during pregnancy. Model fit was assessed using the Hosmer and Lemeshow Goodness-of-Fit test. $p < 0.05$ for 2-tailed statistical tests was used to indicate significance. Statistical analysis was performed using the SPSS 17.0 (SPSS, Chicago, Ill., USA).

Results

Since the last follow-up study, 2 women had died from causes unrelated to DM or hypertension (1 died of acute gastrointestinal bleeding and another died in the Accident and Emergency Department of an acute illness); 47 women refused to participate and 16 women could not be contacted. A total of 139 (68.4%) of the previous cohort (94 with NGT and 45 with GD) completed both the physical examination and biochemical blood assay. There was no significant difference in the maternal age, weight and height at booking, and GD status during the index pregnancy between the responders and nonresponders.

As compared to the previous follow-up at 8 years postpartum, type 2 DM had increased from 9% (n = 6/67) to 24.4% (n = 11/45; 2.7-fold increase) and 2.2–5.3% (2.4-fold increase) among the women with NGT and GD during pregnancy [14].

Amongst the 6 women who were known to have type 2 DM before the present follow-up, 5 were actually diagnosed at the previous follow-up study while 1 was diagnosed IGT at that time. Four of them were put on oral hypoglycemic treatment. The remaining 10 women (62.5%) with type 2 DM were undiagnosed prior to the present study. Hypertension occurred in 31 subjects (22%) in the cohort and 10 (32.3%) of them were also undiagnosed. One woman was incidentally found to have severe anemia during the present study and confirmed to have malignancy on further investigation.

Women with prior history of GD and women with NGT were of similar age, parity, smoking status, body weight and BMI at a median follow-up of 15 years after the index pregnancy (table 1). Women with prior history of GD had significantly higher prevalence of hypertension (35.6% vs. 16.0%, $p = 0.01$), type 2 DM (24.4% vs. 5.3%, $p < 0.001$) and IGR (26.6% vs. 14.9%, $p < 0.001$), as well as higher plasma triglyceride levels (1.33 ± 0.80 vs. 1.06 ± 0.57 mmol/l, $p = 0.003$) than women with NGT. There were no significant differences in plasma levels of other lipids and the prevalence of MetS between the 2 groups.

Type 2 DM increased by about 2.5-fold from 9% at 8 years to 24.4% at 15 years postpartum amongst women with a history of GD, which represents an average conversion rate of 1.6% per year. When taking into consideration the glycemic status at the 8-year follow-up, women who had a prior history of GD and became AGT at 8 years after delivery were more obese as demonstrated by their higher BMI, waist circumference, waist-to-hip ratio and percentage of fat compared to women who had a prior history of GD but remained NGT at 8 years after delivery (table 2).

The prevalence of hypertension was significantly lower in women who had NGT and remained NGT at 8 years after delivery when compared to the other 3 groups.

Table 1. Demographic characteristics, cardiometabolic status of women with NGT and GD at follow-up 15 years after the index pregnancy

Glycemic status at index pregnancy	NGT (n = 94)	GD (n = 45)	p value
Mean age at follow-up, years	43.2 ± 4.6	43.8 ± 4.3	0.49
Parity			
1	10 (10.6%)	9 (20.0%)	0.22
≥2	84 (89.4%)	36 (80.0%)	
Current smoker	9 (9.3%)	2 (4.8%)	0.53
Body weight, kg	59.1 ± 9.5	59.0 ± 10.2	0.97
Body height, cm	155 ± 6	155 ± 6	0.49
BMI	24.4 ± 3.5	24.7 ± 4.5	0.70
Waist circumference, cm	81.5 ± 9.7	82.5 ± 10.4	0.60
Hip circumference, cm	98.3 ± 7.1	98.03 ± 7.2	0.85
Waist-to-hip ratio	0.82 ± 0.08	0.84 ± 0.06	0.22
Body fat, %	32.1 ± 6.8	33.1 ± 7.5	0.43
Hypertension	15 (16.0%)	16 (35.6%)	0.01
Fasting plasma glucose, mmol/l	4.9 ± 0.5	5.4 ± 0.9	0.002
2-hour plasma glucose, mmol/l	6.4 ± 2.1	8.1 ± 2.9	0.001
Maternal glycemic status at follow-up			
NGT	75 (79.8%)	22 (48.9%)	<0.001
IFG and/or IGT	14 (14.9%)	12 (26.6%)	
DM	5 (5.3%)	11 (24.4%)	
Plasma HDL-C level, mmol/l	1.59 ± 0.35	1.49 ± 0.33	0.12
Plasma LDL-C level, mmol/l	2.68 ± 0.80	2.72 ± 0.61	0.75
Plasma triglyceride level, mmol/l	1.06 ± 0.57	1.33 ± 0.80	0.03
Plasma total cholesterol, mmol/l	4.73 ± 0.84	4.79 ± 0.58	0.69
Metabolic syndrome	14 (14.9%)	10 (22.2%)	0.41

Data expressed as either mean ± SD, or number (%).
HDL-C = High-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.

Amongst women who had NGT during pregnancy, women with AGT at 8 years after delivery had a higher prevalence of MetS (42.9% vs. 10.0%) than women with NGT at 8 years after delivery. Women who had GD during pregnancy and AGT at the 8-year follow-up were significantly more insulin resistant (table 2).

Table 3 summarizes the results of the logistic regression on the prediction of type 2 DM at 15 years with maternal age, BMI and GD status at index pregnancy, Matsuda-ISI, β-cell function and insulinogenic indices at 8 years. Insulin sensitivity indices, represented by Matsuda-ISI and QUICKI, remained independent predictors of both DM and MetS at 15 years postpartum, with or without adjustment for β-cell function and/or AGT status at 8 years postpartum. The same findings cannot be reproduced with the insulin resistance measured by the HOMA model. Insulinogenic index at 15 min at 8 years postpartum was found to be a predictor of MetS at 15 years but not a predictor of type 2 DM. There is a trend that β-cell function, represented by HOMA-BCF, at 8 years is predictive of AGT at 8 years postpartum, adjusting for insulin sensitivity, but does not reach statistical significance. GD status during pregnancy remained an independent predictor of DM at 15 years postpartum but not a predictor of MetS after adjustment for insulin resistance and β-cell function.

In the multivariate model, a history of GD at index pregnancy 15 years ago increased the odds of future progression to AGT, DM and hypertension by 5.2 (2.2–12.1), 8.0 (2.2–28.3) and 3.3 (1.4–7.8), respectively. After being adjusted for the conversion of type 2 DM, maternal GD status was still predictive of women's hypertension at 15 years postpartum (odds ratio: 2.5, 95% CI: 1.0–6.2; table 4).

Discussion

A recent study has highlighted an increasing prevalence of GD by an average of 60% in several ethnic groups during the past 20 years [23]. The increase in the preva-

Table 2. Demographic characteristics, cardiometabolic status of women with either NGT or GD at follow-up 15 years after the index pregnancy who either remained NGT or converted to AGT

	NGT at index pregnancy (n = 94)		GD at index pregnancy (n = 44)		p values[a]
	NGT at 8-year follow-up (n = 80)	AGT at 8-year follow-up (n = 14)	NGT at 8-year follow-up (n = 25)	AGT at 8-year follow-up (n = 19)	
Body weight, kg	58.6 ± 8.49	62.0 ± 14.2	55.6 ± 8.0	63.1 ± 11.5	0.047
Body height, kg	155.3 ± 5.7	155.6 ± 5.4	155.6 ± 5.0	154.0 ± 6.2	0.77
BMI	24.3 ± 3.1	25.5 ± 5.2	23.0 ± 3.3	26.6 ± 4.7[e]	0.01
Waist circumference, cm	80.8 ± 8.1	86.0 ± 15.6	78.8 ± 8.9	86.9 ± 10.8[c, e]	0.01
Hip circumference, cm	98.0 ± 6.1	99.8 ± 11.5	96.0 ± 5.7	100.2 ± 8.1	0.19
Waist-to-hip ratio	0.82 ± 0.05	0.86 ± 0.08	0.82 ± 0.06	0.87 ± 0.06[f]	0.01
Body fat, %	31.7 ± 6.2	34.1 ± 9.5	30.0 ± 5.8	36.5 ± 7.8[c, e]	0.01
Hypertension	10 (12.5%)[b]	5 (35.7%)	9 (36.0%)	7 (36.8%)	0.01
Maternal glycemic status at 15-year follow-up					
NGT	70 (87.5%)	5 (35.7%)	18 (72.0%)	3 (15.8%)	<0.001
IFG and/or IGT	10 (12.5%)	4 (28.4%)	4 (20.0%)	7 (36.9%)	
DM	0	5 (35.7%)	2 (8.0%)	9 (47.4%)	
Plasma HDL-C level, mmol/l	1.6 ± 0.3	1.6 ± 0.4	1.5 ± 0.3	1.5 ± 0.4	0.52
Plasma LDL-C level, mmol/l	2.7 ± 0.7	2.6 ± 1.1	2.6 ± 0.5	2.9 ± 0.7	0.67
Plasma triglyceride level, mmol/l	1.0 ± 0.5	1.5 ± 0.6	1.3 ± 0.6	1.4 ± 1.0	0.01
Plasma total cholesterol, mmol/l	4.7 ± 0.8	4.8 ± 1.1	4.7 ± 0.6	4.9 ± 0.6	0.79
Metabolic syndrome	8 (10.0%)	6 (42.9%)[c]	4 (16.0%)	5 (26.3%)	0.01
Insulin resistance and β-cell function at 8 years					
β-Cell function	153.5 ± 157.4	130.9 ± 96.1	142.6 ± 189.6	172.3 ± 149.5	0.88
HOMA-IR	1.9 ± 2.3	2.1 ± 1.3	2.0 ± 2.9	3.4 ± 3.0	0.14
Matsuda-ISI	7.2 ± 4.5	5.1 ± 3.6	6.4 ± 4.1	3.7 ± 1.9[c]	0.01
QUICKI	0.37 ± 0.05	0.36 ± 0.05	0.37 ± 0.04	0.34 ± 0.04[d]	0.04

Data expressed as either mean ± SD, or number (%).

HDL-C = High-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; LDL = low-density lipoprotein cholesterol.

[a] p values compare the 4 subgroups by one-way ANOVA.

[b] $p \leq 0.01$ (compared with all other 3 groups).

[c] $p < 0.01$ (compared with NGT during pregnancy and remains NGT at 8-year follow-up).

[d] $p = 0.03$ (compared with NGT during pregnancy and remains NGT at 8-year follow-up).

[e] $p \leq 0.01$ (compared with GDM during pregnancy and remains NGT at 8-year follow-up).

[f] $p = 0.02$ (compared with GDM during pregnancy and remains NGT at 8-year follow-up).

lence of GD seems genuine despite the possible influence of the changes in the screening strategies and diagnostic criteria, as well as increasing obesity and the aging of the pregnant population [23]. Both the actual rate and the increase in the prevalence were highest in Asians and Hispanics amongst different ethnic groups, while rapid progression to type 2 DM and MetS was noted in the Indian population [23, 24].

The prevalence of GD now appears to be highest among Indian, Chinese and other Asians [25], while women born in South Asia are also at high risk [26]. In the early 1990s, the prevalence rate of GD was found to be 14.2% among Hong Kong Chinese on the basis of universal OGTT [27]. Large epidemiological studies also demonstrated a high prevalence of DM in young Chinese as well as an increase in undiagnosed prediabetes and diabetes [28–30].

In this cohort of Chinese women who were relatively young at a median age of 27 years during pregnancy in which GD was diagnosed by universal OGTT, type 2 DM increased by about 2.5-fold from 9% at 8 years to 24.4% at 15 years postpartum. None of the subjects had hypertension prior to their pregnancy except 3 who developed gestational hypertension and 1 with pre-eclampsia. Our study also showed that the history of GD increased the odds of future hypertension at 15 years by 3.3; the odds

Table 3. Prediction of type 2 DM and MetS at 15 years postpartum using logistic regression with GD status at index pregnancy, insulin sensitivity indices, β-cell function and insulinogenic indices at 8 years postpartum after adjustment for age, BMI at booking during pregnancy and AGT status at 8 years

	DM at 15 years	p	MetS at 15 years	p
Matsuda-ISI	0.55 (0.36–0.84)	0.006	0.66 (0.49–0.88)	0.005
Matsuda-ISI[b]	0.38 (0.20–0.70)	0.002	0.59 (0.41–0.85)	0.004
Matsuda-ISI[a, b]	0.43 (0.23–0.82)	0.010	0.62 (0.43–0.89)	0.009
QUICKI	0.14 (0.026–0.74)	0.021	0.17 (0.042–0.68)	0.012
QUICKI[b]	0.015 (0.001–0.26)	0.004	0.078 (0.011–0.55)	0.011
QUICKI[a, b]	0.028 (0.01–0.78)	0.035	0.11 (0.015–0.79)	0.028
HOMA-IR	1.08 (0.90–1.30)	0.43	1.05 (0.88–1.26)	0.56
HOMA-IR[b]	1.35 (0.89–2.06)	0.16	1.04 (0.79–1.37)	0.77
HOMA-IR[a, b]	1.11 (0.71–1.74)	0.64	0.97 (0.73–1.30)	0.86
AUC (I)/AUC (G)	1.00 (0.98–1.01)	0.71	1.00 (1.00–1.02)	0.18
AUC (I)/AUC (G)[c]	1.11 (0.95–1.30)	0.20	1.06 (0.94–1.21)	0.34
AUC (I)/AUC (G)[a, c]	1.08 (0.93–1.26)	0.32	1.06 (0.93–1.20)	0.41
HOMA-BCF	1.00 (1.00–1.00)	0.95	1.00 (1.00–1.00)	0.62
HOMA-BCF[c]	0.99 (0.99–1.00)	0.058	1.00 (0.99–1.00)	0.25
HOMA-BCF[a, c]	0.99 (0.99–1.00)	0.058	1.00 (0.99–1.00)	0.30
Insulinogenic index 30 min	1.02 (0.82–1.27)	0.84	1.02 (0.88–1.19)	0.80
Insulinogenic index 30 min[c]	0.98 (0.85–1.13)	0.80	1.00 (0.89–1.12)	0.99
Insulinogenic index 30 min[a, c]	0.99 (0.74–1.31)	0.94	1.00 (0.89–1.14)	0.96
Insulinogenic index 15 min	1.03 (0.83–1.27)	0.80	1.79 (1.14–2.82)	0.012
Insulinogenic index 15 min[c]	1.01 (0.75–1.35)	0.95	1.86 (1.12–3.07)	0.016
Insulinogenic index 15 min[a, c]	1.11 (0.63–1.95)	0.73	1.65 (1.07–2.55)	0.023
Gestational diabetes[c]	5.29 (1.47–19.1)	0.011	0.87 (0.30–2.49)	0.79
Gestational diabetes[d]	5.67 (1.66–19.4)	0.006	1.04 (0.37–2.93)	0.94
Gestational diabetes[e]	5.01 (1.56–16.1)	0.007	1.23 (0.45–3.40)	0.69

Data expressed in odds ratio (95% CI). AUC (G) = Area under the curve of glucose level at OGTT; AUC (I) = area under the curve of insulin level at OGTT; HOMA-IR = homeostasis model assessment of insulin resistance. Prediction by insulin sensitivity, insulin resistance indices and β-cell functions were adjusted for maternal age, BMI at booking during pregnancy and gestational diabetic status, together with [a] adjustment for abnormal glucose tolerance at 8-year follow-up, [b] adjustment for HOMA-BCF, or [c] adjustment for Matsuda-IRI.

Prediction by gestational diabetes were adjusted for maternal age, BMI at booking during pregnancy and with [c] adjustment for Matsuda-IRI, [d] adjustment for QUICKI, or [e] adjustment for HOMA-BCF.

for hypertension (2.5-fold) are independent of the occurrence of type 2 DM. This is similar to the result of a recent cohort study which showed increased cardiovascular disease following GD with a hazard ratio of 1.7; the hazard ratio was 1.1 after adjustment for the development of type 2 DM [31]. This indicated that women with a prior history of GD had a substantial increase of cardiovascular risk which was partially attributed to the subsequent development of type 2 DM [31].

Among women who had NGT at pregnancy but subsequently progressed to AGT at 8 years after delivery, there appeared to be a 4-fold increase in the risk of MetS at 15 years after delivery. However, this observation was not found in women with GD during pregnancy. This may suggest an association between MetS and AGT in women without GD during pregnancy.

Studies have confirmed the link between insulin resistance during pregnancy and the development of gestational hypertension and pre-eclampsia [32–34], which in turn are associated with future risk of hypertension and cardiovascular risk. We demonstrated that women with a history of GD who became AGT at 8 years postpartum were significantly more insulin resistant than women who were NGT at pregnancy and remained NGT at 8 years. In addition, insulin sensitivity (as assessed by Matsuda-ISI and QUICKI) at 8 years was independently predictive of the presence of type 2 diabetes at 15 years after adjustment for GD status, maternal age, BMI at the index

Table 4. Pregnancy-related variables in women who developed AGT, DM, hypertension and MetS

	AGT	DM	Hypertension	MetS
Gestational diabetes	5.2 (2.2–12.1)	8.0 (2.2–28.3)	3.3 (1.4–7.8)[a]	2.1 (0.8–5.6)
Advanced maternal age	2.5 (0.6–10.6)	5.0 (0.9–28.1)	1.4 (0.3–6.2)	0.8 (0.1–4.0)
Family history of DM	2.8 (1.1–7.6)	2.4 (0.7–8.6)	2.4 (0.9–6.5)	2.3 (0.8–6.7)
BMI at booking ≥23	2.3 (1.0–5.3)	2.2 (0.7–7.2)	2.1 (0.9–5.0)	6.0 (2.1–17.2)

[a] Odds ratio after adjustment for conversion to DM: 2.5 (1.0–6.2).

pregnancy and/or AGT status at 8 years postpartum. We could not find the same prediction with β-cell functions represented by HOMA-BCF and the insulinogenic indices. Although it has been well accepted that the interplay between insulin resistance and decrease in β-cell capacity predates the occurrence of frank DM [35–42], Tabák et al. [43] have recently demonstrated that β-cell function might not decline until 2 years prior to the occurrence of DM. Their finding also suggests that insulin sensitivity could start to decline as long as 13 years prior to the occurrence of DM while the trajectory of β-cell function could follow a rise between 3 and 4 years and decline 2 years prior to DM [43]. However, there is also evidence demonstrating that β-cell function starts to decline in the first year postpartum in women with mild gestational diabetes and glucose intolerance in pregnancy [44]. Our present findings may suggest that our group has a different severity as the subjects were predominantly IGT while there could also be ethnic differences in the changes in insulin resistance and β-cell function following a pregnancy with GD. Our findings appear to show that insulin sensitivity indices based on Matsuda and QUICKI models can be better predictors than β-cell function on the progression to DM in the longer term independent of AGT status at 8 years postpartum.

Detecting women who are insulin resistant though without progression to AGT at an intermediate follow-up (8 years postpartum) certainly can identify those at high risk of progression to DM at a longer follow-up interval (15 years postpartum). The results also confirm that women who had NGT at pregnancy and at 8 years postpartum would have very low risk of DM in the long term. The strength of the current study is the presence of comprehensive 5-point OGTT results and a full insulin profile for comparison using various models of insulin sensitivity and β-cell function in the prediction of DM progression in women with a history of GD.

In this study, we also found that being overweight at booking remained the most significant predictor of MetS at 15 years postpartum. A history of GD was not found to be a significant risk factor of MetS. Several follow-up studies on women with a prior history of GD has revealed an increased future risk of MetS [24, 45–48] which in turn was strongly associated with cardiovascular risk [49–51]. Another study also demonstrated that some constituents of MetS might already be apparent before the diagnosis of GD, implying a strong association between GD and MetS [52].

Finally, we have to acknowledge the several weaknesses of the study, namely a rather small sample size of the cohort and the unavoidable drop-out rate in a long-term follow-up study design. This may account for the lack of predictability of β-cell function at the baseline on DM and of GDM on future MetS. Moreover, a detailed history of dietary patterns and levels of physical activity at the baseline was lacking. Such information would be important as any lifestyle modification after the diagnosis of GD and AGT will alter the predetermined course of progression into DM.

Conclusions

We have found in this unselected population with a prior history of GD that the conversion rate increased at an average of 1.6% per year. A prior history of GD increased in the risk progression to type 2 DM by 8-fold as compared to the controls after adjustment for maternal age, being overweight in early pregnancy and family history of DM. The increasing awareness on the risk of type 2 DM after GD and the implication of insulin resistance at some years after the pregnancy could help us to refine a woman's future diabetic risk. This would provide us with an opportunity to follow up and offer dietary, lifestyle and pharmacological interventions to prevent or delay the onset of type 2 DM in these high-risk women.

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Disclosure Statement

No potential conflicts of interest relevant to this article are reported.

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