Gestational Diabetes Mellitus: Clinical Predictors and Long-Term Risk of Developing Type 2 Diabetes

A retrospective cohort study using survival analysis

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OBJECTIVE — We sought to determine the long-term risk of type 2 diabetes following a pregnancy complicated by gestational diabetes mellitus (GDM) and assess what maternal antepartum, postpartum, and neonatal factors are predictive of later development of type 2 diabetes.

RESEARCH DESIGN AND METHODS — This was a retrospective cohort study using survival analysis on 5,470 GDM patients and 783 control subjects who presented for postnatal follow-up at the Mercy Hospital for Women between 1971 and 2003.

RESULTS — Risk of developing diabetes increased with time of follow-up for both groups and was 9.6 times greater for patients with GDM. The cumulative risk of developing type 2 diabetes for the GDM patients was 25.8% at 15 years postdiagnosis. Predictive factors for the development of type 2 diabetes were use of insulin (hazard ratio 3.5), Asian origin compared with Caucasian (2.1), and 1-h blood glucose (1.3 for every 1 mmol increase above 10.1 mmol). BMI was associated with an increased risk of developing type 2 diabetes but did not meet the assumption of proportional hazards required for valid inference when using Cox proportional hazards.

CONCLUSIONS — While specific predictive factors for the later development of type 2 diabetes can be identified in the index pregnancy, women with a history of GDM, as a group, are worthy of long-term follow-up to ameliorate their excess cardiovascular risk.

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Pregnancy has long been recognized as a diabetogenic state characterized by the development of significant insulin resistance and compensatory hyperinsulinemia (1). Indeed, it has been described as a "transient excursion into the metabolic syndrome"—a spectrum of metabolic abnormalities associated with insulin resistance including relative hyperglycemia, hyperlipidemia, and disturbance of coagulation (2). Thus, pregnancy can unmask even slight defects in insulin secretion, resulting in glucose intolerance and gestational diabetes mellitus (GDM).

GDM affects 3–8% of pregnant women (3) and, while recognized as a risk factor for adverse perinatal outcome, is also known to be associated with the later development of type 2 diabetes. Studies vary in their estimates of risk, but the longest follow-up data suggest that up to 50% of women may develop diabetes over 20–30 years (4). Because of this, women with GDM should be regarded as worthy of close surveillance so that early lifestyle changes may be instituted to modify their excess cardiovascular risk (2).

Many studies (5–9) have attempted to identify clinical predictors for the later development of type 2 diabetes. Fasting blood glucose (FBG) and duration of follow-up have consistently been found to be associated with subsequent development of type 2 diabetes. The association is less certain, however, for maternal BMI, maternal age, and gestational age at diagnosis of GDM.

Many of these studies were limited by small patient numbers or short length of follow-up (<12 months). Loss to follow-up (censoring) is to be expected with increasing time from the index pregnancy, and analysis of studies needs to take account of this. Our study of a large cohort of women who have been followed for over 15 years uses survival analysis techniques, which take into account censoring within the cohort, to assess what factors measured at the time of GDM diagnosis are associated with later development of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population and diagnosis of GDM

For over 30 years, women booked at the Mercy Hospital for Women in Melbourne, Australia, have been universally tested for GDM. Women with risk factors for GDM or clinical signs of diabetes are tested with an oral glucose tolerance test (OGTT) at booking and then again between 26 and 28 weeks if the initial tests were negative. Otherwise, universal testing with an OGTT is recommended for all women at 26–28 weeks' gestation.

GDM is defined as a fasting plasma glucose level ≥5.5 mmol/l and/or a 2-h plasma glucose level ≥8.0 mmol/l after a fasting 75-g OGTT. Criteria for diagnosis at the Mercy Hospital for Women changed on 1 January 1999 to conform

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Abbreviations: BwtGC, birth weight gestational centile; FBG, fasting blood glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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with the Australian Diabetes in Pregnancy Society guidelines (10). Before this date, the diagnosis was made following a 50-g OGTT with a 1-h capillary plasma glucose level of ≥9.0 mmol/l and a 2-h capillary plasma glucose level of ≥7 mmol/l. The two diagnostic methods identified approximately the same proportion of women (11).

All women who are diagnosed with GDM receive advice about diet and exercise and are monitored in a specialized clinic involving a diabetes physician. Self-monitoring of blood glucose levels is performed and insulin therapy commenced for persistent FBG values >5.5 mmol/l or 2-h postprandial blood glucose values >6.5 mmol/l.

Maternal antepartum, postpartum, and neonatal variables are collected prospectively and entered into a standardized relational database. Variables recorded are as follows: *1*) maternal factors at time of GDM diagnosis, i.e., age, country of birth, parity, height, weight, date and gestation of diagnosis, and family history of type 2 diabetes; *2*) antenatal factors, i.e., use of insulin and values of the diagnostic OGTT (fasting 1- and 2-h blood glucose levels); and *3*) neonatal factors, i.e., birth weight and gestation. Constructed variables are BMI (kg/m^2) and birth weight gestational centile (BwtGC) using standardized growth charts based on 28,000 Mercy Hospital for Women births between October 1993 and December 2003 (not corrected for ethnicity). Control subjects are antenatal patients with normal OGTTs who were recruited from antenatal clinics in the years before 1997. They were otherwise unmatched to the GDM population.

Follow-up testing

Before the commencement of a formal follow-up program in 1981, all GDM patients were encouraged to attend appointments for follow-up; however, only 10% did so. The formal program consists of diabetes educator review, OGTT at 6 weeks postpartum, and written explanation of the reasons for further testing. Postpartum testing consists of a 75-g OGTT with diabetes diagnosed according to the 1998 World Health Organization criteria as adopted by the Australian Diabetes Society (12). This lowered the diagnostic FBG threshold from ≥7.8 mmol/l (prior to 1 January 1999) to ≥7.0 mmol/l (on or after 1 January 1999). Those with normal results are recalled for testing in 2 years, while those with impaired glucose tolerance are recalled in 1 year. If the diagnosis of type 2 diabetes is made, the patient is referred to a diabetes physician or general practitioner for ongoing management. The structure of the follow-up program has been previously published (13).

Statistical analysis

Cohort characteristics were described for categorical variables by *n* (%) and for continuous variables using mean ± SD or median (25th–75th percentile) according to their distribution. The quality of cohort was assessed by both the median failure time for censored observations and the Clark-Altman completion score (14). The unadjusted overall time to failure (development of type 2 diabetes) was described using the Kaplan-Meier failure curve. Univariate Cox proportional hazards regression was used to assess associations, measured as hazard ratios (HRs), between covariates and failure time (15). Multivariate Cox proportional hazards regression was performed using multiple imputation of missing covariate values and complete case analysis. The multiple imputation technique used the imputation by chained equations method (16) to create 20 imputed datasets, from which parameter point and variance estimates (adjusted using Rubin's rules) were computed. Complete case analysis was undertaken using semipurposeful selection techniques. Rescaling of covariates, based on clinical meaningful changes from the mean (height, age, birth weight, BwtGC, and OGTT values) or lowest value (BMI), was made before multivariate regression analysis. The assumptions of proportional hazards and linearity of continuous covariates were checked for all final models. Significance level was set at $P = 0.05$. Analysis was performed using Stata statistical software, version 9 (Stata, College Station, TX).

RESULTS

Quality of database

The proportion of patients under observation for this study was 43.8% at 2.5 years, 28.3% at 5 years, 11.8% at 10 years, and 5.1% at 15 years. Time under observation was assessed by the following: *1*) the median analysis time for censored observations, which was 2.2 years (range 0.05–29.9) for the censored GDM patients and 8.6 years (0.6–30.5) for the control group; and *2*) the Clark-Altman completeness score, given as $C = 100 \times$ (observed, possibly censored time for each patient)/(potential follow-up time for each patient). For the GDM patients, this equaled 29%, indicating that, on average, these patients were followed up for slightly less than one-third of the average maximal follow-up time.

Baseline characteristics

The cohort consisted of 7,778 patients (6,989 GDM patients and 789 control subjects). Postnatal follow-up did not occur in 1,525 patients (1,519 GDM patients and 6 control subjects), leaving 6,253 who presented for at least one follow-up visit and were therefore available for analysis (5,470 GDM patients and 783 control subjects). Of the 5,470 patients with a diagnosis of GDM, 405 (7.4%) were diagnosed with type 2 diabetes, and 16 (2.0%) control patients developed diabetes during the follow-up period. The first date of entry was 26 April 1971 and the last 4 July 2003. The last follow-up date was 17 November 2003. The baseline characteristics are presented in Table 1.

Risk of development of type 2 diabetes

The Kaplan-Meier failure curve (Fig. 1) indicates that the unadjusted failure rate was higher in the GDM patients, for whom the cumulative probability of developing diabetes within 1 year was 1.7% (95% CI 1.3–2.1), 2 years 2.6% (2.1–3.2), 5 years 8.1% (7.1–9.2), 10 years 17.3% (15.5–19.3), and 15 years 25.8% (23.0–28.9). The mean annual risk of developing diabetes over these 15 years was 1.7% (1.4–1.9). In the control group, no patient developed diabetes during the first 5 years, with the cumulative probability of 2% (1.0–3.8) at 10 years and 3.9% (2.0–7.3) at 15 years. At any time during follow-up, the hazard of developing type 2 diabetes was 9.6 (5.9–16.7) times greater for patients with GDM than for the control group.

Predictors of development of type 2 diabetes

Table 1 also presents the results of univariate Cox proportional hazards regression analysis for the GDM group. All covariates except maternal height, parity, and birth weight were statistically associated with increased risk of development of type 2 diabetes.

Multivariable Cox proportional hazards regression was performed to assess any independent associations between covariates and time to development of di-

Table 1—*Characteristics of GDM patients compared with control subjects and univariate HRs for subsequent development of type 2 diabetes among the GDM group*

	Control subjects (n = 783)	GDM patients (n = 5,470)		
Covariate	Baseline	Baseline	HR*	*P*
Race				
Caucasian	702 (89.6)	3,901 (71.3)	1	
Asian	81 (10.4)	1,559 (28.5)	1.75 (1.42–2.16)	<0.001
Aboriginal	—	10 (0.2)	3.26 (0.81–13.1)	
Height (cm)	162 ± 7.0	160 ± 6.5	1.0 (0.99–1.02)	0.82
Age (years)	30.5 ± 4.6	30.7 ± 5.1	1.03 (1.01–1.05)	0.002
Parity	3 (2–3)	2 (2–3)	1.02 (0.95–1.10)	0.58
BMI (kg/m^2)	25.8 ± 3.6	26.9 ± 4.9	1.11 (1.09–1.13)	<0.001
Birth weight (g)	3,420 ± 501	3,269 ± 555	1.00 (1.00–1.00)	0.07
BwtGC	48 ± 27.9	47 ± 28.7	1.01 (1.00–1.01)	<0.001
Gestational age (weeks)	39.2 ± 3.4	38.4 ± 2.7	0.94 (0.92–0.96)	<0.001
Insulin use in pregnancy	—	684 (12.5)	8.9 (7.1–11.1)	<0.001
Family history of diabetes	131 (17)	1,313 (24)	1.4 (1.1–1.7)	0.002
FBG (mmol)	4.5 ± 0.6	5.2 ± 1.1	1.22 (1.19–1.25)	<0.001
1-h blood glucose (mmol)	7.4 ± 1.2	10.1 ± 1.4	1.53 (1.48–1.58)	<0.001
2-h blood glucose (mmol)	5.7 ± 1.0	8.1 ± 1.3	1.35 (1.32–1.39)	<0.001

Data are means ± SD, median (25th–75th percentile), or *n* (%). *HR (95% CI HR).

abetes. Regression analysis was performed on two datasets. One was formed using multiple imputation techniques to impute missing covariate values for those patients with incomplete covariate data; the proportion of imputed values was <6.5% for all covariates except BMI (19.3% of values imputed). For the second, complete case analysis was used; this dataset contained 3,578 patients, a 38% reduction in size of the GDM cohort. Because of its small number, the group of 10 aboriginal patients was excluded from all multivariate analysis.

HR estimates and 95% CIs for both datasets are presented in Table 2. When adjusted for measured covariates, the rate of diabetes was 3.5 times greater in patients requiring insulin, 2.1 times greater in Asians compared with Caucasians, and 1.05 times greater for each 10% increase in BwtGC. One-hour blood glucose was a predictor of diabetes; for each 1 mmol increase above 10.1 mmol, the rate of diabetes increased by 1.3 times. Fasting and 2-h blood glucose were not found to be independent risk factors. The proportional hazards assumption, required for valid inference in Cox proportional hazards regression, was met for all covariates

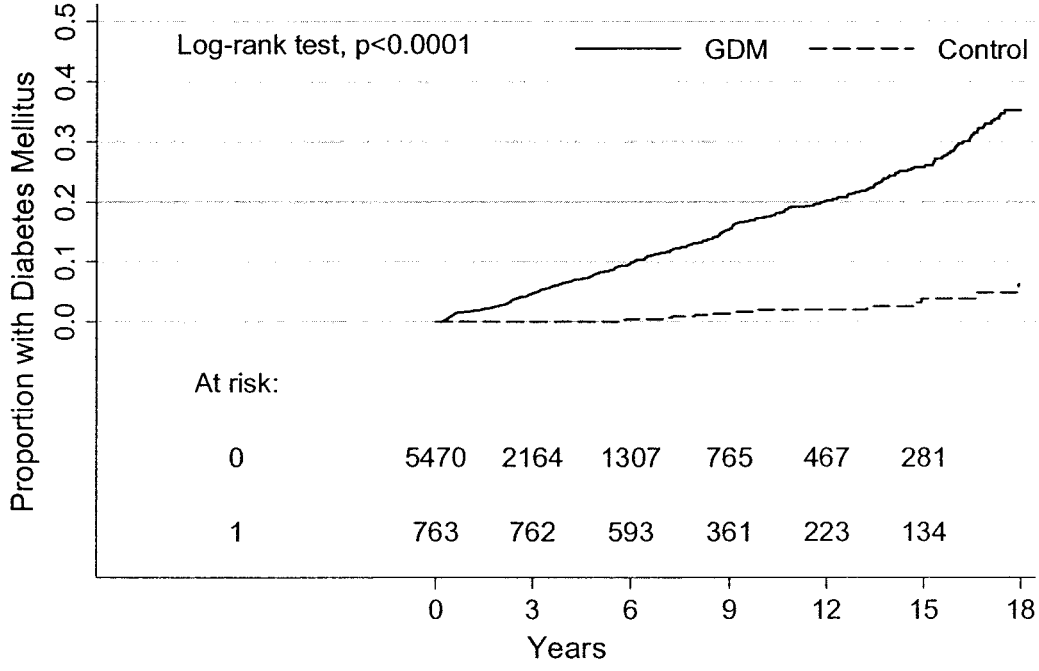

Figure 1—*Kaplan-Meier failure curve by OGTT status.*

Table 2—*HRs and 95% CIs for significant covariates using imputation and complete case methods*

Covariate	Imputation	Complete case
n	5,470	3,578
Insulin usage	3.5 (2.6–4.7)	3.4 (2.5–4.7)
Asian race	2.1 (1.7–2.7)	2.4 (1.9–3.2)
FBG (mmol)	1.1 (0.9–1.2)*	1.0 (0.9–1.1)*
1-h blood glucose (mmol)	1.3 (1.21.4)	1.3 (1.2–1.4)
2-h blood glucose (mmol)	1.0 (0.9–1.1)*	1.0 (0.9–1.1)*
BwtGC (per 10-unit increase from mean)	1.05 (1.0–1.1)†	1.03 (1.0–1.1)†
BMI (5-unit increase from BMI = 20 kg/m^2)	1.4 (1.21.6)	1.6 (1.41.8)

All *P* values <0.001, except *$P > 0.10$ and †$P = 0.02$.

except BMI. Additive hazard modeling suggested that, for BMI, the hazard increased after a lag time of 5–7 years from the index pregnancy. Its exclusion/inclusion had no substantive influence on HRs of the other covariates in the model.

CONCLUSIONS — Our study differs from many in the literature in that it involves a large cohort of patients followed up over many years and uses survival analysis to account for diminished cohort retention when assessing cumulative long-term risk of diabetes and significant predictors. In a systematic review of 28 published studies, Kim et al. (17) found that few reported life-table or survival analysis in their results. The cumulative incidence rates ranged from 2.6% at 6 weeks to 70% at 28 years after delivery. However, once adjusted for cohort retention, the differences between studies were markedly reduced.

Development of type 2 diabetes

We found the risk of development of type 2 diabetes increased with time from the index pregnancy in both the GDM and control groups. For the GDM group, the cumulative proportion of patients developing diabetes was 1.7% at 1 year postpartum, 17% at 10 years, and 25% at 15 years. This differed from the findings of Kim et al. (17) who reported that cumulative incidence increased markedly in the first 5 years after delivery but then reached a plateau after 10 years. Our findings concur with those of Albareda et al. (18) who used life-table analysis in this setting and found a cumulative incidence of diabetes of 14% at 11 years.

Many other studies only reported incidence of type 2 diabetes up to 1 year postpartum, and these ranged from 3% (19) to 38% (20). Heterogeneity of population and different diagnostic criteria may account for the large range in outcome. Application of survival analysis methods after adjustment of GDM diagnostic criteria to these and other such databases could be helpful in determining what population features are important in the different outcomes.

Most authors (including us) regard the risk of diabetes as a risk of type 2 diabetes. We have previously reported (21) the prevalence of GAD antibodies (a marker for autoimmune or type 1 diabetes) in women in our follow-up study. This suggested that ~5% of the women who developed diabetes had type 1 diabetes, with the prevalence of anti-GAD antibodies in all women who had had GDM being 1.8%.

Predictive factors in development of type 2 diabetes

We found that insulin use in pregnancy was the strongest predictor for the long-term development of type 2 diabetes, with an HR of 3.5. Other significant predictors were Asian origin when compared with Caucasian, elevated 1-h blood glucose levels, and increasing BMI. Increasing BwtGC, while statistically significant, was not thought to be a clinically significant predictor.

Insulin use in pregnancy has been inconsistently associated with long-term development of type 2 diabetes. Some studies have shown it to be predictive (7,19,22), while others have not found any association (6,23). The use of insulin in pregnancy for management of GDM depends heavily on doctor/patient preference and local protocols; therefore, it is perhaps not surprising that the association is inconsistent in different study populations.

It has long been recognized that some racial groups are more susceptible to diabetes than others (24). There has also been evidence that racial background is an independent predictor for the development of type 2 diabetes after GDM. In a U.K. study (25), 35% of Indo-Asian subjects had persistent glucose intolerance 3 months postpartum compared with 7% of Caucasian and 5% of Afro-Caribbean subjects. Wein et al. (26) (from the same follow-up program as our study) found that patients of Asian ethnicity had a twofold increased risk of developing diabetes in the first 6 months postpartum. Not surprisingly, 9 years later, our study accords with this in that we found Asian origin to be associated with a significant increase in risk of development of type 2 diabetes at long-term follow-up. The hazard of developing diabetes for women of Asian background was 2.1 times more than those of non-Asian background.

Interestingly, underweight Vietnamese women seem to carry the highest risk of development of GDM and have the most severe disease as evidenced by insulin use in pregnancy (27). In contrast, it is overweight Caucasian women who tend to have more severe disease. Asian-born women with GDM also seem to have lower serum cholesterol levels than their Caucasian counterparts (28). Together, these results suggest significant underlying metabolic differences in the pathogenesis of GDM and, perhaps, type 2 diabetes, between Asian and Caucasian women—differences that certainly warrant further investigation. Clearly, racial background should be included as a covariate in any future studies of GDM and development of type 2 diabetes.

Fasting hyperglycemia is generally regarded as indicating a more significant metabolic abnormality than postprandial glucose level because it is thought to reflect insulin resistance rather than β-cell abnormality. However, we found that, when adjusted for 1-h blood glucose, the FBG in the diagnostic OGTT during pregnancy was not a significant predictor of later development of type 2 diabetes. FBG has been studied more often than 1- and 2-h blood glucose levels. In our study, we found that 1-h blood glucose was a predictor of type 2 diabetes; however, when adjusted for 1-h blood glucose, 2-h blood glucose was not predictive. Physiologically, the 1-h blood glucose is thought to reflect first-phase insulin release, which is believed to be deficient in GDM and type 2 diabetic patients and may explain its apparent better-predictive value (26). Validation studies would be needed to confirm the evidence that 1-h blood glu-

cose is a better predictor of development of type 2 diabetes.

Previously published data are inconsistent on the predictive value of birth weight. When not adjusted for gestational age, birth weight >4 kg has variably been associated (29) and not associated (6) with later development of abnormal glucose tolerance. When adjusted for gestational age, one study has shown a positive association (26) and another (7) no association. We found a 1.05 times greater risk of development of type 2 diabetes for each 10% increase in BwtGC, but birth weight itself was not associated with increased risk in our study. While statistically significant, the clinical significance of this increase in hazard suggests that birth weight, when adjusted for gestation, is not an important predictor of outcome. In addition, insulin use is a confounding variable when considering birth weight as a predictor, and this may further account for its lack of predictive power.

Increasing BMI is associated with an increased hazard of developing type 2 diabetes. The hazard appears not to be constant but to increase only after a lag time of 5–7 years from the index pregnancy, and any inference based upon the HRs for BMI in Tables 1 and 2 should be viewed as tentative.

Gestational age at diagnosis of GDM was not tested as a predictor of subsequent type 2 diabetes. As described above, OGTT was recommended to all antenatal patients and performed at 26–28 weeks gestation. A small number of patients may have been diagnosed with GDM before this if they presented with risk factors or glucosuria; however, the gestation at diagnosis was not recorded in the database. Inability to test the association between gestational age at diagnosis and later development of type 2 diabetes relates to the setup of the database 30 years ago and not our handling of the data obtained from it. We do not believe that the omission of gestational age at diagnosis as a predictor invalidates the data presented in the study or the conclusions drawn.

When using survival analysis methodology, it is important to assess both the amount of information (follow-up time) on which inferences will be based and the biases that may be introduced should this information be limited or differ between groups under analysis. Our study had a median duration of follow-up in the censored group of 2.2 years and a completion score of 29% in the GDM group. While both measures indicate the limited nature of follow-up, should type 2 diabetes develop in any of these censored patients, the cumulative incidence would be greater than we reported.

Crowther et al. (30) have conclusively established the importance of treating GDM during pregnancy with respect to a number of pregnancy outcomes. The impact of GDM goes beyond pregnancy. Our study uses survival analysis to assess a large cohort of women with GDM followed over many years to determine cumulative risk of and predictors for later development of type 2 diabetes. While it is possible to identify factors present during the incident pregnancy that increase the long-term risk of type 2 diabetes, women with a history of GDM are, as a group, worthy of long-term follow-up and early intervention to modify and ameliorate their cardiovascular risk. A better understanding of the molecular basis of insulin resistance and the metabolic syndrome may lead to future pharmacological possibilities. In the meantime, innovative strategies are needed to engage these women in lifestyle modification programs involving increased physical activity and a healthier diet.

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