Gestational Diabetes Mellitus Increases the Risk of Cardiovascular Disease in Women With a Family History of Type 2 Diabetes

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OBJECTIVE — We sought to determine whether a history of gestational diabetes mellitus (GDM) further increases the risk of cardiovascular disease (CVD) in parous women with first-degree relatives with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Women with (n = 332) and without (n = 663) a history of GDM were compared regarding *1*) the revised National Cholesterol Education Program Adult Treatment Panel III metabolic syndrome criteria, *2*) the prevalence of type 2 diabetes, and *3*) self-reported CVD.

RESULTS — Women with prior GDM were younger (48.6 ± 0.7 vs. 52.4 ± 0.6 years [means ± SE]; $P < 0.001$) and less likely to be postmenopausal (48.3 vs. 57.9%; $P < 0.005$). Although both groups were obese (BMI 34.4 ± 1.2 vs. 33.7 ± 0.6 kg/m^2), women with prior GDM were more likely to have metabolic syndrome (86.6 vs. 73.5%; $P < 0.001$) and type 2 diabetes (93.4 vs. 63.3%; $P < 0.001$). Moreover, they had a higher prevalence of CVD (15.5 vs. 12.4%; adjusted odds ratio 1.85 [95% CI 1.21–2.82]; $P = 0.005$) that occurred at a younger age (45.5 ± 2.2 vs. 52.5 ± 1.9 years; $P = 0.02$) and was independent of metabolic syndrome (1.74 [1.10–2.76]; $P = 0.02$) and type 2 diabetes (1.56 [1.002–2.43]; $P < 0.05$).

CONCLUSIONS — Among women with a family history of type 2 diabetes, those with prior GDM were even more likely to not only have CVD risk factors, including metabolic syndrome and type 2 diabetes, but also to have experienced CVD events, which occurred at a younger age. Thus, women with both a family history of type 2 diabetes and personal history of GDM may be especially suitable for early interventions aimed at preventing or reducing their risk of CVD and diabetes.

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Gestational diabetes mellitus (GDM) is a common complication of pregnancy, affecting ~14% of pregnancies each year (1), and will likely further increase as obesity becomes more prevalent in the U.S. (2,3). One-third to one-half of women with a history of GDM will develop type 2 diabetes within 3–5 years (4,5), and 70% will develop type 2 diabetes if followed >10 years (6). The public health burden of type 2 diabetes attributable to GDM is significant, with 10–31% of parous women who are diagnosed with type 2 diabetes having a history of GDM (7).

Women with type 2 diabetes have a significant risk of long-term morbidity and mortality due to cardiovascular disease (CVD) (8–13), with heart disease being the leading cause of death (14). Furthermore, type 2 diabetes negates the protective effect of being female; thus, the risk of CVD is similar in women with type 2 diabetes to that in men (15,16). Metabolic and cardiovascular alterations that increase the risk of type 2 diabetes and CVD cluster together in the metabolic syndrome, which is characterized by central body adiposity, dyslipidemia, hypertension, and elevated fasting glucose levels (17). Several studies have demonstrated evidence of the metabolic syndrome in women with a history of GDM (18–23); however, an assessment of CVD events in these women has not been reported.

We hypothesized that among a group of women, all of whom had first-degree relatives with type 2 diabetes, those with a history of GDM would have a greater number and severity of risk factors for CVD and that this would translate into a greater prevalence of cardiovascular events by middle age.

RESEARCH DESIGN AND METHODS

— We analyzed cross-sectional data from parous women, all of whom had first-degree relatives with type 2 diabetes and participated in the GENetics of Non-Insulin dependent Diabetes (GENNID) study (24). The GENNID

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Abbreviations: CVD, cardiovascular disease; GENNID, GENetics of Non-Insulin dependent Diabetes; GDM, gestational diabetes mellitus.

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

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Table 1—*Subject characteristics according to a history of GDM*

	No GDM	Prior GDM	*P*
n	662	332	
Age (years)	52.4 ± 0.6	48.6 ± 0.7	<0.001
Number of living children	3.5 ± 0.2	3.3 ± 0.1	0.6
Postmenopausal	57.9	48.3	0.005
BMI (kg/m^2)	33.7 ± 0.6	34.4 ± 1.2	0.6
Race/ethnicity*			0.001
Caucasian	202 (30.5)	83 (25.0)	
African American	191 (28.9)	132 (39.8)	
Latina	261 (39.4)	107 (32.2)	
Other	7 (0.01)	10 (0.03)	
Education beyond high school	31.7	36.3	0.2
Alcohol use	52.5	55.6	0.3
Tobacco smoker	41.0	43.8	0.4

Data are means ± SE or *n* (%). *Race not recorded for one subject in the No GDM group.

study was performed at multiple centers in the U.S. between 1993 and 2001 and involved the collection of phenotypic data and genetic material from families with documented type 2 diabetes in order to explore the genetics of this disease. Among parous women who did not have pregestational diabetes, 332 gave a history of GDM (responded "yes" to the questions "have you been tested for gestational diabetes" and "were you told that you had gestational diabetes") and 662 gave no history of GDM on a medical history questionnaire to form the basis of this cross-sectional study. Among the women with prior GDM, 36.7% were probands and 13.4% were in the same family; 19.9% of women without GDM were probands and 20.4% were in the same family.

Local institutional review board approval was obtained by each study center. All subjects gave written informed consent before participation.

Ascertainment of medical history and medications

Subjects completed questionnaires regarding medical history, current medications, race/ethnicity, education, occupation, diet, and tobacco and alcohol use. Outcomes of interest included the responses to separate questions that asked whether the participant had "high blood pressure;" "high blood lipids, fat, cholesterol, triglycerides;" "coronary artery disease;" "suffered a stroke;" "been diagnosed with diabetes;" "routinely takes insulin;" and "routinely takes pills for diabetes." The responses for a history of coronary artery disease and stroke were combined to create one variable for CVD. The questionnaire did not ask about a history of peripheral artery disease; thus, this disease could not be included as a component of CVD.

Assessment of CVD risk factors and features of the metabolic syndrome

Subjects underwent a physical examination for weight, height, waist circumference, and blood pressure measurements (24). Blood was drawn after a 10-h overnight fast for measurement of fasting plasma glucose, fasting plasma insulin, total cholesterol, HDL cholesterol, and triglycerides. Subjects were asked to refrain from taking medication before the fasting blood draw.

The metabolic syndrome was defined by the National Cholesterol Education Program Adult Treatment Panel III, which was revised by the American Heart Association and the National Heart, Lung, and Blood Institute, as having three or more of the following: blood pressure ≥130/85 mmHg or receiving antihypertensive medication, waist circumference >88 cm, HDL cholesterol <1.3 mmol/l (50 mg/dl) or receiving drug treatment for reduced HDL, triglycerides ≥1.7 mmol/l (150 mg/dl) or receiving drug treatment for elevated triglycerides, and fasting plasma glucose ≥5.6 mmol/l (100 mg/dl) or taking antihyperglycemic medication (17).

Diabetes was defined as reporting a history of diabetes or antihyperglycemic therapy in the medical history questionnaire or having a fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or a 2-h postload plasma glucose ≥11.1 mmol/l (200 mg/dl) during a 75-g oral glucose tolerance test.

Assays

Plasma glucose, insulin, triglycerides, and total and HDL cholesterol were measured using standard techniques as detailed elsewhere (24). Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. LDL cholesterol was calculated by the Friedewald formula.

Statistical analysis

As not all women had all of the physical examination measurements or laboratory assessments performed, the sample sizes for those variables with missing data are indicated in the results.

Statistical analyses were performed using Intercooled Stata 8.2 (Stata, College Station, TX). Continuous variables were compared between the groups by independent sample *t* tests if normally distributed or Wilcoxon's rank-sum test if nonparametric. Categorical variables were compared by χ^2 test.

Linear regression analyses were performed to assess the relationships between the GDM groups and the continuous outcome variables with adjustment for confounders. Robust model clustering on the proband was performed to account for subjects who were family members. Dependent variables that were not normally distributed were transformed, either by square-root or logarithmic transformation based on visual examination of the histogram plot.

Logistic regression was performed to determine the association of GDM with coronary artery disease, stroke, the composite variable for CVD (coronary artery disease and/or stroke), the metabolic syndrome, and type 2 diabetes. To determine whether the associations between GDM and the outcomes of interest were independent of proband status, we performed analyses adjusting for proband status. Furthermore, to examine whether proband status was an effect modifier on the relationship between GDM and the outcomes (i.e., whether the association between GDM and the outcomes differed by proband status), we performed multiple logisitic regression analyses including an interaction term between proband status and GDM.

Two-sided *P* values <0.05 were considered statistically significant.

RESULTS — The study subjects were, on average, middle-aged, obese (Table 1), and 29.9 years after the index pregnancy (range 1.2–74.0). Women with prior

Table 2—*CVD risk factors according to a history of GDM*

	No GDM*	Prior GDM*	*P*	Adjusted *P*†
Waist (cm)	104.0 ± 0.7 (597)	106.4 ± 1.0 (293)	0.05	0.2
Systolic blood pressure (mmHg)	127.9 ± 0.8 (604)	127.9 ± 1.1 (297)	1.0	0.07
Diastolic blood pressure (mmHg)	76.4 ± 0.4	77.1 ± 0.7	0.4	0.3
HDL cholesterol (mmol/l)	1.09 ± 0.01	1.09 ± 0.02	0.9	1.0
Non-HDL cholesterol (mmol/l)	3.83 ± 0.05	3.95 ± 0.07	0.1	0.02
LDL cholesterol (mmol/l)	3.08 ± 0.04 (630)	3.21 ± 0.05 (308)	<0.05	0.01
Total cholesterol (mmol/l)	4.93 ± 0.05 (631)	5.05 ± 0.06 (313)	0.08	0.009
Triglycerides (mmol/l)	1.669 ± 0.068	1.732 ± 0.096	0.5	0.07
Fasting plasma glucose (mmol/l)	8.04 ± 0.15 (620)	9.39 ± 0.24 (302)	<0.001	<0.001
Fasting insulin (pmol/l)	83.5 (7.6–566.4) (299)	102 (15–1656.7) (299)	0.005	<0.001

Data are means ± SE, means ± SE (*n*), or median (range) (*n*). *No GDM $n = 633$ and Prior GDM $n = 313$ except where noted in the results column. †Adjusted for age, menopausal status, and clustering on the proband.

GDM were younger, more likely to be African American, and fewer were postmenopausal. All subsequent comparisons between the groups were adjusted for age and menopausal status. In addition, race/ethnicity was assessed as a potential confounder and included in adjusted analyses.

CVD risk factors, features of the metabolic syndrome, and type 2 diabetes

Although both groups were obese, women in the prior GDM group had a more atherogenic lipid profile and higher fasting plasma glucose and insulin levels; the latter compatible with them being more insulin resistant (Table 2).

More women in the prior GDM group reported a history of hypertension (46.8 vs. 37.0%; $P < 0.001$), were taking antihypertensive medications (44.5 vs. 35.4%; $P = 0.007$), and had hypertension diagnosed at an earlier age (40.0 ± 1.0 vs. 47.8 ± 0.9 years; $P < 0.001$). In addition, women with prior GDM were more likely to report a history of dyslipidemia (33.9 vs. 26.3%; $P = 0.015$), were taking medications for dyslipidemia (18.4 vs. 13.7%; $P = 0.02$), and were diagnosed at a younger age (47.6 ± 1.3 vs. 51.9 ± 1.0 years; $P = 0.01$). Specifically, more women in the prior GDM group were taking statins (15.1 vs. 10.1%; $P = 0.01$). The associations between GDM and hypertension (odds ratio [OR] 1.88 [95% CI 1.34–2.64]; $P < 0.001$) and dyslipidemia (1.76 [1.28–2.44]; $P = 0.001$) remained significant after adjusting for age, menopausal status, and race/ethnicity.

Women with prior GDM had a higher prevalence of type 2 diabetes (93.4 vs. 63.3%; OR 10.08 [95% CI 6.04–16.83]; $P < 0.001$ adjusting for age, menopausal status, and race/ethnicity), were taking oral antihyperglycemic therapy (59.7 vs. 35.9%; $P < 0.001$) and/or insulin (40.3 vs. 19.2%; $P < 0.001$), and were diagnosed at a younger age (37.2 ± 0.7 vs. 46.6 ± 0.6 years; $P < 0.001$). The association between GDM and type 2 diabetes remained significant after further adjustment for proband status (OR 8.62 [95% CI 5.12–14.49]; $P < 0.001$) and did not differ by proband status (interaction term not significant). An analysis stratified by race/ethnicity also demonstrated a significant association between GDM and type 2 diabetes in the three racial/ethnic groups sampled: Caucasians (8.91 [3.71–21.41]), African Americans (32.55 [7.23–146.48]), and Latinas (6.86 [3.31–14.23]).

Of the entire study population, 89.2% (prior GDM, $n = 597$; no GDM, $n = 291$) had data available for all of the metabolic syndrome criteria. This subgroup was similar to the overall study population with regard to age (prior GDM versus no GDM: 47.7 ± 0.7 vs. 51.3 ± 0.6 years, respectively; $P < 0.001$), number of children (3.3 ± 0.1 vs. 3.5 ± 0.2; $P = 0.5$), proportion postmenopausal (44.3 vs. 55.1%; $P = 0.004$), and BMI (34.7 ± 1.3 vs. 33.7 ± 0.7 kg/m^2; $P = 0.5$). Women with prior GDM were more likely to have the metabolic syndrome (OR 3.28 [95% CI 2.10–5.12]; $P < 0.001$ adjusting for age, menopausal status, and race/ethnicity) (Table 3). The association between prior GDM and the metabolic syndrome remained significant after adjusting for proband status (2.59 [1.65–4.07]; $P < 0.001$). Additionally, the interaction term between GDM and proband status was not significant ($P = 0.07$), indicating that the association between GDM and the metabolic syndrome did not differ by proband status. An analysis stratified by race/ethnicity also

Table 3—*Proportion of subjects meeting the individual National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome according to a history of GDM*

Criteria	No GDM	Prior GDM	OR (95% CI)	Adjusted OR* (95% CI)	*P**
n	575	278			
Waist circumference	80.9%	84.5%	1.28 (0.86–1.91)	1.54 (1.01–2.36)	0.047
Blood pressure	55.6%	61.0%	1.25 (0.95–1.63)	1.67 (1.23–2.28)	0.001
HDL cholesterol	76.9%	77.4%	1.03 (0.75–1.41)	0.98 (0.70–1.38)	0.9
Triglycerides	30.7%	31.0%	1.02 (0.76–1.35)	1.15 (0.85–1.56)	0.4
Fasting plasma glucose	72.8%	94.9%	6.88 (4.10–11.54)	8.46 (4.86–14.73)	<0.001
Metabolic syndrome	73.5%	86.6%	2.33 (1.58–3.41)	3.18 (2.08–4.86)	<0.001

Odds of the outcome variable in women with Prior GDM compared with No GDM. *Adjusted for age and menopausal status and clustering on the proband.

Table 4—*Frequency of CVD (coronary artery disease and stroke) and adjusted ORs with 95% CIs for the association between a history of GDM and CVD*

	No GDM	Prior GDM	Adjusted OR (95% CI)*	*P**
CVD	81/653 (12.4)	51/329 (15.5)	1.85 (1.21–2.82)	0.005
Coronary artery disease	70/653 (10.7)	40/329 (12.2)	1.58 (1.00–2.49)	<0.05
Stroke	31/631 (4.9)	19/305 (6.2)	1.67 (0.87–3.22)	0.1

Data are *n* (number with the condition)/*N* (total number of subjects) (%).*Adjusted for age and menopausal status and clustering on the proband.

demonstrated a significant association between GDM and the metabolic syndrome in the three racial/ethnic groups sampled: Caucasians (3.35 [1.60–7.03]), African Americans (3.63 [1.58–8.33]), and Latinas (2.82 [1.30–6.11]).

History of CVD

CVD (self-reported history of coronary artery disease and/or stroke) was significantly more common in women with prior GDM (adjusted OR 1.85 [95% CI 1.21–2.82]; $P = 0.005$) (Table 4). Adjustment for race/ethnicity, in addition to age and menopausal status, did not change the association between GDM and CVD (OR 1.66 [95% CI 1.07–2.57]; $P = 0.02$). Furthermore, the association between GDM and CVD remained significant after adjusting for proband status (1.59 [1.02–2.49]; $P = 0.04$) and did not differ by proband status (interaction term $P = 0.8$). An analysis stratified by race/ethnicity demonstrated similar associations between GDM and CVD in the three racial/ethnic groups sampled: Caucasians (1.62 [0.84–3.12]), African Americans (1.27 [0.62–2.61]), and Latinas (2.91[1.06–8.02]), although not all of these associations were significant likely due to the reduced sample size in the racial/ethnic groups. Coronary artery disease was increased in women with prior GDM (adjusted OR 1.58 [95% CI 1.00–2.49]; $P < 0.05$) and was diagnosed at a younger age (45.5 ± 2.2 vs. 52.5 ± 1.9 years; $P = 0.02$). Although there was a tendency toward a higher prevalence of self-reported stroke (1.67 [0.87–3.22]) and earlier age of diagnosis (50.9 ± 2.4 vs. 57.5 ± 2.9 years) in women with prior GDM, these differences were not statistically significant ($P = 0.1$ for both), likely due to the small number of women who self-reported stroke (prior GDM 19 of 305; no prior GDM 31 of 631).

Association between GDM and CVD after adjusting for the metabolic syndrome and type 2 diabetes

To determine whether there was evidence of increased CVD risk in women with prior GDM above and beyond the risk attributable to the increased prevalence of the metabolic syndrome or type 2 diabetes, logistic regression models were constructed adjusting for the metabolic syndrome or type 2 diabetes among the 890 women in whom complete data for the metabolic syndrome criteria were available. A history of GDM was associated with CVD independent of the metabolic syndrome (adjusted OR 1.74 [95% CI 1.10–2.76]; $P = 0.02$) and type 2 diabetes (1.56 [1.002–2.43]; $P < 0.05$). Further adjustment for proband status revealed similarly significant relationships between GDM and CVD independent of the metabolic syndrome and proband status (OR 1.72 [95% CI 1.07–2.74]; $P = 0.02$) and type 2 diabetes and proband status (1.56 [1.001–2.43]; $P < 0.05$). In addition, the interaction terms between GDM and proband status were not significant ($P = 0.7$ in both models), indicating that the effect of GDM did not differ by proband status.

Association between GDM and CVD, metabolic syndrome, and type 2 diabetes in the GENNID population excluding the probands

In a subgroup analysis of the GENNID population, which excluded the probands (prior GDM, $n = 210$; no GDM, $n = 530$), a history of GDM was associated with CVD (OR 1.74 [95% CI 1.06–2.86]), adjusting for age and menopausal status. Similarly, chronic hypertension (1.73 [1.16–2.59]), metabolic syndrome (3.04 [1.86–5.0]), and type 2 diabetes (8.09 [4.89–13.36]) were associated with a history of GDM adjusting for age and menopausal status.

CONCLUSIONS

— In this population of women with a family history of type 2 diabetes, we found that prior GDM was associated with an increased prevalence of CVD. Moreover, the diagnosis of CVD occurred at a significantly younger age in these women. Thus, a history of GDM, among women whom are all at risk of CVD due to their family history of type 2 diabetes (25,26), identifies individuals with a propensity for cardiovascular risk factors that manifest as a significantly higher prevalence of CVD. Furthermore, the increased prevalence of CVD in these women was above and beyond the risk associated with the metabolic syndrome, type 2 diabetes, and proband status.

In keeping with their higher prevalence of CVD, women with prior GDM had greater central adiposity, higher fasting insulin levels compatible with them being more insulin resistant, higher LDL and non-HDL cholesterol levels, and a significantly increased prevalence of hypertension compared with women without a history of GDM. Studies performed in other populations have similarly shown that women with a history of GDM are more obese (27), have greater waist circumferences (22,23,27), are dyslipidemic (22,28), and are insulin resistant (23). While these studies have evaluated risk factors for CVD and features of the metabolic syndrome, they have not reported the prevalence of CVD itself. Thus, our study of parous women with a family history of type 2 diabetes is unique in that we report that these cardiovascular risk factors translate into a significantly higher prevalence of CVD events in women with prior GDM.

Women with a history of GDM also had an increased odds of developing type 2 diabetes relative to women without GDM, which is consistent with other studies (4–6). Our results further extend these previous observations by showing that among women with a family history of type 2 diabetes, prior GDM confers added risk of the metabolic syndrome and type 2 diabetes.

In the past few years, it has become apparent that lifestyle and pharmacological interventions are capable of slowing or possibly preventing the development of type 2 diabetes in high-risk individuals (29–31). Based on the need to prevent type 2 diabetes in women with a history of GDM, it will be important to know from the Diabetes Prevention Program whether both the lifestyle intervention and met-

formin treatment reduced the rate of development of diabetes in this group of women, an effect that was demonstrated with troglitazone treatment in the TRoglitazone In the Prevention Of Diabetes (TRIPOD) study (32). Whether these approaches are also capable of reducing the development of CVD in women with a history of GDM is unknown, but some indication may be obtained from the long-term follow-up of the Diabetes Prevention Program cohort.

While our study clearly has strengths based on the large sample size, the racial/ethnic diversity of the participants, and inclusion of participants from several regions of the U.S. (24), it also has some potential limitations. First, we were not able to assess the prevalence of peripheral artery disease. Second, the possibility of misclassification of the exposure (a history of GDM) and outcome variables (a history of CVD) may have occurred since these diagnoses were based on questionnaire data. Third, screening for GDM was described in 1964 by O'Sullivan and Mahan (33) but was not universally recommended in women until 1978–1980 (34, 35). Fourth, survivor and recall bias may have influenced the results, with survivor bias likely resulting in underestimation and recall bias in overestimation of the association. While bias may have also occurred due to more women with GDM being probands, we demonstrated that the association between a history of GDM and CVD was independent of proband status in analyses adjusting for proband status or excluding probands.

In conclusion, this study provides evidence that a history of GDM is associated with a higher prevalence of CVD in a population with a family history of diabetes. Furthermore, women with a history of GDM experience the cardiovascular events at a younger age compared with women without a history of GDM. Interventions have been shown to reduce the progression to type 2 diabetes in subjects at risk for the disease, including women with a history of GDM, and offer primary prevention of CVD events in established type 2 diabetes (36). We believe our findings provide strong rationale to further consider efforts to target women who have a history of GDM with interventions in order to improve both their metabolic and cardiovascular health.

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