Increased risk of cardiovascular disease in young women following gestational diabetes

Gestational diabetes and cardiovascular risk

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Received 11 April 2008 and accepted 8 May 2008.
Objective: To determine whether women with gestational diabetes (GDM) have an increased risk of cardiovascular disease (CVD) following pregnancy.

Research Design and Methods: All women aged 20 to 49 years with live births between April 1994 and March 1997 in Ontario, Canada were identified. Women with GDM were matched with up to ten women without GDM, and were followed for CVD.

Results: The matched cohorts included 8,191 women with GDM and 81,262 women without. Mean age at entry was 31 years, and median follow up was 11.5 years. The hazard ratio for CVD events was 1.71 (95% confidence interval 1.08–2.69). After adjustment for subsequent type 2 diabetes, the hazard ratio was attenuated (1.13, 95% confidence interval 0.67–1.89).

Conclusions: Young women with GDM had a substantially increased risk for CVD compared to women without GDM. Much of this increased risk was attributable to subsequent development of type 2 diabetes.
Gestational diabetes (GDM) is a common condition affecting 2 to 4% of pregnant women, (1) and is associated with adverse outcomes for both the fetus and the mother. Previous GDM is a major risk factor for type 2 diabetes, which occurs in 20 to 60% of affected women within 5 years. (2) Women with a history of GDM are also at increased risk of other cardiovascular risk factors such as obesity, hypertension, dyslipidemia and the metabolic syndrome, (3-5) and of subclinical atherosclerosis. (6) Taken together, these findings suggest that GDM identifies a population of young women at increased risk for cardiovascular disease (CVD). We used population-based administrative data to determine whether women with GDM have a heightened risk for CVD compared to women without GDM, and whether any increase in risk is independent of subsequent type 2 diabetes.

RESEARCH DESIGN AND METHODS

We conducted a population-based retrospective cohort study using administrative databases from Ontario, Canada, which included hospital discharge abstracts, physician service claims and demographic data. The Ontario Diabetes Database is a validated registry of physician-diagnosed non-gestational diabetes, defined using these administrative data. (7) Individuals are linked between all data sources via a unique health card number, which is reproducibly encrypted in all of these data sources. Women between the ages of 20 and 49 who had a hospitalization record indicating a live birth between April 1994 and March 1997 were selected. For women who had more than one birth during this period, one birth was selected at random. Those who had pre-gestational diabetes or who had had a CVD event (as defined below) in the 3 prior years were excluded.

Baseline characteristics were age at delivery, region of residence and socioeconomic status (measured as the neighborhood income quintile). Subjects with missing data were excluded. Women were defined as having GDM using an algorithm analogous to that used by the validated registry to exclude GDM: one hospitalization record or two ambulatory physician claims bearing the diagnosis of diabetes or GDM between 120 days before and 180 days after delivery.

The primary outcome (CVD events) was defined as a hospitalization for acute myocardial infarction, stroke, coronary artery bypass, coronary angioplasty or carotid endarterectomy. The prespecified secondary outcome (coronary artery disease [CAD] events) was hospitalization for acute myocardial infarction, coronary artery bypass or coronary angioplasty. Subsequent diagnosis with diabetes was identified if the woman entered the diabetes registry post-partum. Although the registry does not distinguish between types, the majority of women developing diabetes in this group would have type 2 diabetes. All women were followed until March 2007, with censoring on death.

Subjects with GDM were matched with up to ten subjects without GDM on the baseline characteristics. Kaplan-Meier survival curves were constructed for both outcomes. Cox proportional hazards regression was used to model the association of GDM with each outcome, accounting for the matched design of the study. For each outcome, an unadjusted
model and a model adjusting for subsequent diagnosis of diabetes as a time-dependent covariate were built. The assumption of proportionality was verified by plotting $\log(-\log[survival])$ vs log(time) to assess parallelism.

The study was approved by the institutional review board of Sunnybrook Health Sciences Centre.

RESULTS

There were 356,891 potentially eligible women with live births during the study period. However, 3,127 were excluded because of pre-existing diabetes, and 43 were excluded because of previous CVD. A further 2,036 were excluded because of missing data, mostly socioeconomic status. Of the remaining 351,685 subjects, 8,194 (2.3%) had GDM during the index pregnancy. The matched cohorts included 8,191 women with GDM and 81,262 without GDM. The mean age of both cohorts was 31 years.

The median follow-up time was 11.5 years. Diabetes developed during follow-up in 2,214 (27.0%) of the women with GDM and 2,596 (3.2%) of the women without GDM. Event-free survival for both CVD events and CAD events are plotted in Figure 1. Significant associations were found between GDM and both outcomes, but these associations were attenuated following adjustment for subsequent diabetes.

CONCLUSIONS

Our study is the first of its kind to show that young women with GDM have a substantially increased risk for CVD relative to women without GDM. The subsequent development of type 2 diabetes accounts for much of this increased risk, which reinforces the vital need for diabetes prevention strategies in this high-risk population.

Our findings are consistent with a cross-sectional study conducted by Carr et al., (5) which reported that women with a history of GDM had odds ratios for CVD and CAD similar to those reported here (1.85 and 1.58, respectively). However, this study was cross-sectional and relied on retrospective self-report to ascertain exposures and outcomes. In contrast, our cohort study used a more rigorous endpoint assessment, and followed a much larger population of women over many years.

Our study used administrative data, where clinical information such as cardiovascular risk factors is unavailable. Women with GDM exhibit chronic insulin resistance, (8) which is associated with a clustering of risk factors that are in the causal pathway to CVD. Therefore, women with GDM likely have very different risk factor profiles than those without GDM, and adjusting for these differences might obscure a clinically important association between GDM and CVD.

In summary, women with GDM are at increased risk for CVD events compared to women without GDM, with much of this risk attributable to the subsequent development of type 2 diabetes. Since diabetes prevention interventions in women with a history of GDM have also been shown to slow progression of atherosclerosis, (9) this study highlights the importance of diabetes prevention for this high-risk population.

ACKNOWLEDGEMENTS

We thank Ellen Chan and Ping Li for assistance with data acquisition. Drs. Shah and Retnakaran are each supported by the Canadian Institutes of
Health Research and the Canadian Diabetes Association. Dr. Booth is supported by the Canadian Institutes of Health Research, the Ontario Women’s Health Council and the Banting and Best Diabetes Centre at the University of Toronto.

REFERENCES
**Figure legend**

Figure 1. Kaplan-Meier survival curves for cardiovascular disease and coronary artery disease events, and hazard ratios derived from Cox proportional hazards regression.

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**Coronary artery disease events**

- **No GDM**
- **GDM**

- **HR=2.09 (1.19–3.67) unadjusted**
- **HR=1.35 (0.70–2.58) adjusted for subsequent diabetes**

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**Cardiovascular disease events**

- **No GDM**
- **GDM**

- **HR=1.71 (1.08–2.69) unadjusted**
- **HR=1.13 (0.67–1.89) adjusted for subsequent diabetes**

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