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RESEARCH

Mild glucose intolerance in pregnancy and risk of cardiovascular disease: a population-based cohort study

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∞∞∞   See related commentary by Cruickshank and Banerjee at www.cmaj.ca

ABSTRACT

Background: Pregnant women commonly receive screening for gestational diabetes mellitus by use of a 50 g glucose challenge test, followed by a diagnostic oral glucose tolerance test for those whose glucose challenge test result is abnormal. Although women with gestational diabetes have an increased risk of cardiovascular disease, it is not known whether mild glucose intolerance during pregnancy is also associated with cardiovascular disease. Thus, we sought to determine whether pregnant women with an abnormal glucose challenge test result but without gestational diabetes have an increased risk of cardiovascular disease.

Methods: We conducted a retrospective population-based cohort study that included all women in Ontario aged 20–49 years with live deliveries between April 1994 and March 1998. We excluded women with pregestational diabetes. The population was stratified into 3 cohorts: women with gestational diabetes ($n = 13\,888$); women who received an antepartum oral glucose tolerance test (suggestive of an abnormal result of the glucose challenge test) but who did not have gestational diabetes ($n = 71\,831$); and women who did not receive an oral glucose tolerance test (suggestive of a normal result of the glucose challenge test) ($n = 349\,977$). The primary outcome was cardiovascular disease (admission to hospital for acute myocardial infarction, coronary bypass, coronary angioplasty, stroke or carotid endarterectomy).

Results: Compared with women who did not receive an oral glucose tolerance test, women with gestational diabetes and women who received an oral glucose tolerance test but did not have gestational diabetes had a higher risk of cardiovascular disease over 12.3 years of median follow-up (adjusted hazard ratio [HR] for women with gestational diabetes 1.66, 95% confidence interval [CI] 1.30–2.13, $p < 0.001$; adjusted HR for those with an oral glucose test but not gestational diabetes 1.19, 95% CI 1.02–1.39, $p = 0.03$).

Interpretation: Mild glucose intolerance in pregnancy may be associated with an increased risk of cardiovascular disease.

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I t has been hypothesized that type 2 diabetes mellitus and cardiovascular disease may arise from a "common soil," reflecting shared underlying determinants that may contribute to the concurrent development of both these conditions in at-risk individuals.[1] Indeed, women with a history of gestational diabetes mellitus have a markedly increased risk of type 2 diabetes and cardiovascular disease in the years after an index pregnancy.[2,3] To identify gestational diabetes, pregnant women commonly receive screening late in the second trimester by use of a 50 g glucose challenge test. This is followed by a diagnostic oral glucose tolerance test for women whose glucose challenge test result is abnormal. Although the purpose of this screening is to detect gestational diabetes, it has recently emerged that any degree of abnormal glucose homeostasis on antepartum screening (not just gestational diabetes) predicts an increased risk of prediabetes or diabetes at 3-months postpartum and of diabetes in the years after delivery.[4–8] If the long-term risk of diabetes associated with gestational diabetes extends to lesser degrees of antepartum dysglycemia, the cardiovascular risk associated with gestational diabetes may also extend to women with mild glucose intolerance during pregnancy. To test this hypothesis, we used population-based health care data to determine whether pregnant women who have an abnormal glucose challenge test result but not gestational diabetes have an increased risk of subsequent cardiovascular disease.

Methods

Study population and design

We conducted a retrospective population-based cohort study in Ontario. We used administrative databases that track hospital discharge abstracts, physician service claims and demographic data. Because of the single-payer universal health care system in Ontario, these data capture virtually all care received by residents of the province. Individuals are linked between the data sources by a unique health card number that

is reproducibly encrypted within each source.

The study population consisted of all women in Ontario between the ages of 20 and 49 with a hospital record showing a live birth between Apr. 1, 1994, and Mar. 31, 1998. For women who had more than 1 delivery during this period, 1 birth was selected at random for inclusion. We excluded women who had pregestational diabetes recorded in the Ontario Diabetes Database, a validated registry of physician-diagnosed nongestational diabetes.[9]

Standard obstetrical care, as recommended by the practice guidelines of the Canadian Diabetes Association and the Society of Obstetricians and Gynecologists of Canada,[10–12] involves screening of pregnant women late in the second trimester by use of a 50 g glucose challenge test. If the result of the glucose challenge test is abnormal (defined by a plasma glucose level ≥ 7.8 mmol/L at 1 hour after ingestion of 50 g glucose), the woman is referred for a diagnostic oral glucose tolerance test. Administrative data sources do not include the results of laboratory tests, only the claims from laboratories for reimbursement for each test that was performed. Therefore, because we could not track the results of the glucose challenge tests, we instead identified claims for an oral glucose tolerance test within 16 weeks before delivery as presumptive evidence of an abnormal result of a glucose challenge test. The oral glucose tolerance test was identified on the basis of 2 or more claims for glucose tests for a patient on the same day. As previously described,[3] women with gestational diabetes were identified by use of an algorithm analogous to that used by the Ontario Diabetes Database to exclude gestational diabetes.

The study population was stratified into 3 mutually exclusive cohorts: women with gestational diabetes; women who received an antepartum oral glucose tolerance test but did not have gestational diabetes; and women who did not receive an oral glucose tolerance test. All women were followed until Mar. 31, 2008, with censoring on death. The primary outcome was clinical cardiovascular disease, defined as admission to hospital for acute myocardial infarction, coronary artery bypass, coronary angioplasty, stroke or carotid endarterectomy.

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

Statistical analysis

We constructed Kaplan–Meier survival curves for cardiovascular disease for each of the study groups. We used Cox proportional hazards regression to model the risk of cardiovascular disease in each of the 3 groups, after adjustment for the following potential confounders (all obtained from administrative data sources): age, year of delivery, rural versus urban residence (based on home postal code), income (based on the neighbourhood income of the woman's postal code), comorbidity (defined by Charlson score ≥ 1),[13] pre-existing hypertension[14] and gestational hypertension (including pre-eclampsia and eclampsia). We further adjusted the models for subsequent diagnosis of diabetes (identified by postpartum entry into the Ontario Diabetes Database) as a time-dependent covariate. The assumption of proportionality was verified for all models by plotting log(–log[survival]) versus log(time) to assess parallelism. The absolute risk differences between the group with no oral glucose tolerance test and the other 2 groups were calculated at the median follow-up time.[15]

Results

The baseline characteristics of the women at cohort entry are shown in

Table 1: Demographic and clinical characteristics of pregnant women at cohort entry

Characteristic	% of patients			
	Gestational diabetes n = 13 888	Received an oral glucose tolerance test n = 71 831	Did not receive an oral glucose tolerance test n = 349 977	p value*
Age, yr				< 0.001
20–24	9.6	14.8	18.7	
25–29	27.5	33.3	33.8	
30–34	37.9	35.4	33.2	
35–39	20.6	14.3	12.4	
40–44	4.2	2.1	1.8	
45–49	0.2	0.1	0.1	
Year of delivery				< 0.001
1994/95	29.2	28.7	31.5	
1995/96	26.7	26.7	27.9	
1996/97	23.8	23.3	22.2	
1997/98	20.3	21.3	18.4	
Rural residence	9.4	6.6	14.1	< 0.001
Income quintile				< 0.001
Unavailable	0.7	0.2	0.5	
Lowest	25.5	21.3	21.8	
2nd	22.6	22.0	21.0	
3rd	20.1	20.8	20.1	
4th	18.5	20.4	20.1	
Highest	12.7	15.2	16.6	
Comorbidity	0.4	0.2	0.2	< 0.001
Pre-existing hypertension	3.7	1.8	1.4	< 0.001
Gestational hypertension	9.6	5.1	4.4	< 0.001

*χ^2 test.

Table 1. We included 13 888 women with gestational diabetes, 71 831 women who had an antepartum oral glucose tolerance test (suggestive of an abnormal glucose challenge test result) but no gestational diabetes, and 349 977 women without an oral glucose tolerance test (suggestive of a normal glucose challenge test result). The mean age of women with gestational diabetes was 31.1. The mean age of women who received an antepartum oral glucose tolerance test was 29.7, and the mean age of women who did not have an oral glucose tolerance test was 29.2.

Over a median follow-up duration of 12.3 years, the cardiovascular event rates per 10 000 person-years were 4.2, 2.3 and 1.9 among women with gestational diabetes, those who received an oral glucose tolerance test and those who did not receive an oral glucose tolerance test, respectively. Figure 1 shows the event-free survival for cardiovascular disease in the 3 groups.

After adjustment for age, year of delivery, residence location (rural v. urban), income, comorbidity, pre-existing hypertension and gestational hypertension (model A), the Cox proportional hazard ratios (HRs) for cardiovascular disease among women with gestational diabetes and those who received an oral glucose tolerance test were 1.66 (95% confidence interval [CI] 1.30–2.13, $p < 0.001$) and 1.19 (95% CI 1.02–1.39, $p = 0.03$) (Table 2), respectively, compared with the women who did not have an oral glucose tolerance test. Compared with women who did not have an oral glucose tolerance test, the absolute risk differences were 0.16% for women with gestational diabetes and 0.05% for those who received an oral glucose tolerance test. After further adjust-

ment for the subsequent development of diabetes (model B), the HRs for cardiovascular disease were attenuated (gestational diabetes group HR 1.25, 95% CI 0.96–1.62, $p = 0.1$; oral glucose tolerance test group HR 1.16 (95% CI 0.99–1.36, $p = 0.06$) (Table 3).

Interpretation

We found that referral for an oral glucose tolerance test during pregnancy, even in the absence of gestational diabetes, may be associated with increased risk of subsequent cardiovascular disease. Because the antepartum oral glucose tolerance test is typically performed after an abnormal result of the glucose challenge test, these data raise the possibility that mild glucose intolerance during pregnancy (as reflected by an abnormal glucose challenge test result) may identify women who are at increased risk of subsequent cardiovascular disease. Further studies are needed to address the important possibility that, even in the absence of gestational diabetes, antepartum glucose tolerance screening as currently performed in clinical practice may provide insight into the future vascular risk for young women.

In the years after their index pregnancy, women with a history of gestational diabetes have an increased prevalence of several cardiometabolic derangements, including traditional vascular risk factors (e.g., type 2 diabetes, hypertension, dyslipidemia, obesity and metabolic syndrome[2,16–20]); nontraditional risk factors (e.g., subclinical inflammation and hypoadiponectinemia[19,21–23]); and early vascular dysfunction (e.g.,

No. at risk

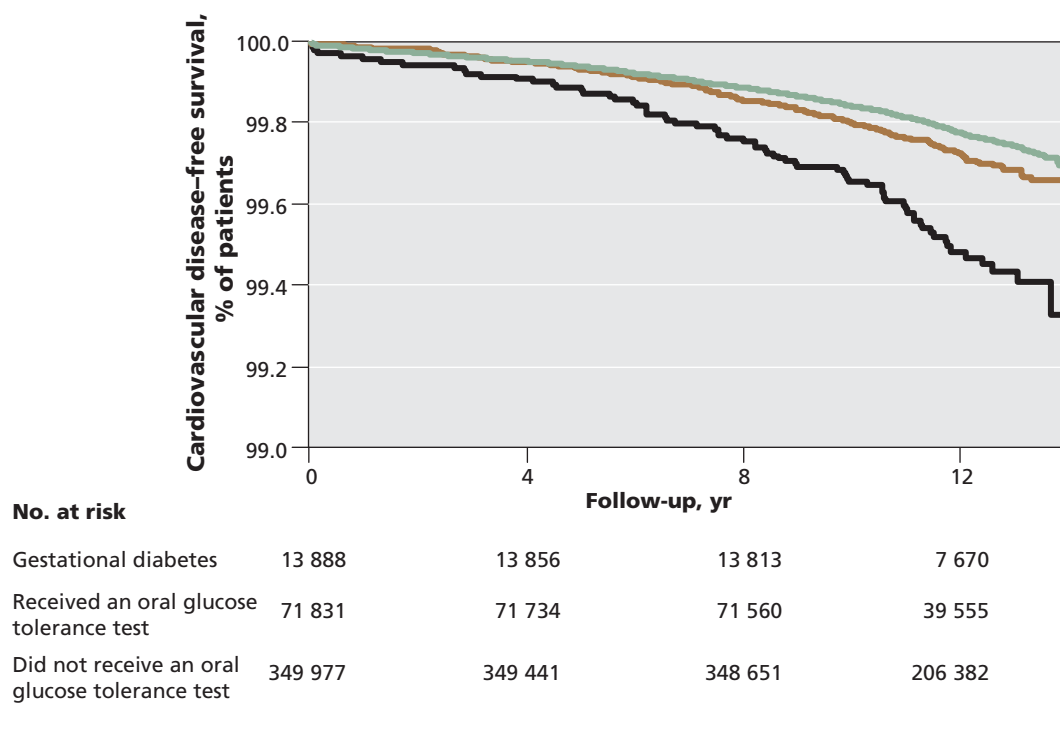|				
Gestational diabetes	13 888	13 856	13 813	7 670
Received an oral glucose tolerance test	71 831	71 734	71 560	39 555
Did not receive an oral glucose tolerance test	349 977	349 441	348 651	206 382

Figure 1: Kaplan–Meier curves for time to development of cardiovascular disease in women with gestational diabetes (black line), women who received an antepartum oral glucose tolerance test but who did not have gestational diabetes (presumed to have had an abnormal result of the glucose challenge test; brown line) and women who did not receive an antepartum oral glucose tolerance test (green line).

impaired endothelium-dependent vasodilatation and subclinical atherosclerosis[22,24,25]). Thus, it is not surprising that gestational diabetes has been reported to be associated with increased risk of future cardiovascular disease.[3,20] However, the results of our study raise the possibility that this relation may extend to milder levels of gestational glucose intolerance (similar to recent findings about fetal macrosomic risks associated with gestational diabetes[26]). Specifically, in our analysis, woman who received an oral glucose tolerance test during pregnancy had an increased risk of future cardiovascular disease compared to the general population but a lower risk than women with gestational diabetes. Further studies are needed to address the possibility that mild antepartum dysglycemia may predict future cardiovascular risk.

The biologic plausibility of this concept is supported by 3 lines of thought. First, because any degree of abnormal glucose homeostasis during pregnancy predicts an increased future risk of prediabetes or diabetes (both of which carry vascular risk),[4-8] it stands to reason that cardiovascular disease may also ensue. Second, similar to postpartum dysglycemia,

other cardiometabolic risk factors associated with previous gestational diabetes (e.g., hypertension, dyslipidemia, obesity) are also continuous and hence may also extend to lesser degrees of antepartum glycemia. Indeed, in an ongoing prospective longitudinal cohort study, we have observed that there is an increased prevalence of metabolic syndrome at 3-months postpartum among women with mild glucose intolerance during pregnancy. The risk is proportional to the degree of gestational dysglycemia (unpublished observation, 2009).

Finally, although there has been limited study of the vascular implications of mild glucose intolerance during pregnancy, previous observations support the current findings.[27] In particular, decreased brachial artery flow-mediated dilatation, which is suggestive of endothelial dysfunction, has been reported in women with gestational impaired glucose tolerance.[27] Flow-mediated dilatation has been independently and negatively associated with the area-under-the-curve for glucose in antepartum oral glucose tolerance tests.[27] Considering that endothelial dysfunction is predictive of both future type 2 diabetes and cardiovascular disease,[28,29] these data are consistent with the hypothesis that antepartum glucose intolerance is linked to both of these outcomes.

Because of these associations with type 2 diabetes and cardiovascular disease, it is natural to consider the potential role of dysglycemia in mediating vascular risk in women with glucose intolerance during pregnancy. In an earlier study, adjustment for type 2 diabetes attenuated the relation between gestational diabetes and cardiovascular disease.[3] Similarly, in the current analysis, the relations of both gestational diabetes and mild glucose intolerance in pregnancy with cardiovascular disease were attenuated after adjustment for the development of type 2 diabetes. However, when we consider the relatively low underlying cardiovascular risk potential of the study population (i.e., young women of child-bearing age) and the long period generally required for the development of macrovascular disease in patients with type 2 diabetes, it seems unlikely that diabetes necessarily precedes the onset of cardiovascular disease in this setting. Instead, these considerations suggest that, in women with glucose intolerance during pregnancy, type 2 diabetes and vascular disease may develop in parallel, which is consistent with the "common soil" hypothesis for these

Table 2: Adjusted* hazard ratios for the risk of cardiovascular disease for women after pregnancy (model A)

Characteristic	Hazard ratio (95% CI)		p value
Gestational diabetes	1.66	(1.30–2.13)	< 0.001
Oral glucose tolerance test	1.19	(1.02–1.39)	0.03
No oral glucose tolerance test	Ref		
Age, yr			
20–24	0.09	(0.04–0.20)	< 0.001
25–29	0.11	(0.05–0.24)	< 0.001
30–34	0.15	(0.07–0.34)	< 0.001
35–39	0.23	(0.10–0.52)	< 0.001
40–44	0.36	(0.15–0.83)	0.02
45–49	Ref		
Year of delivery			
1994/95	0.99	(0.82–1.21)	0.9
1995/96	1.06	(0.87–1.29)	0.6
1996/97	1.12	(0.91–1.38)	0.3
1997/98	Ref		
Rural residence	1.20	(1.01–1.43)	0.04
Income quintile			
Unavailable	0.69	(0.22–2.18)	0.5
Lowest	1.48	(1.21–1.80)	< 0.001
2nd	1.25	(1.02–1.53)	0.03
3rd	1.09	(0.88–1.34)	0.4
4th	1.09	(0.89–1.35)	0.4
Highest	Ref		
Comorbidity	5.67	(3.40–9.45)	< 0.001
Pre-existing hypertension	3.30	(2.60–4.20)	< 0.001
Gestational hypertension	2.23	(1.84–2.70)	< 0.001

Note: CI = confidence interval.
*Model A was adjusted for age, year of delivery, rural residence, income, comorbidity, pre-existing hypertension and gestational hypertension.

conditions.[1] Further study of the natural history of metabolic and vascular disease in this patient population is needed.

The importance of identifying predictors of vascular risk in this population is underscored by the fact that cardiovascular disease is the leading cause of death among Canadian women.[30] Our findings raise the possibility that glucose tolerance screening during pregnancy, as currently practiced, may help to identify women at risk of future cardiovascular disease, who may then benefit from surveillance for and modification of vascular risk factors. Women with gestational diabetes are likely one such group, given their markedly increased risk of cardiovascular disease.

The current findings suggest that the vascular risk among women with mild glucose intolerance during pregnancy, although elevated, is much lower than among women with gestational diabetes. Indeed, there is likely heterogeneity in cardiovascular risk within this group, with certain women being at particularly high risk. This heterogeneity of vascular risk may relate to the degree of gestational dysglycemia, similar to our earlier report that the magnitude of postpartum diabetic risk is proportional to this factor.[4] For example, it has been shown that, among women with mild glucose intolerance during pregnancy, women with isolated hyperglycemia at 1 hour during the antepartum oral glucose tolerance test have the most severe metabolic phenotype (resembling that of gestational diabetes) and, thus, would potentially benefit from diabetes prevention practices.[5,31,32] Our findings raise the possibility that, in addition to women with gestational diabetes, at least a subset of women with a lesser degree of antepartum dysglycemia may also benefit from closer cardiovascular surveillance. Future study should focus on elucidating the factors which may help to identify women who are at highest risk of cardiovascular disease within this population. Because antepartum screening for gestational diabetes is currently performed in clinical care, it may be convenient and potentially cost-effective if this testing could be secondarily used to detect women at risk of cardiovascular disease, for whom preventive action may be particularly beneficial.

Limitations

A limitation of our study is that the possibility of misclassification exists because we used the performance of the antepartum oral glucose tolerance test as a surrogate indicator for an abnormal result of the preceding glucose challenge test. Specifically, some women may have been referred directly for an oral glucose tolerance test in the absence of a glucose challenge test because of a perceived high risk for gestational diabetes (e.g., because of family history). In the absence of gestational diabetes, these women would have been misclassified as having had an abnormal glucose challenge test. This possibility limits the conclusions that can be drawn from this analysis. Conversely, there may have been women who had an abnormal glucose challenge test result but did not receive the oral glucose tolerance test. In this case, the resultant misclassification would bias the results in favour of the null hypothesis and therefore against the findings of the study.

Another limitation is that data about postpartum cardiovascular risk factors such as lipid levels were not available. Thus, our findings cannot provide insight on the mechanisms that may link mild gestational dysglycemia with future vascular disease. Nevertheless, by showing an independent association after adjustment for clinical covariates available at the time of glucose screening during pregnancy (age, rural or urban setting, socio-economic status, comorbidity, hypertension), our

Table 3: Adjusted* hazard ratios for the risk of cardiovascular disease for women after pregnancy (model B)

Characteristic	Hazard ratio (95% CI)		p value
Gestational diabetes	1.25	(0.96–1.62)	0.1
Oral glucose tolerance test	1.16	(0.99–1.36)	0.06
No oral glucose tolerance test	Ref		
Age, yr			
20–24	0.09	(0.04–0.21)	< 0.001
25–29	0.11	(0.05–0.26)	< 0.001
30–34	0.16	(0.07–0.35)	< 0.001
35–39	0.24	(0.11–0.55)	< 0.001
40–44	0.37	(0.16–0.85)	0.02
45–49	Ref		
Year of delivery			
1994/95	1.00	(0.82–1.21)	1.0
1995/96	1.06	(0.87–1.30)	0.5
1996/97	1.12	(0.91–1.38)	0.3
1997/98	Ref		
Rural residence	1.21	(1.01–1.44)	0.03
Income quintile			
Unavailable	0.63	(0.20–1.99)	0.4
Lowest	1.44	(1.18–1.75)	< 0.001
2nd	1.23	(1.01–1.50)	0.04
3rd	1.08	(0.87–1.33)	0.5
4th	1.09	(0.89–1.34)	0.4
Highest	Ref		
Comorbidity	5.46	(3.27–9.10)	< 0.001
Pre-existing hypertension	3.13	(2.46–3.98)	< 0.001
Gestational hypertension	2.15	(1.77–2.60)	< 0.001
Incident diabetes	2.95	(2.30–3.78)	< 0.001

Note: CI = confidence interval.
*Model B was adjusted for all of the factors listed in Table 2 (model A) as well as the development of diabetes.

analysis supports the clinical message that women with mild glucose intolerance based on this testing may be at increased risk for future cardiovascular disease.

Conclusion

Even in the absence of gestational diabetes, women who receive an oral glucose tolerance test in pregnancy (typically after abnormal results of a glucose challenge test) may have an increased incidence of subsequent cardiovascular disease. These data raise the possibility that mild glucose intolerance in pregnancy may identify a population of women who are at increased risk of cardiovascular disease in the future. Further study is needed to determine whether findings on antepartum glucose tolerance screening may provide previously unrecognized insight into the risk of vascular disease in young women.

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This article has been peer reviewed.

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Contributors: Ravi Retnakaran conceived the hypothesis and study idea and wrote the original draft of the manuscript. Both of the authors contributed to the data analysis, revised the manuscript for intellectual content and approved the final version submitted for publication.

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