Modestly Elevated Glucose Levels During Pregnancy Are Associated With a Higher Risk of Future Diabetes Among Women Without Gestational Diabetes Mellitus

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OBJECTIVE — To determine whether 1-h oral glucose challenge test (OGCT) or 3-h oral glucose tolerance test (OGTT) results below gestational diabetes mellitus (GDM) criteria are associated with developing diabetes.

RESEARCH DESIGN AND METHODS — A retrospective cohort study was performed among women without GDM who had a pregnancy OGCT ($n = 24{,}780$) or OGTT ($n = 6{,}222$). Subsequent diabetes was ascertained by ICD-9 codes or pharmacy or laboratory data over a median follow-up of 8.8 years.

RESULTS — Diabetes risk increased across OGCT quartiles: adjusted hazard ratio (HR) 1.67 (95% CI 1.07–2.61) for 5.4–6.2 mmol/l, 2.13 (1.39–3.25) for 6.3–7.3 mmol/l, and 3.60 (2.41–5.39) for ≥7.4 mmol/l compared with ≤5.3 mmol/l. Women with one abnormal OGTT result had a higher risk compared with those with normal values (HR 2.08 [95% CI 1.35–3.20]).

CONCLUSIONS — Women with modestly elevated glucose levels below the threshold for GDM had a higher risk for diabetes.

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G estational diabetes mellitus (GDM) is glucose intolerance first recognized during pregnancy (1) and is associated with an increased risk of developing type 2 diabetes (2–4). We hypothesized that mild glucose elevations during the two-step approach for GDM testing—the 50-g 1-h oral glucose challenge test (OGCT) followed by the diagnostic 100-g 3-h oral glucose tolerance test (OGTT) for an elevated OGCT (1)—would be associated with increased risk for subsequent diabetes. We therefore determined whether women with OGCT quartiles 2–4 have a higher risk of diabetes relative to quartile 1 and whether those with one abnormal OGTT value have a greater risk relative to those with normal values.

RESEARCH DESIGN AND METHODS
— We performed a retrospective cohort study in the Group Health integrated health plan in Washington state. We studied the first pregnancy delivered during 1985–2002 in women without preexisting diabetes or GDM who received care ≥1 year before delivery and ≥6 weeks postpartum. The Group Health institutional review board approved the study.

Quartiles of pregnancy OGCT results were created (Table 1). The OGTT was classified as normal, one abnormal value, or two or more abnormal values, the latter consistent with diagnosis of GDM by Carpenter/Coustan criteria: fasting glucose ≥5.3, 1-h glucose ≥10.0, 2-h glucose ≥8.6, and 3-h glucose ≥7.8 mmol/l(1). We excluded women who had GDM determined by an OGTT (1) or ICD-9 code 648.8. Preterm delivery (<37 weeks gestation) was determined by ICD-9 code 644.2. Type 2 diabetes after pregnancy was determined through 31 August 2005 as previously described (5): ICD-9 codes 250.x0 and 250.x2 without complications and 250.2–250.9 with complications, fasting glucose ≥7.0 mmol/l or random glucose ≥11.1 mmol/l on two occasions (1), or a prescription for medication to treat diabetes. The earliest date of meeting one criterion was the event date. Incidence rates were calculated using the dates of discharge from the delivery and the subsequent periods of enrollment. Cox's proportional hazards models were used to estimate hazard ratios (HRs). Statistical significance was considered for $P < 0.05$.

RESULTS — Among the 24,780 women who had an OGCT (mean ± SD age at delivery 30.1 ± 6.2 years), 24.9% were primigravidas and 16.8% delivered preterm. Higher quartiles were associated with greater age and multiparity ($P < 0.001$ for both). During a median follow-up of 8.8 years, the risk of diabetes was higher for quartiles 2–4 compared with that for quartile 1 (Table 1).

Among the 6,222 women who completed an OGTT (age 32.2 ± 5.7 years), 19.3% were primigravidas and 17.5% delivered preterm. Abnormal values were associated with greater age ($P < 0.001$). During a median follow-up of 9.7 years, diabetes was more likely in women with one abnormal result (Table 1).

Table 1—*Risk of developing subsequent diabetes by OGCT or OGTT values*

	Diabetes events	Incidence rate 100,000 person-years	Model 1*	Model 2†
OGCT quartiles (mmol/l)				
<5.4 (ref.)	30/6,768	0.96	1.0	1.0
5.4–6.2	50/6,304	1.64	1.68 (1.07–2.66)	1.72 (1.09–2.70)
6.3–7.3	65/6,245	2.05	2.05 (1.33–3.16)	2.13 (1.38–3.29)
>7.3	99/5,463	3.41	3.40 (2.25–5.11)	3.65 (2.42–5.52)
OGTT number of abnormal values				
0 (ref.)	51/3,639	2.53	1.0	1.0
1	35/1,253	5.18	2.06 (1.34–3.17)	2.07 (1.34–3.18)

Data are HR (95% CI) or *n* unless otherwise indicated. *Unadjusted. †Adjusted for age, primigravidity, and preterm delivery.

CONCLUSIONS — In this large cohort study, women with OGCT results between 5.4 and 7.3 mmol/l had a 1.7- to 2-fold higher risk of developing diabetes compared with women with the lowest glucose values. Among women with an OGTT, those with one abnormal value had a twofold greater risk of subsequent diabetes compared with women with no abnormal values. The higher risk of diabetes in women who fell below the criteria for GDM was not attenuated by adjustment for age, primigravidity, or preterm delivery. Our finding is consistent with a study that reported higher frequencies of subsequent glucose intolerance in women with one abnormal OGTT value (6); however, that study was limited by the small sample size and its lack of longitudinal assessment.

Women with mildly elevated OGCT and OGTT results are more likely to have preeclampsia (7), fetal macrosomia (8,9), shoulder dystocia (8), cesarean delivery (9), and preterm birth (9). Similarly, women with one abnormal OGTT value have a greater risk of macrosomia, preeclampsia, and cesarean delivery (10). Thus, women who have intermediate values on their OGCT and OGTT have a higher risk of complications commonly associated with GDM compared with women with the lowest values.

The risk of diabetes in women with mildly elevated OGCT or OGTT results likely occurs because they have an intermediate form of glucose intolerance. Glucose metabolism is determined by insulin sensitivity and β-cell function, with a continuum between normal glucose tolerance, impaired glucose tolerance, and diabetes (11). Women with GDM are insulin resistant and have impaired β-cell function. Women with one abnormal OGTT value similarly have less β-cell compensation for their insulin resistance compared with women with normal OGTTs (12,13).

Our study's major strengths include the evaluation of a large, contemporary cohort of women screened for GDM using the two-step approach (1) with a median longitudinal follow-up of 9 years. One limitation is that subsequent diabetes was not systematically assessed, which may introduce bias in those selected for testing. Furthermore, we could not evaluate whether the OGCT and OGTT results were associated with a higher risk of diabetes above and beyond known risk factors because our database did not include race/ethnicity, family history, or BMI. In summary, women without GDM who had mildly elevated glucose results on their GDM screening tests had a greater risk of diabetes. Whether women who fall within this intermediate range of glucose intolerance during pregnancy may benefit from increased diabetes surveillance and lifestyle interventions proven to reduce the risk of developing diabetes (14,15) is unknown.

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