Modestly Elevated Glucose Levels During Pregnancy Are Associated with A Higher Risk of Future Diabetes Among Women Without Gestational Diabetes

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Running Title: Pregnancy Glucose Tests and Subsequent Diabetes

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ABSTRACT

Objective: To determine whether 1-hour oral glucose challenge test (OGCT) or 3-hour oral glucose tolerance test (OGTT) results below gestational diabetes criteria are associated with developing future diabetes.

Research Design and Methods: A retrospective cohort study was performed among women without gestational diabetes who had a pregnancy OGCT (N=24,780) or OGTT (N=6,222). The risk of subsequent diabetes was ascertained by ICD-9 codes, pharmacy or laboratory data over a median follow-up of 8.8 years.

Results: Future 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 (95%CI 1.39-3.25) for 6.3-7.3 mmol/l; and 3.60 (95%CI 2.41-5.39) for ≥7.4 mmol/l compared to ≤5.3 mmol/l. Women with one abnormal OGTT result had a higher risk compared to those with normal values (adjusted HR, 2.08, 95%CI 1.35-3.20).

Conclusions: Women with modestly elevated glucose levels below the threshold for gestational diabetes had a higher risk of future diabetes.
Gestational diabetes is glucose intolerance first recognized during pregnancy (1) and is associated with an increased risk of developing future type 2 diabetes (2-4). We hypothesized that mild glucose elevations during the “two-step approach” for gestational diabetes testing, the 50-gram 1-hour oral glucose challenge test (OGCT) followed by the diagnostic 100-gram 3-hour oral glucose tolerance test (OGTT) for an elevated OGCT (1), would be associated with increased risk of subsequent diabetes. We therefore determined whether women with 1) OGCT quartiles 2 through 4 have a higher risk of diabetes relative to quartile 1, and 2) one abnormal OGTT value have a greater risk relative to 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 pre-existing diabetes or gestational diabetes who received care for ≥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 a diagnosis of gestational diabetes by Carpenter/Coustan criteria: fasting ≥5.3 mmol/l; 1-hour ≥10.0; 2-hour ≥8.6; 3-hour glucose ≥7.8 (1). We excluded women who had gestational diabetes 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 August 31, 2005 as previously described (5): ICD-9 code (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 date of delivery discharge and the subsequent periods of enrollment. Cox’s proportional hazards models were used to estimate hazard ratios (HR). Statistical significance was considered for P<0.05.

RESULTS

Among the 24,780 women who had an OGCT (age at delivery 30.1±6.2 years, mean±SD): 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 to 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).

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 to women with the lowest glucose values. Among women with an OGTT, those with one abnormal value had a 2-fold greater risk of subsequent diabetes compared to women with no abnormal values. The higher risk of diabetes in women who fell below the criteria for gestational diabetes 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 no 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 having a higher risk of complications commonly associated with gestational diabetes compared to women with the lowest values.

The risk of subsequent diabetes in women with mildly elevated OGCT or OGTT results likely occurs since they have an intermediate form of glucose intolerance. Glucose metabolism is determined by insulin sensitivity and β-cell function with a continuum between normal, impaired glucose tolerance and diabetes (11). Women with gestational diabetes 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 to women with normal OGTTs (12; 13).

Our study’s major strengths include the evaluation of a large, contemporary cohort of women screened for gestational diabetes 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 who were 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 since our database did not include race/ethnicity, family history, or BMI. In summary, women without gestational diabetes who have mildly elevated glucose results on their gestational diabetes screening tests had a greater risk of future diabetes. Whether women who fall within this intermediate range of glucose intolerance during pregnancy may benefit from increased diabetes surveillance as well as lifestyle interventions proven to reduce the risk of developing diabetes (14; 15) is unknown.

ACKNOWLEDGMENTS

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REFERENCES

11. Jensen CC, Cnop M, Hull RL, Fujimoto WY, Kahn SE: Beta-cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S. *Diabetes* 51:2170-2178, 2002

Table 1. Risk of developing subsequent diabetes by OGCT or OGTT values
<table>
<thead>
<tr>
<th>OGCT Quartiles (mmol/l)</th>
<th>Incidence rate 100,000 person-years</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>Model 1 Unadjusted</th>
<th>Model 2 Adjusted for age, primigravidity and preterm delivery</th>
</tr>
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<tbody>
<tr>
<td>&lt;5.4 (reference)</td>
<td>30/6,768 0.26</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>5.4-6.2</td>
<td>50/6,304 0.45</td>
<td>1.68 (1.07-2.66)</td>
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<tr>
<td>6.3-7.3</td>
<td>65/6,245 0.56</td>
<td>2.05 (1.33-3.16)</td>
<td>2.13 (1.38-3.29)</td>
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<tr>
<td>&gt;7.3</td>
<td>99/5,463 0.93</td>
<td>3.40 (2.25-5.11)</td>
<td>3.65 (2.42-5.52)</td>
<td></td>
</tr>
<tr>
<td>OGTT</td>
<td>Incidence rate 100,000 person-years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Abnormal Values</td>
<td>No. diabetes events/n</td>
<td>0 (reference) 51/3,639 0.69</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>
|                        |                                     | 1 35/1,253 1.42                      | 2.06 (1.34-3.17)   | 2.07 (1.34-3.18)