Early Pregnancy Insulin Resistance and Subsequent Gestational Diabetes Mellitus

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Gestational diabetes mellitus (GDM), which complicates 3–7% of all pregnancies, is associated with increased maternal and fetal morbidity (1). Identification of early risk markers may result in improved understanding of disease pathogenesis and identification of potential targets for intervention. We sought to determine the association between early pregnancy insulin resistance and subsequent abnormal glucose tolerance in pregnancy.

RESEARCH DESIGN AND METHODS

— We conducted two institutional review board–approved, prospective, nested, case-control studies within Massachusetts General Hospital's Obstetrical Maternal Study (MOMS) comparing subjects with GDM and subjects with abnormal glucose loading test (GLT) results but no GDM with control subjects. Consecutive MOMS participants with singleton gestations between February 2002 and February 2004 who provided fasting blood samples between 16–18 weeks' gestation, underwent GLT testing at 24–28 weeks' gestation, and delivered after 34 weeks were eligible. To limit confounding by other etiologies of insulin resistance, women with pregestational diabetes, preeclampsia, or gestational hypertension were excluded. All eligible women who met the criteria for GDM (1) were included. Women with an abnormal 1-h post-GLT glucose level (≥7.8 mmol/l) but no GDM were randomly selected from 115 eligible women. Control subjects (~2:1) were randomly selected from 1,016 eligible women who had normal 1-h post-GLT glucose levels. The mean age at GLT testing was comparable between case and control subjects (Table 1).

Plasma glucose was measured using standard techniques. Serum insulin was measured using a radioimmunoassay from Linco Research (St. Louis, MO). Clinical data were obtained from a previously validated and prospectively maintained electronic clinical record (2). Analyses were performed with Stata (Stata, College Park, TX). The homeostasis model assessment (HOMA) was used as an index of insulin resistance (3). The population that did not have GDM or an abnormal GLT served as the reference group in all analyses. $P < 0.05$ was considered statistically significant.

RESULTS

— Baseline characteristics (Table 1) demonstrate that fasting glucose, fasting insulin, and HOMA were significantly higher in women who subsequently developed GDM compared with control subjects. Fasting glucose and HOMA were also significantly higher in the group with abnormal GLT and no GDM than in the control subjects.

The risk of GDM was significantly increased for each log-unit increase in HOMA in both univariate analysis (OR 4.9 [95% CI 2.1–11.2], $P < 0.01$) and after adjustment for maternal age, race, BMI, gestational age at serum sampling, systolic and diastolic blood pressure, and parity (adjusted OR 4.2 [1.3–13.5], $P = 0.02$). Similarly, for each millimole increase in fasting glucose, the risk of GDM increased significantly in univariate- (OR 5.9 [2.2–15.6], $P < 0.01$) and multivariable-adjusted (adjusted OR 4.7 [1.5–14.9], $P = 0.01$) models. Neither HOMA (adjusted OR 2.5 [0.73–9.1], $P = 0.14$) nor fasting glucose (adjusted OR 3.4 [0.81–14.0], $P = 0.09$) was significantly associated with subsequent abnormal GLT with no GDM.

CONCLUSIONS

— In this prospective study, we found that women in whom GDM was diagnosed at 24–28 weeks of gestation demonstrated higher levels of fasting glucose, fasting insulin, and HOMA at ~17 weeks in pregnancy compared with women who had normoglycemic pregnancies. The risk of GDM increased significantly with increasing HOMA and fasting glucose levels, independent of other variables that are known to be associated with GDM. While there are prior reports with similar findings (4–7), such studies either examined small numbers of high-risk women (4,5) or used surrogate markers of insulin resistance (6). Similar results have been noted in nonpregnant populations, where HOMA has been shown to be associated with the later development of type 2 diabetes (8,9). Our findings lend support to the hypothesis that increased insulin resistance and increased fasting glucose at 16–18 weeks' gestation are associated with the subsequent development of overt glucose intolerance later in pregnancy.

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Abbreviations: GDM, gestational diabetes mellitus; GLT, glucose loading test; HOMA, homeostasis model assessment.

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

Table 1—*Clinical and laboratory characteristics of the study population*

	Control subjects	Subjects with abnormal GLT* and no GDM	Subjects with GDM†
n	73	37	35
Baseline characteristics			
Age (years)	31.4 ± 5.7	32.9 ± 4.4	33.6 ± 5.1
Gestational age at fasting serum sampling (weeks)	17.3 ± 1.3	17.2 ± 1.2	17.3 ± 1.3
Nulliparous (%)	47	59	43
BMI (kg/m^2)	26 ± 5	26 ± 4	29 ± 6‡
Systolic blood pressure (mmHg)	111 ± 12	113 ± 11	115 ± 10
Diastolic blood pressure (mmHg)	69 ± 8	70 ± 9‡	73 ± 8‡
Race (%)			
Non-Hispanic white	79	57	69
Hispanic	15	16	14
African American	1	8	9
Asian	3	3	3
Other/Unknown	1	16	6
Fasting glucose (mmol/l)	4.4 ± 0.4	4.6 ± 0.4‡	4.8 ± 0.6‡
Fasting insulin (μU/ml)	10.1 ± 5.9	11.5 ± 6.3	15.8 ± 9.6‡
HOMA§	2.0 ± 1.3	2.4 ± 1.7‡	3.5 ± 2.5‡
GLT glucose (mmol/l)	5.9 ± 0.9	8.6 ± 0.7‡	9.3 ± 0.1‡
Gestational age at GLT testing (weeks)	27.8 ± 1.0	28.3 ± 1.0‡	27.4 ± 2.2
Delivery characteristics			
Gestational age at delivery (weeks)	39.2 ± 1.2	39.3 ± 1.5	38.9 ± 1.3
Birth weight (g)	3,494 ± 456	3,456 ± 444	3,518 ± 528

Data are means ± SD. *An abnormal GLT was defined as a glucose level ≥7.8 mmol/l 1 h following a nonfasting 50-g oral glucose load (ref. 1). †GDM was defined using the results of a fasting 100-g oral glucose tolerance test, according to criteria of the American Diabetes Association (ref. 1). ‡$P < 0.05$ compared with control subjects. §HOMA = [fasting glucose (in mmol/l) × fasting insulin (in μU/ml)]/22.5 (ref. 4).

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