

# Hepatic Insulin Resistance Is an Early Determinant of Declining $\beta$ -Cell Function in the First Year Postpartum After Glucose Intolerance in Pregnancy

RAVI RETNAKARAN, MD<sup>1,2</sup>  
 YING QI, MSc<sup>1</sup>  
 CHANG YE, MSc<sup>1</sup>  
 ANTHONY J.G. HANLEY, PHD<sup>1,2,3</sup>

PHILIP W. CONNELLY, PHD<sup>2,4</sup>  
 MATHEW SERMER, MD<sup>5</sup>  
 BERNARD ZINMAN, MD<sup>1,2,6</sup>

**OBJECTIVE**—The increased risk of type 2 diabetes in women with glucose intolerance in pregnancy is mediated by deterioration of their  $\beta$ -cell function, which occurs as early as the first year postpartum. We thus sought to identify early determinants of their declining  $\beta$ -cell function.

**RESEARCH DESIGN AND METHODS**—Women with recent gestational glucose intolerance (166) underwent oral glucose tolerance test at 3 and 12 months postpartum. They were stratified into those in whom  $\beta$ -cell function (Insulin Secretion-Sensitivity Index-2 [ISSI-2]) declined over this time (decliners;  $n = 92$ ) and those in whom it did not (nondecliners;  $n = 74$ ).

**RESULTS**—Between 3 and 12 months, hepatic insulin sensitivity (1/homeostasis model assessment of insulin resistance [HOMA-IR]) decreased in decliners but not in nondecliners. Over this time, the change in 1/HOMA-IR emerged as an independent predictor of the change in ISSI-2 ( $t = 5.5$ ;  $P < 0.0001$ ). Increased hepatic insulin sensitivity independently predicted a lower likelihood of declining  $\beta$ -cell function (odds ratio = 0.13 [95% CI 0.06–0.29];  $P < 0.0001$ ).

**CONCLUSIONS**—Hepatic insulin resistance is an early determinant of declining  $\beta$ -cell function after gestational dysglycemia.

*Diabetes Care* 34:2431–2434, 2011

Women who develop gestational diabetes mellitus (GDM) and gestational impaired glucose tolerance (GIGT) have a chronic defect in  $\beta$ -cell function that underlies their presentation with dysglycemia in response to the severe insulin resistance of late pregnancy (1,2). After the pregnancy, their increased risk of developing type 2 diabetes is mediated by progressive deterioration of the  $\beta$ -cell function over time, which occurs as early as the first year postpartum (3–5). Thus, we sought to identify early determinants of declining  $\beta$ -cell function in a cohort of women with GDM and

GIGT evaluated at 3 and 12 months postpartum.

## RESEARCH DESIGN AND METHODS

This analysis was conducted within an ongoing observational cohort study in which women recruited at the time of antepartum GDM screening were undergoing longitudinal evaluation in pregnancy and in the postpartum years. The study protocol has been described previously (2,5,6). In brief, participants undergo an oral glucose tolerance test (OGTT) in late pregnancy, enabling classification of gestational glucose tolerance

(GDM, GIGT, normal). At 3 and 12 months postpartum, they undergo reassessment, including 2-h 75-g OGTT. The study has been approved by the institutional research ethics board, and all participants have provided written informed consent. As reported previously (5), among the first 392 women who completed their 12-month visit, there were 182 women with either GDM or GIGT. The current analysis was restricted to 166 women with GDM or GIGT, after exclusion of those who had diabetes at 3 months ( $n = 5$ ) or any missing glucose/insulin values on OGTTs ( $n = 11$ ) (Supplementary Fig. 1).

As described previously (5),  $\beta$ -cell function was assessed with the Insulin Secretion-Sensitivity Index-2 (ISSI-2) and whole-body insulin sensitivity was measured by Matsuda index. The homeostasis model assessment of insulin resistance (HOMA-IR) primarily reflects hepatic insulin resistance (7–9); its reciprocal (1/HOMA-IR) provides a measure of hepatic insulin sensitivity. As a secondary measure of hepatic insulin sensitivity, fasting C-peptide:insulin was calculated. Fasting C-peptide:insulin is a measure of steady-state hepatic insulin extraction, which decreases with worsening hepatic insulin sensitivity (10–13).

Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Univariate differences were assessed between women in whom  $\beta$ -cell function declined between 3 and 12 months and those in whom it did not (Table 1 and Supplementary Table 1). Univariate correlations between the baseline-adjusted change in ISSI-2 and potential predictors thereof were assessed by Spearman analysis (Supplementary Table 2). Multiple linear regression analyses were performed to identify predictors of the change in ISSI-2 between 3 and 12 months postpartum (Supplementary Table 3). Logistic regression analysis was performed to identify independent predictors of declining ISSI-2 (Supplementary Table 4).

From the <sup>1</sup>Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, Canada; the <sup>2</sup>Division of Endocrinology, University of Toronto, Toronto, Canada; the <sup>3</sup>Department of Nutritional Sciences, University of Toronto, Toronto, Canada; the <sup>4</sup>Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Canada; the <sup>5</sup>Division of Obstetrics and Gynecology, Mount Sinai Hospital, Toronto, Canada; and the <sup>6</sup>Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Canada.

Corresponding author: Ravi Retnakaran, rretnakaran@mtsinai.on.ca.

Received 30 April 2011 and accepted 10 August 2011.

DOI: 10.2337/dc11-0817

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-0817/-DC1>.

© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

**RESULTS**—Table 1 shows the comparison of characteristics at 3 and 12 months postpartum between women in whom  $\beta$ -cell function (ISSI-2) declined over this time (decliners;  $n = 92$ ) and those in whom it did not (nondecliners;  $n = 74$ ). Lipids, adipokines, and C-reactive protein are shown in Supplementary Table 1. Although glucose measures did not differ between the groups at 3 months, each postload glucose value on the OGTT was higher in the decliners than in the nondecliners by 12 months postpartum. Matsuda index, 1/HOMA-IR, fasting C-peptide:insulin, and ISSI-2 were all lower in the decliners at 12 months, as was the prevalence of breastfeeding. Although decliners lost less weight, the two groups did not differ in their baseline-adjusted changes in waist, BMI, and whole-body insulin sensitivity (Matsuda) between 3 and 12 months. In contrast, however, both measures of hepatic insulin sensitivity (1/HOMA-IR and fasting C-peptide:insulin) decreased in decliners but increased in nondecliners.

On Spearman correlation analysis (Supplementary Table 2), the factor most strongly associated with the baseline-adjusted change in ISSI-2 between 3 and 12 months was the change in 1/HOMA-IR ( $r = 0.45$ ;  $P < 0.0001$ ). Similarly, the change in fasting C-peptide:insulin was also a significant correlate of the change in ISSI-2 ( $r = 0.22$ ;  $P = 0.008$ ), whereas the change in whole-body insulin sensitivity (Matsuda) did not reach significance ( $r = 0.15$ ;  $P = 0.08$ ).

On multiple linear regression analyses (Supplementary Table 3) adjusted for age, ethnicity, family history of diabetes, breastfeeding, BMI, and ISSI-2 at 3 months, the only independent determinant of the change in ISSI-2 was the change in hepatic insulin sensitivity, measured by either 1/HOMA-IR ( $t = 5.5$ ;  $P < 0.0001$ ) or fasting C-peptide:insulin ( $t = 3.24$ ;  $P = 0.0015$ ). The changes in weight or Matsuda index were not significant predictors.

On logistic regression analysis (Supplementary Table 4), an increase in 1/HOMA-IR independently predicted a lower likelihood of declining  $\beta$ -cell function (OR = 0.13 [95% CI 0.06–0.29];  $P < 0.0001$ ), after adjustment for age, ethnicity, family history of diabetes, breastfeeding, and BMI at 3 months. Similarly, an increase in fasting C-peptide:insulin also predicted a lower risk of declining  $\beta$ -cell function (OR = 0.95 [0.91–0.98];  $P = 0.0018$ ), whereas the changes in weight

**Table 1—Demographic, clinical, and metabolic characteristics of study population stratified into two groups: women in whom  $\beta$ -cell function did not decline between 3 and 12 months postpartum (nondecliners) and women in whom  $\beta$ -cell function declined between 3 and 12 months postpartum (decliners)**

	Nondecliners	Decliners	P
<i>n</i>	74	92	
At 3 months postpartum			
Age (years)	35.3 [31.8–38.5]	35.2 [33.8–38.3]	0.4204
Ethnicity (%)			0.4097
White	77.0	72.8	
Asian	13.5	10.9	
Other	9.5	16.3	
Family history of diabetes (%)	62.2	53.3	0.2492
Current smoking (%)	4.1	6.5	0.7325
Current breastfeeding (%)	97.3	91.3	0.1876
Blood pressure (mmHg)			
Systolic	108 [104–117]	111 [103–116]	0.6593
Diastolic	65 [59–70]	64 [59–71]	0.9634
Physical activity			
Sport index	2.0 [1.8–2.5]	1.8 [1.5–2.5]	0.6019
Leisure-time index	2.8 [2.5–3.3]	2.8 [2.5–3.3]	0.8009
Waist circumference (cm)	87 [82–99]	90 [84–96]	0.5303
Weight (kg)	70.2 [59.0–81.0]	69.9 [62.1–80.7]	0.7014
BMI (kg/m <sup>2</sup> )	26.5 [23.2–31.2]	26.6 [24.0–30.2]	0.6745
Fasting insulin (pmol/L)	36.5 [28.0–59.0]	26.0 [20.0–49.5]	0.0130
Whole-body insulin sensitivity			
Matsuda index	8.3 [5.7–14.0]	9.8 [6.0–12.9]	0.5413
Hepatic insulin sensitivity			
1/HOMA-IR	0.94 [0.56–1.32]	1.3 [0.65–1.71]	0.0112
Fasting C-peptide:insulin	15.6 [12.9–21.5]	18.5 [14.5–27.0]	0.0115
$\beta$ -Cell function			
ISSI-2	785 [624–952]	914 [748–1,207]	0.0004
OGTT			
Fasting glucose (mmol/L)	4.8 [4.3–5.0]	4.7 [4.3–5.0]	0.1234
30-min glucose (mmol/L)	8.4 [7.4–9.5]	8.7 [7.5–9.8]	0.5027
1-h glucose (mmol/L)	8.6 [7.1–10.1]	8.7 [7.2–10.0]	0.9948
2-h glucose (mmol/L)	6.4 [5.3–7.3]	6.7 [5.5–7.9]	0.4479
AUC <sub>gluc</sub>	14.1 [12.3–15.8]	14.2 [12.4–15.9]	0.9288
Glucose tolerance status (%)			0.1356
NGT	78.4	72.8	
Isolated IFG	2.7	0	
Isolated IGT	17.6	27.2	
Combined IFG and IGT	1.4	0	
At 12 months postpartum			
Current breastfeeding (%)	96.0	83.7	0.0123
Physical activity			
Sport index	2.1 [1.8–3.0]	2.0 [1.8–2.5]	0.3252
Leisure-time index	3.0 [2.8–3.5]	3.0 [2.8–3.3]	0.7867
Work index	2.9 [2.5–3.4]	2.9 [2.4–3.4]	0.7499
Waist circumference (cm)	85 [79–96]	89 [82–95]	0.2181
Weight (kg)	68.1 [56.5–78.0]	68.3 [59.3–78.7]	0.3084
BMI (kg/m <sup>2</sup> )	25.4 [21.5–29.4]	25.9 [23.4–29.3]	0.2976
Fasting insulin (pmol/L)	31.0 [20.0–48.0]	45.5 [27.5–73.0]	0.0015
Whole-body insulin sensitivity			
Matsuda index	9.1 [5.8–13.9]	7.2 [4.4–10.9]	0.0436
Hepatic insulin sensitivity			
1/HOMA-IR	1.11 [0.73–1.68]	0.73 [0.45–1.18]	0.0015
Fasting C-peptide:insulin	17.7 [14.0–23.9]	15.1 [10.9–20.9]	0.0116

Table 1—Continued

	Nondecliners	Decliners	P
<b>β-Cell function</b>			
ISSI-2	1,034 [825–1,241]	710 [572–902]	<0.0001
<b>OGTT</b>			
Fasting glucose (mmol/L)	4.8 [4.5–4.9]	4.9 [4.6–5.2]	0.0570
30-min glucose (mmol/L)	8.0 [7.1–9.3]	8.7 [7.8–9.8]	0.0070
1-h glucose (mmol/L)	7.4 [5.8–9.2]	9.1 [7.4–10.5]	<0.0001
2-h glucose (mmol/L)	5.9 [4.9–7.3]	6.7 [5.8–7.9]	0.0007
AUC <sub>gluc</sub>	12.6 [10.8–14.8]	14.8 [12.7–16.8]	<0.0001
Glucose tolerance status (%)			0.3613
NGT	78.4	73.9	
Isolated IFG	1.4	0	
Isolated IGT	20.3	23.9	
Combined IFG and IGT	0	0	
Diabetes	0	2.2	
<b>Baseline-adjusted changes between 3 and 12 months</b>			
Change in sport index	0.16 [0.07]	0.26 [0.08]	0.3903
Change in leisure-time index	0.16 [0.05]	0.24 [0.06]	0.2940
Change in waist	−1.3 [0.7]	−2.1 [0.8]	0.4594
Change in BMI	−0.5 [0.2]	−1.1 [0.2]	0.0585
Change in weight	−1.5 [0.5]	−2.9 [0.5]	0.0482
Change in Matsuda index	−0.8 [0.6]	0.2 [0.7]	0.2701
Change in 1/HOMA-IR	−0.31 [0.05]	0.07 [0.05]	<0.0001
Change in fasting C-peptide:insulin	−2.6 [1.1]	1.6 [1.2]	0.0107

Baseline-adjusted changes are shown as adjusted mean [SE] and are adjusted for the value at 3 months postpartum. All other continuous data are shown as median [interquartile range]. Categorical data are shown as percentages. *P* values refer to differences between the two groups as determined by Kruskal-Wallis test for continuous variables and either  $\chi^2$  test or Fisher exact test for categorical variables. AUC<sub>gluc</sub>, area under the glucose curve; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

and Matsuda index were not significant predictors.

**CONCLUSIONS**—Although studies beginning at 15–30 months postpartum have shown that insulin resistance contributes to declining  $\beta$ -cell function after GDM (3,4), the current data specifically implicate hepatic insulin resistance as relevant to the earlier deterioration of  $\beta$ -cell function in the first year postpartum. Interestingly, Buchanan and colleagues (14) have demonstrated that increased endogenous glucose production in pregnancy (indicative of hepatic insulin resistance) independently predicts the subsequent development of diabetes by 11–26 months postpartum. The current findings thus may reflect the early postpartum continuation of this chronic hepatic insulin resistance in those women in whom  $\beta$ -cell function deteriorates, leading to type 2 diabetes. Indeed, this model may be further supported by the demonstration of altered hepatic lipid storage as an early abnormality in women with GDM, even when maintaining normal glucose tolerance (15). It should also

be noted that, when compared with nondecliners, the decliners had slightly higher hepatic insulin sensitivity at 3 months postpartum, which then deteriorated over the next 9 months, accompanied by worsening glycemia. This observation suggests that consideration of the pattern of change in hepatic insulin sensitivity over time may be more informative than a single one-time measurement.

Limitations of this study include the observational design that precludes definitive commentary on causality and the use of surrogate indexes. Nevertheless, these data raise the possibility that worsening hepatic insulin resistance may provide an early marker for identifying those women with GDM/GIGT who are most likely to progress to prediabetes/diabetes. Further study is thus needed to determine whether the liver or aspects of its physiology could provide a target for risk stratification and possibly modification in this high-risk patient population.

**Acknowledgments**—This study was supported by operating grants from the Canadian

Institutes of Health Research (CIHR; MOP-67063 and MOP-84206), the Canadian Diabetes Association (CDA; OG-3-08-2543-RR), and the Heart and Stroke Foundation of Ontario (NA 6747). R.R. holds a CIHR Clinical Research Initiative New Investigator Award and CDA Clinician-Scientist incentive funding. A.J.G.H. holds a Tier-II Canada Research Chair in Diabetes Epidemiology. B.Z. holds the Sam and Judy Pencer Family Chair in Diabetes Research at Mount Sinai Hospital and University of Toronto.

No potential conflicts of interest relevant to this article were reported.

R.R. designed the analysis plan, researched data, wrote the manuscript, and was involved in the design and implementation of the overall study. Y.Q. and C.Y. performed the statistical analyses. A.J.G.H., P.W.C., M.S., and B.Z. were involved in the design and implementation of the overall study.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

The authors thank Mount Sinai Hospital Department of Pathology and Laboratory Medicine and Patient Care Services.

## References

- Buchanan TA, Xiang AH, Kjos SL, Watanabe R. What is gestational diabetes? *Diabetes Care* 2007;30(Suppl. 2):S105–S111
- Retnakaran R, Qi Y, Sermer M, Connelly PW, Hanley AJ, Zinman B. Glucose intolerance in pregnancy and future risk of pre-diabetes or diabetes. *Diabetes Care* 2008;31:2026–2031
- Xiang AH, Kawakubo M, Trigo E, Kjos SL, Buchanan TA. Declining  $\beta$ -cell compensation for insulin resistance in Hispanic women with recent gestational diabetes mellitus: association with changes in weight, adiponectin, and C-reactive protein. *Diabetes Care* 2010;33:396–401
- Xiang AH, Kjos SL, Takayanagi M, Trigo E, Buchanan TA. Detailed physiological characterization of the development of type 2 diabetes in Hispanic women with prior gestational diabetes mellitus. *Diabetes* 2010; 59:2625–2630
- Retnakaran R, Qi Y, Sermer M, Connelly PW, Hanley AJ, Zinman B.  $\beta$ -Cell function declines within the first year postpartum in women with recent glucose intolerance in pregnancy. *Diabetes Care* 2010; 33:1798–1804
- Retnakaran R, Qi Y, Connelly PW, Sermer M, Hanley AJ, Zinman B. Risk of early progression to prediabetes or diabetes in women with recent gestational dysglycaemia but normal glucose tolerance at 3-month postpartum. *Clin Endocrinol (Oxf)* 2010;73: 476–483
- Hoffman RP. Indices of insulin action calculated from fasting glucose and insulin

- reflect hepatic, not peripheral, insulin sensitivity in African-American and Caucasian adolescents. *Pediatr Diabetes* 2008;9: 57–61
8. Tripathy D, Almgren P, Tuomi T, Groop L. Contribution of insulin-stimulated glucose uptake and basal hepatic insulin sensitivity to surrogate measures of insulin sensitivity. *Diabetes Care* 2004;27: 2204–2210
  9. Hoffman RP, Vicini P, Cobelli C. Pubertal changes in HOMA and QUICKI: relationship to hepatic and peripheral insulin sensitivity. *Pediatr Diabetes* 2004;5:122–125
  10. Polonsky KS, Rubenstein AH. C-peptide as a measure of the secretion and hepatic extraction of insulin. Pitfalls and limitations. *Diabetes* 1984;33:486–494
  11. Gower BA, Granger WM, Franklin F, Shewchuk RM, Goran MI. Contribution of insulin secretion and clearance to glucose-induced insulin concentration in African-American and Caucasian children. *J Clin Endocrinol Metab* 2002;87:2218–2224
  12. Retnakaran R, Hanley AJ, Sermer M, Zinman B. The impact of insulin resistance on proinsulin secretion in pregnancy: hyperproinsulinemia is not a feature of gestational diabetes. *Diabetes Care* 2005;28: 2710–2715
  13. Meier JJ, Holst JJ, Schmidt WE, Nauck MA. Reduction of hepatic insulin clearance after oral glucose ingestion is not mediated by glucagon-like peptide 1 or gastric inhibitory polypeptide in humans. *Am J Physiol Endocrinol Metab* 2007;293: E849–E856
  14. Buchanan TA, Xiang AH, Kjos SL, Trigo E, Lee WP, Peters RK. Antepartum predictors of the development of type 2 diabetes in Latino women 11–26 months after pregnancies complicated by gestational diabetes. *Diabetes* 1999;48:2430–2436
  15. Prikoszovich T, Winzer C, Schmid AI, et al. Body and liver fat mass rather than muscle mitochondrial function determine glucose metabolism in women with a history of gestational diabetes mellitus. *Diabetes Care* 2011;34:430–436