Determinants of Insulin Resistance in Infants at Age 1 Year

Impact of gestational diabetes mellitus

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OBJECTIVE—The offspring of women with gestational diabetes mellitus (GDM) display a propensity for the early accrual of cardiometabolic risk factors, including insulin resistance, in childhood and adolescence. Thus, we sought to identify early life determinants of insulin resistance in infants of women with and without GDM.

RESEARCH DESIGN AND METHODS—In total, 104 full-term, singleton infants born to women with (n = 36) and without (n = 68) GDM were evaluated at age 1 year, with insulin resistance assessed by homeostasis model (HOMA-IR).

RESULTS—HOMA-IR at 1 year did not differ between infants born to mothers with and without GDM (P = 0.74). The sole independent predictor of infant HOMA-IR in the non-GDM group was birth weight (t = 3.33, P = 0.002). In contrast, weight gain in the 1st year was the only independent predictor of HOMA-IR in infants of women with GDM (t = 2.19, P = 0.039).

CONCLUSIONS—In the 1st year of life, weight gain in infants born to women with GDM is associated with insulin resistance, unlike in their peers.

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The offspring of women with gestational diabetes mellitus (GDM) exhibit a propensity for the early accrual of cardiometabolic risk factors in childhood and adolescence (1). Indeed, compared with their peers, offspring exposed to GDM in utero are more likely to develop insulin resistance in childhood and by as early as age 5 years (2,3). However, little is known about perinatal and early life risk factors associated with infant insulin resistance after exposure to maternal GDM. Thus, we sought to evaluate insulin resistance and its determinants in the offspring of women with and without GDM at age 1 year.

RESEARCH DESIGN AND METHODS

This analysis was performed within an ongoing prospective observational study in which the infants of women with or without GDM are undergoing serial assessment in the early years of life. The study protocol has been previously described (4). In brief, pregnant women are recruited in late second trimester and undergo a 3-h, 100-g oral glucose tolerance test (OGTT) for diagnosis of GDM (National Diabetes Data Group criteria) (5). The offspring are then evaluated in the 1st year of life. The protocol has been approved by institutional research ethics boards, and all mothers provided written informed consent for their infant's participation. The current analysis was restricted to the first 104 singleton, full-term infants whose mothers had consented to infant blood work at age 1 year as of July 2011.

As previously described (6,7), the antepartum OGTT enabled assessment of maternal insulin sensitivity (Matsuda index) and lipids. All women diagnosed with GDM on the OGTT received treatment with diet/exercise counseling, and six women also received insulin. Data on obstetrical outcomes were obtained from an institutional database tracking labor and delivery. At age 12 months, participating infants attended the clinical investigation unit after requested overnight fast (or at least 4–5 h, if they required feeding). Fasting blood samples were drawn from the infants for the measurement of glucose and insulin. Specific insulin was measured by electrochemiluminescence immunoassay kit and Elecsys 1010 immunoassay analyzer (Roche, Laval, Canada). Insulin resistance was evaluated by homeostasis model assessment of insulin resistance (HOMA-IR) (8), an established measure that has been used in young children (9).

All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). The infants of women with and without GDM were compared by Wilcoxon two-sample test (continuous variables) or either χ^2 or Fisher exact test (categorical variables) (Table 1). Univariate associations between parental/infant factors and infant HOMA-IR were assessed by Spearman correlation adjusted for infant age (Supplementary Table 1). Multiple linear regression analyses of HOMA-IR were performed in each group with core variables age, sex, race/ethnicity, birth weight, and 1st-year weight gain (Supplementary Table 2). Exploratory multiple linear regression analyses were also performed with single addition of infant feeding, maternal BMI, insulin sensitivity,

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Table 1—*Comparison of infants born to women with and without GDM at age 1 year*

	Non-GDM (n = 68)	GDM (n = 36)	P value
Core variables			
Age (months)	12.0 [12.0–13.0]	12.0 [12.0–13.0]	0.99
Sex (% female)	48.5	58.3	0.34
Race/ethnicity (%)			0.75
Caucasian	75.0	77.8	
Other	25.0	22.2	
Total length of gestation (weeks)	39.0 [38.0–40.0]	39.0 [38.0–39.0]	0.64
Birth weight (g)	3,415 [3,144–3,628]	3,411 [3,110–3,635]	0.89
Small for gestational age (%)	2.9	0.0	0.54
Weight gain in 1st year (g)	6,196 [5,577–6,715]	6,496 [5,307–7,015]	0.61
Weight at 1 year (g)	9,565 [8,683–10,280]	9,863 [8,893–10,567]	0.45
Fasting glucose (mmol/L)	4.5 [4.3–4.8]	4.5 [4.2–4.8]	0.67
Fasting insulin (pmol/L)	7.5 [3.5–13.5]	7.5 [5.0–14.0]	0.67
HOMA-IR at 1 year	0.21 [0.09–0.39]	0.21 [0.13–0.38]	0.74
Parental history			
Family history of diabetes (%)	51.5	58.3	0.50
Paternal BMI (kg/m^2)	27.0 [23.9–29.3]	26.8 [24.1–28.7]	0.71
Maternal prepregnancy BMI (kg/m^2)	23.1 [21.2–26.5]	24.9 [22.3–30.1]	0.08
Maternal BMI categories (%)			0.14
<20	13.6	2.9	
≤20 to <25	57.6	48.6	
≤25 to <30	15.2	22.9	
≥30	13.6	25.7	
Maternal metabolic function in pregnancy			
Area under the glucose curve on OGTT	21.3 [19.0–23.8]	27.7 [26.3–28.6]	<0.0001
Matsuda index at OGTT	6.0 [3.5–7.7]	3.7 [3.0–5.2]	0.003
Lipids (mmol/L)			
LDL cholesterol	3.95 [2.98–4.47]	3.55 [3.03–4.31]	0.27
HDL cholesterol	1.68 [1.39–1.96]	1.60 [1.41–1.74]	0.21
Triglycerides	2.10 [1.78–2.70]	2.49 [1.99–2.97]	0.04
Infant feeding in 1st year (months)			
Duration of exclusive breastfeeding	5.0 [1.0–6.0]	6.0 [0–6.0]	0.73
Age of introduction of formula	4.0 [0.3–8.0]	2.0 [0–5.0]	0.11
Age of introduction of solids	6.0 [5.0–6.0]	6.0 [6.0–6.0]	0.21

Continuous variables are median [interquartile range]; categorical variables are percentages. P values refer to overall differences across the groups as determined by Wilcoxon two-sample test for continuous variables or χ^2 or Fisher exact test for categorical variables.

and lipids (LDL, HDL, and triglycerides), respectively.

RESULTS—Parental and infant characteristics were compared between infants of women with GDM (n = 36) and infants of women without GDM (n = 68) (Table 1). It is notable that there were no significant differences between these groups in birth weight, weight at 1 year, and HOMA-IR at 1 year (both median HOMA-IR = 0.21, P = 0.74). In pregnancy, women with GDM had lower insulin sensitivity (P = 0.003) and higher triglycerides (P = 0.04) than those without GDM. There were no dissimilarities between the groups in infant feeding practices.

On age-adjusted Spearman correlation analysis (Supplementary Table 1), birth weight was associated with HOMA-IR in infants of women without GDM (r = 0.32, P = 0.02) but not in infants of women with GDM (r = −0.18, P = 0.34). Conversely, weight gain in the 1st year was associated with HOMA-IR in infants whose mothers had GDM (r = 0.44, P = 0.02) but not in those whose mothers did not have GDM (r = 0.04, P = 0.78). On multiple linear regression analyses (Supplementary Table 2*A*), the sole independent predictor of infant HOMA-IR in the non-GDM group was birth weight (t = 3.33, P = 0.002). In contrast, weight gain in the 1st year emerged as the only independent predictor of HOMA-IR in infants of women with GDM (t = 2.19, P = 0.039) (Supplementary Table 2*B*).

Finally, in each group, we performed exploratory multiple linear regression analyses with single addition to the models of infant feeding, maternal BMI, insulin sensitivity, or lipid variables, respectively. In each case, the sole independent determinant of infant HOMA-IR in the non-GDM group was birth weight. Conversely, 1st-year weight gain was an independent predictor in each model in the GDM group (data not shown).

CONCLUSIONS—In this study, there were no differences between the infants of GDM mothers and their peers in birth weight, 1st-year weight gain, or HOMA-IR at age 1 year. However, the early life determinants of insulin resistance differed markedly between these two groups. Indeed, whereas birth weight was the only predictor of infant insulin resistance in the non-GDM group, weight gain in the 1st year was the sole independent determinant in infants of women with GDM.

Unlike their peers, women with GDM received antepartum glucose-lowering treatment. Through its intended effect of limiting excessive fetal growth, it is possible that this treatment may have obscured the relationship between birth weight and infant HOMA-IR that was otherwise readily detectable in the untreated non-GDM group. Alternatively, the relationship between 1st-year weight gain and HOMA-IR in the GDM infants could reflect metabolic programming resulting from fetal exposure to the altered intrauterine environment that antedates the diagnosis of GDM (10,11). Indeed, rapid early postnatal growth has been associated with increased weight gain, adiposity, and insulin resistance in children and adults born small for gestational age (12–15). Our data raise the intriguing possibility that this growth velocity model may similarly apply to the offspring of GDM pregnancies, leading to their early life accrual of insulin resistance and cardiometabolic risk.

A limitation of this study is the lack of assessment of maternal gestational weight gain and neonatal body composition (particularly fat mass) at birth and during the

1st year. In addition, the number of subjects was relatively modest. Nevertheless, as the first study comparing determinants of insulin resistance between infants of GDM pregnancies and their peers at 1 year, this analysis highlights the need for longitudinal evaluation of these groups into early childhood. Ultimately, the insight so derived may inform strategies for breaking the vicious cycle of cardiometabolic disease linking women with GDM and their children.

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C.A.B. researched data, contributed to analysis, and wrote the manuscript. J.K.H. and R.R. were involved in the design/implementation of the overall study, designed the analysis plan, and supervised the analysis and manuscript. C.Y. performed the statistical analyses. A.J.H., P.W.C., M.S., and B.Z. were involved in the design/implementation of the overall study. All authors contributed to critical revision of the manuscript. R.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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