Gestational Glucose Tolerance and Cord Blood Leptin Levels Predict Slower Weight Gain in Early Infancy

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Objective To determine the extent to which known prenatal and perinatal predictors of childhood obesity also predict weight gain in early infancy.

Study design We studied 690 infants participating in the prospective cohort Project Viva. We measured length and weight at birth and at 6 months. Using multivariable linear regression, we examined relationships of selected maternal and infant factors with change in weight-for-length *z*-score (WFL-*z*) from 0 to 6 months.

Results Mean (standard deviation) change in WFL-*z* from 0 to 6 months was 0.23 (1.11), which translates to 4500 grams gained from birth to 6 months of life in an infant with average birth weight and length. After adjustment for confounding variables and birth weight-for-gestational age *z*-score (-0.28 [95% confidence interval, -0.37, -0.19] per unit), cord blood leptin (-0.40 [95% confidence interval, -0.61, -0.19] per 10 ng/mL), and gestational diabetes -0.50 [95% confidence interval, -0.88, -0.11] versus normal glucose tolerance) were each associated with slower gain in WFL-*z* from 0 to 6 months.

Conclusions Higher neonatal leptin and gestational diabetes predicted slower weight gain in the first 6 months of life. The hormonal milieu of the intrauterine environment may determine growth patterns in early infancy and thus later obesity. *(J Pediatr 2011;158:227-33)*.

The prevalence of obesity among children younger than 5 years of age, and even among infants, has increased dramatically in the last 30 years.[1,2] Weight gain in infancy predicts later risk for obesity.[3-5] Consequently, it has become important to identify modifiable risk factors in early life that contribute to the accumulation of excess weight.

Three systematic reviews reported strong associations between rapid weight gain in infancy and obesity later in childhood and adulthood.[3-5] For example, Baird et al[5] reported that more versus less rapid weight gain in the first year of life was associated with 1.2- to 5.7-fold increased risk of later obesity. More recent studies suggest that the strongest associations are with excess weight gain the first 3 to 6 months of life[6,7] and that these observations apply to gain in weight-for-length, not merely weight, which is highly associated with length.[8] Recent studies have also shown that the associations are present not only for the outcome of obesity defined by body mass index but also for direct measures of adiposity such as skinfold thickness and air-displacement plethysmography, blood pressure, and other cardiometabolic outcomes in childhood and early adulthood.[8-11]

A robust literature has emerged regarding prenatal and perinatal predictors of childhood adiposity,[12-18] including prepregnancy body mass index,[12] excessive gestational weight gain,[13,14] gestational glucose tolerance,[15] maternal smoking,[16] placental production of corticotrophin-releasing hormone, a proxy for fetal glucocorticoid exposure,[17] and higher adiponectin and lower leptin levels in umbilical cord blood at delivery.[18] However, few studies have examined whether these factors also predict weight gain in early infancy. Investigating these potential determinants of infant growth could lead to intervention strategies to prevent childhood obesity and its consequences.

The objective of this study was to determine the extent to which known prenatal and perinatal predictors of childhood obesity also predict weight gain in early infancy. To address this aim, we analyzed longitudinal data from Project Viva, a prospective prebirth cohort study of pregnant women and their children.

Methods

Study subjects were participants in Project Viva, a prospective, observational cohort study of gestational factors, pregnancy outcomes, and offspring health.[19] We

BMI	Body mass index
CRH	Corticotrophin-releasing hormone
GDM	Gestational diabetes
IGT	Impaired glucose tolerance
LFA-*z*	Length-for-age *z*-score
WFA-*z*	Weight-for-age *z*-score
WFL-*z*	Weight-for-length *z*-score

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recruited pregnant women at their initial prenatal visit at Harvard Vanguard Medical Associates, a large multispecialty group practice in eastern Massachusetts between April 1999 and July 2002. Details of recruitment and retention procedures are available elsewhere.[19] The human subjects committees of all participating institutions approved the study protocols, and all mothers gave informed consent.

Of the 2128 children born to mothers in the Project Viva, we excluded 45 infants born <34 weeks gestation and 1046 without research measures of newborn length, which were missing primarily because we did not attempt to measure infants born at night or on weekends. Of the 1037 remaining infants, we obtained weight and length measurements among 690 infants at the 6-month visit (67% follow-up). When we compared the mother-infant pairs from our final cohort of 690 to the 347 excluded participants, we found that mothers in our final cohort had similar prevalence of excessive gestational weight gain (58.2% versus 58.0%) and mean prepregnancy body mass index (BMI) (24.6 versus 25.9 kg/m^2). Infants had similar mean measures of cord blood adiponectin (28.7 versus 30.4 μg/mL), leptin (9.6 v. 9.1 ng/mL), and birth weight-for-gestational age *z*-score (0.27 versus 0.18). However, compared with excluded mothers, mothers in our sample had lower rates of gestational diabetes (5.1% versus 7.1%) and smoking during pregnancy (9.5% versus 18.8%), and they had lower mean measures of 2nd trimester corticotrophin-releasing hormone (CRH) (146.9 versus 172.6 pg/mL). More mothers in our sample reported completion of a college degree (72.0% versus 55.9%), household income >$70 000 (63.6%% versus 52.8%), and were married or cohabitating (93.5% versus 86.5%). Among the infants, white race was more frequent in our final sample (69.7% versus 57.5%).

We calculated maternal BMI (kg/m^2) from maternal self-report of height and weight at the start of pregnancy obtained in structured interviews during the first trimester.

We calculated total gestational weight gain as the difference between the last recorded weight before delivery and the self-reported prepregnancy weight. We categorized women as having gained inadequate, adequate, or excessive weight according to 2009 Institute of Medicine guidelines for weight gain during pregnancy.[20] We previously reported the validity of self-reported prepregnancy weight in our cohort.[21]

As part of routine clinical care, women underwent glycemic screening for gestational diabetes (GDM) between 26 and 28 weeks gestation with a nonfasting oral glucose challenge test, in which venous blood was sampled 1 hour after a 50-g oral glucose load. Women with a glucose concentration >140 mg/dL after the 50-g oral glucose challenge test then received a fasting, 100-g, 3-hour oral glucose tolerance test. Normal results were a blood glucose <95 mg/dL at baseline, <180 mg/dL at 1 hour, <155 mg/dL at 2 hours, and <140 mg/dL at 3 hours.[22]

Based on the results of the glycemic screening tests, we formed four categories for our analyses:[23] (1) normal glucose tolerance, defined as normal results of the 50-g test or test not done because of low-risk status; (2) failed 50-g test with normal results on the 100-g test; (3) impaired glucose tolerance (IGT), defined as failed 50-g test and 0 or 1 cut-points on the 100-g test; and (4) gestational diabetes (GDM), defined as failed 50-g test and 2 or more cut-points on the 100-g test.

We obtained maternal smoking status by self-report during the first and second trimesters.[24] We categorized participants into three groups: (1) any smoking before pregnancy; (2) any smoking during early pregnancy; and (3) no history of smoking.

We measured concentrations of maternal second trimester corticotrophin-releasing hormone (CRH, pg/mL) in plasma samples that were stored in liquid nitrogen.[17] Because CRH is highly correlated with gestational age,[25,26] in our analyses we corrected CRH level for gestational age at the time we obtained the blood sample.

We collected cord blood samples from the umbilical vein after delivery of the infant, refrigerated whole blood for <24 hours, then spun aliquotted samples for storage in liquid nitrogen. We measured concentrations of adiponectin (μg/mL) and leptin (ng/mL) in stored cord blood plasma by radioimmunoassay.[18]

We abstracted infant sex, birth weight, and gestational age from the medical record. We estimated fetal growth as birth weight-for-gestational age *z*-score from a national US reference.[27]

Project Viva staff weighed infants at 6 months with a digital scale (Seca Model 881; Seca Corporation, Hamburg, Germany) and measured length at birth and 6 months with a Shorr measuring board (Shorr Productions, Olney, Maryland). We chose change in weight-for-length *z*-score (WFL-*z*) from 0 to 6 months as our main outcome because it is more likely to represent adiposity than weight alone.[28] As a secondary outcome measure, we used change in weight-for-age *z*-score (WFA-*z*) and length-for-age *z*-score (LFA-*z*) from 0 to 6 months. We calculated age- and sex-specific WFL-*z*, WFA-*z*, and LFA-*z* from the Centers for Disease Control and Prevention 2000 growth chart data.[29]

Mothers reported information about their age, education, household income, marital status, parity, mode of infant feeding, child sex and race/ethnicity, and paternal height and weight in structured interviews and questionnaires. We categorized mode of infant feeding at the 6 month visit in four categories: (1) exclusive breast-feeding; (2) mixed breast- and formula feeding; (3) weaned from breast-feeding; and (4) exclusive formula feeding. From the electronic medical record, we obtained maternal systolic blood pressure during the 3rd trimester of pregnancy.

Statistical Analyses

We first examined bivariate relationships among our main exposures, other covariates, and our outcome. We ranked change in WFL-*z* from 0 to 6 months into quartiles, separately for boys and girls. To calculate unadjusted trend, *P* values of each exposure across quartiles of change in WFL-*z* from 0 to 6 months, we used Mantel-Haenszel χ^2 for categorical characteristics and linear regression for