Impact of Gestational Diabetes Mellitus on Pubertal Changes in Adiposity and Metabolic Profiles in Latino Offspring

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Objective To examine the impact of maternal gestational diabetes mellitus (GDM) status on longitudinal changes in adiposity and metabolic variables in overweight Latino offspring (from age 8-20 years) across puberty.

Study design This longitudinal cohort of 210 overweight Latino children was measured annually for a period of 3 ± 1 years for Tanner stage through physical examination, adiposity by dual-energy X-ray absorptiometry and magnetic resonance imaging, lipids, and glucose and insulin action via the oral glucose tolerance test and frequently sampled intravenous glucose tolerance test. Linear mixed-effects modeling estimated the impact of maternal GDM status on baseline and changes in adiposity and metabolic variables across puberty.

Results In our cohort, 22% of offspring were from GDM pregnancies. At baseline, the GDM offspring were heavier at birth, more likely to have a family history of type 2 diabetes, and less likely to have been breastfed (for any duration). Compared with the non-GDM offspring, the GDM offspring had greater increases in total body fat (+6.5% vs +4.5%; $P = .03$) and steeper declines in acute insulin response (−39% vs −17%; $P < .001$) and disposition index (−57% vs −35%; $P < .001$) across Tanner stages, independent of ethnicity, sex, breastfeeding status, family history of diabetes, and baseline and changes in body composition.

Conclusion These findings confirm the elevated risk for excess adiposity and type 2 diabetes in GDM offspring, and further underscore the need for interventions targeting Latino GDM and their offspring. *(J Pediatr 2013;162:741-5)*.

Over the past 3 decades, increasing evidence has shown that intrauterine exposure to gestational diabetes mellitus (GDM) can put offspring at increased risk for long-term health problems, including obesity, altered glucose metabolism and insulin action, and type 2 diabetes (T2D).[1-3] Observational studies have shown that diabetes in pregnancy is associated with higher prevalence of overweight and obesity in offspring.[4,5] Gillman et al[6] found that offspring of GDM mothers had a 30% increased risk of being overweight, after controlling for energy balance, socioeconomic status, and birth weight. Few studies have examined the effect of GDM on adiposity and fat distribution beyond body mass index (BMI). GDM also has been linked to an increased risk of T2D in offspring. Most notable are the studies conducted in the Pima Indians[1] and in the birth cohort from the Diabetes in Pregnancy Study.[3] In the Pima Indian cohort, 45% of offspring from mothers with GDM (aged 20-24 years) developed diabetes, compared with 9% of offspring of mothers who developed T2D after pregnancy and 1.4% of offspring of mothers without GDM or later T2D.[2] Data from the Diabetes in Pregnancy Study show a higher prevalence of impaired glucose tolerance in offspring of diabetic mothers compared with age- and sex-matched controls.[3]

Few previous studies have examined intrauterine exposure to elevated glucose levels on insulin secretion and sensitivity in offspring, beyond fasting levels. A recent study by Bush et al[7] of 21 mother–child pairs with prepubertal children (aged 5-10 years) found that maternal gestational glucose was associated with lower insulin sensitivity (SI) and greater static β-cell response in prepubertal children, independent of body composition. However, maternal GDM was not significantly associated with the child's disposition index (DI), considered a global estimate of β-cell response to glucose.

Given that puberty is a period marked by insulin resistance and subsequent compensatory insulin secretion,[8] examining the role of maternal GDM on insulin action in the offspring across this key life transition is important. Consequently, in the present study we investigated how maternal GDM status affects longitudinal changes in adiposity, lipid profiles, and glucose and insulin action in overweight Latino offspring (aged 8-20 years) as they traverse puberty. We hypothesized that compared with non-GDM offspring, GDM offspring will have greater adiposity and exhibit more metabolic disorders at baseline and across puberty.

AIR	Acute insulin response
BMI	Body mass index
DI	Disposition index
FSIVGTT	Frequently sampled intravenous glucose tolerance test
GDM	Gestational diabetes mellitus
OGTT	Oral glucose tolerance test
SI	Insulin sensitivity
T2D	Type 2 diabetes
VAT	Visceral adipose tissue

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Methods

Participants were recruited to participate in the Study of Latino Adolescents at Risk diabetes project at the University of Southern California, which began in the 2000 and has been described in detail elsewhere.[9] This study is an ongoing longitudinal study investigating potential risk factors for the development of T2D in Hispanic children. The children were required to meet the following inclusion criteria at study entry: age 8-13 years, BMI ≥85th percentile based on the Centers for Disease Control and Prevention guidelines, Hispanic ancestry (all 4 grandparents of Hispanic origin, based on parental self-report), and family history of T2D in at least one parent, sibling, or grandparent based on parental self-report. Exclusion criteria included use of medications known to affect body composition, diseases known to affect body composition or fat distribution, or any major illness since birth. The Institutional Review Board at the University of Southern California's Health Sciences Campus approved this study. Informed written consent and assent were obtained from both the child and parents before the start of testing.

A licensed pediatric health care provider conducted a detailed medical history examination and determined Tanner stage based on breast development in girls and pubic hair development in boys. The mother reported whether or not she had GDM when pregnant with the child, whether or not she breastfed and if so, for how long, and the child's birth weight.

Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a beam medical scale and wall-mounted stadiometer. BMI and BMI percentiles were determined based on Centers for Disease Control and Prevention 2001 guidelines. Whole body fat and soft lean tissue were measured by dual-energy X-ray absorptiometry (QDR 4500W; Hologic, Bedford, Massachusetts). Subcutaneous abdominal adipose tissue and visceral adipose tissue (VAT) were determined by magnetic resonance imaging performed at the University of Southern California's Imaging Science Center, using a 1.5 Signa LX-Echospeed device with a 1.5-T magnet (GE Healthcare, Waukesha, Wisconsin). A single-slice axial TR 400/16 view of the abdomen at the level of the umbilicus was analyzed for cross-sectional area of adipose tissue.

After an overnight fast, a 2-hour oral glucose tolerance test (OGTT) was conducted using a dose of 1.75 g glucose/kg body weight (maximum dose, 75 g). Blood was sampled and assayed for glucose and insulin at 5 minutes before (fasting state) and 120 minutes after glucose ingestion. Fasting and 2-hour glucose levels were used to diagnose T2D, as defined by the American Diabetes Association.

Within 1 month after the OGTT test, nondiabetic children were asked to come back to the General Clinical Research Center for an overnight visit, during which a frequently sampled intravenous glucose tolerance test (FSIVGTT) was performed. At time 0, glucose (25% dextrose, 0.3 g/kg body weight) was administered intravenously and insulin (0.02 U/kg body weight, Humulin R [regular insulin for human injection]; Eli Lilly, Indianapolis, Indiana) was injected intravenously at 20 minutes. A total of 13 blood samples were collected. Plasma collected during the FSIVGTT was analyzed for glucose and insulin, and values were entered into MINMOD Millenium 2003 version 5.16 (MinMod Inc, Pasedena, California) to determine SI, acute insulin response (AIR), and DI, an index of ß-cell function.

Blood samples obtained for the OGTT and FSIVGTT were immediately centrifuged for 10 minutes at 2500 rpm at 8-10°C to obtain plasma, and aliquots were frozen at −70°C until assayed. Fasting and 2-hour glucose were measured in the OGTT samples with a Dimension Clinical Chemistry system (Dade Behring, Deerfield, Illinois) using an in vitro hexokinase method. Glucose was measured in the FSIVGTT samples in duplicate with a YSI 2700 Biochemistry Analyzer (YSI, Yellow Springs, Ohio) using the glucose oxidase method. Insulin was assayed in duplicate with a specific human insulin enzyme-linked immunosorbent assay kit (Linco, St Charles, Missouri). Fasting lipids were assayed in the OGTT using Vitros Chemistry DT Slides (Johnson & Johnson Clinical Diagnostics, Rochester, New York).

Nonnormally distributed variables, including SI, AIR, DI, and VAT, were log-transformed. Linear mixed-effects modeling was used to assess the impact of GDM on baseline and longitudinal changes in adiposity and in glucose and insulin action over Tanner stages. All models included the following covariates: sex, birth weight, family history of T2D, breastfeeding status (any duration), and SI (when AIR was the dependent variable). We also included body composition as a covariate when glucose/insulin action were dependent variables. With linear mixed-effects modeling, results included an intercept level (ie, Tanner stage 1) of the dependent variable, a rate of change over Tanner stages in the dependent variable, and an interaction effect of Tanner stage and GDM on the dependent variable. Data were analyzed with SPSS version 19.0 (IBM, Armonk, New York), with significance level set at $P < .05$.

Results

A total of 210 overweight Latino children (22% [n = 48] GDM offspring; 57.3% male) were measured annually for a period of 3 ± 1 years. Baseline physical, adiposity, and metabolic characteristics of the children in the GDM and non-GDM groups are summarized in the **Table**. The data indicate a significant main effect of GDM on birth weight, with GDM offspring being an average of 0.2 kg heavier at birth compared with non-GDM offspring ($P = .014$). The percentage of mothers who developed T2D after birth was higher in the GDM group compared with the non-GDM group (59% vs 24%; $P < .001$). There was a significant main effect of GDM on breastfeeding status (of any duration), with GDM offspring being less likely to have been breastfed (44.6% vs 63.8%; $P = .02$).

The following sample sizes were available for each Tanner stage (T): for GDM offspring, T1, n = 22; T2, n = 17; T3, n = 17; T4, n = 20; T5, n = 24; for non-GDM offspring, T1, n = 64; T2, n = 79; T3, n = 49; T4, n = 76; T5, n = 89. There was a significant effect of GDM status on changes in total