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 2012; ■: ■-■).*

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

Table. Physical and metabolic characteristics at baseline (visit 1) in the GDM and non-GDM groups

	GDM (n = 47)	Non-GDM (n = 163)	*P* value
Males, n (%)	24 (51)	96 (58)	NS
Age, years, mean (SD)	10.9 (1.7)	11.2 (1.7)	NS
Birth weight, kg, mean (SD)	3.9 (0.8)	3.7 (0.6)	.014
Family history of T2D, %			<.001
Mother	58.7	24.3	
Father	6.7	2.6	
Both mother and father	10.9	20.8	
Grandparent	27.2	52.4	
Tanner stage, n			NS
1	22	64	
2	12	50	
3	3	17	
4	5	20	
5	5	15	
Breastfeeding of any duration, %	44.6	63.8	.02
Duration of breastfeeding, months, mean (SD)	4.7 (6.9)	5.8 (7.9)	NS
Weight, kg, mean (SD)	65.9 (23.1)	65.8 (18.9)	NS
Height, cm, mean (SD)	149.2 (12.2)	149.7 (10.9)	NS
BMI, mean (SD)	28.8 (6.0)	28.7 (5.5)	NS
BMI percentile, mean (SD)	97.3 (3.0)	97.3 (3.4)	NS
BMI *z*-score, mean (SD)	2.2 (0.4)	2.1 (0.4)	NS
Total fat, kg, mean (SD)	26.2 (12.0)	25.4 (10.1)	NS
Total lean, kg, mean (SD)	37.3 (11.8)	37.4 (9.7)	NS
VAT, cm^3, mean (SD)	49.0 (22.0)	48.9 (22.0)	NS
SAAT, cm^3, mean (SD)	350.5 (151.6)	344.4 (150.3)	NS
Fasting glucose, mg/dL, mean (SD)	89.9 (6.8)	89.0 (6.2)	NS
Two-hour glucose, mg/dL, mean (SD)	129.5 (17.2)	126.5 (18.3)	NS
Fasting insulin, μU/mL, mean (SD)	15.9 (8.8)	17.2 (10.2)	NS
SI, $\times 10^{-4}$ min^{-1}/μU/mL, mean (SD)	2.3 (1.4)	2.1 (1.5)	NS
AIR, μU/mL $\times$ 10 min, mean (SD)	1469.2 (1107.3)	1828.5 (1302.3)	NS
DI, $\times 10^{-4}$ min^{-1}, mean (SD)	2509.8 (1159.5)	2612.1 (1187.2)	NS

NS, not significant; *SAAT*, subcutaneous abdominal adipose tissue.

body fat across Tanner stages, with a 6.5% increase in total body fat across Tanner stages in the GDM group, compared with 4.3% in the non-GDM group ($\beta = 0.46$ vs 0.22; $P = .03$), independent of sex, birth weight, breastfeeding status, total lean mass, and family history of T2D. Changes in total fat mass in the GDM and non-GDM groups across puberty are shown in Figure 1. There were no significant differences between the 2 groups in terms of changes in any other adiposity measures.

Changes in SI, AIR, and DI in the GDM and non-GDM groups are shown in Figure 2. There was a significant effect of GDM status on the slope of AIR, with a 39.0% decline in AIR across Tanner stages in the GDM group, compared with 17% in the non-GDM group ($\beta = -0.14$ vs -0.10; $P < .001$), independent of sex, birth weight, breastfeeding status, and family history of T2D. There was also a significant effect of GDM on slope of DI, with a 50.7% decline in DI across Tanner stages in the GDM group, compared with a 35.2% in the non-GDM group ($\beta = -0.01$ vs -0.10; $P < .001$), independent of sex, birth weight, breastfeeding status, and family history of T2D. These significant main effects of GDM on DI and AIR remained after controlling for baseline and changes in total body fat. There was no significant main effect of GDM on SI or any other metabolic variables.

Discussion

As we hypothesized, GDM offspring exhibited greater increases in total, but not regional, adiposity and steeper declines in acute insulin secretion and β-cell function across pubertal transition compared with non-GDM offspring. Contrary to our hypothesis, there were no differences in any adiposity or metabolic measures between GDM and non-GDM offspring at baseline (primarily in

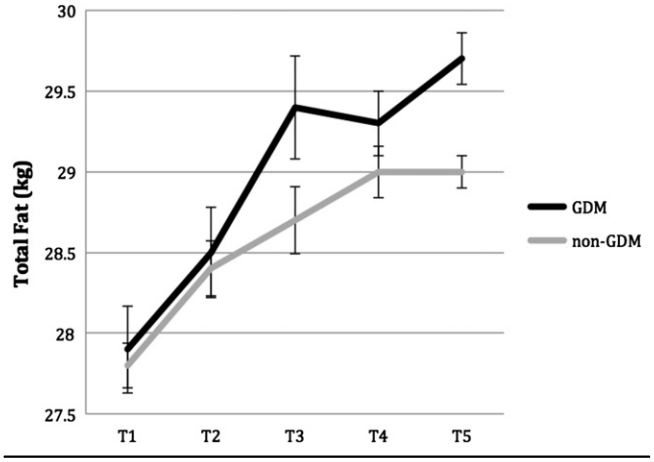

Figure 1. Changes in total body fat mass (in kg) for GDM offspring (n = 47) and non-GDM offspring (n = 163) across puberty. Data are presented as adjusted mean ± SEM of total body fat at each Tanner stage. There was a significant effect of GDM status on changes in total body fat across Tanner, ($P = .03$).

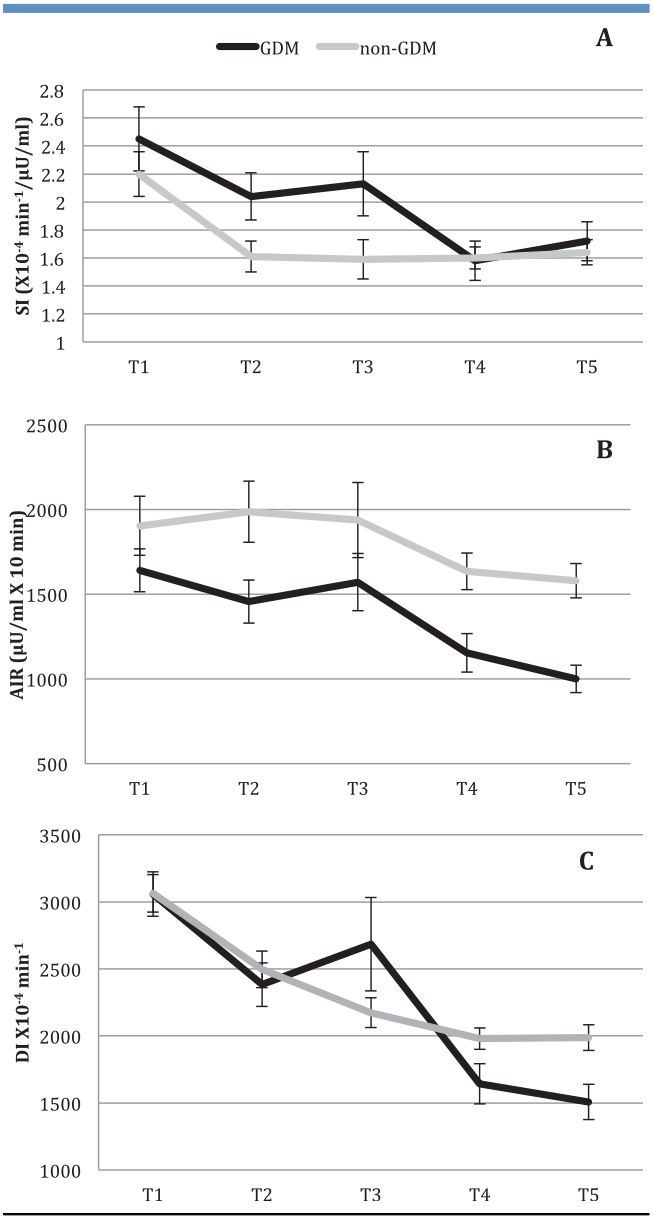

Figure 2. Changes in **A**, SI, **B**, AIR, and **C**, DI for GDM offspring (n = 47) and non-GDM offspring (n = 163) across puberty. Data are presented as adjusted mean ± SEM of insulin action at each Tanner stage. There was a significant effect of GDM status on the slope of AIR ($P < .001$), independent of sex, birth weight, breastfeeding status, and family history of T2D. There was a significant effect of GDM status on the slope of DI ($P < .001$), independent of covariates. There were no significant differences in changes in SI between GDM and non-GDM offspring.

early Tanner stages). There were also no significant differences in SI or VAT at baseline or across puberty between the 2 groups.

Previous studies have shown that GDM offspring are more obese. A large multiethnic cross-sectional study of 9439 mother–child pairs found an association between hyperglycemia during pregnancy and an increased risk of obesity in offspring at age 5-7 years. The strongest risk factor for obesity in Pima Indian children was maternal diabetes, independent of maternal obesity and birth weight.[10] In a multiethnic retrospective cohort study of 461 children aged 6-13 years, maternal GDM was associated with higher BMI, larger waist circumference, increased body fat (as assessed by skinfold thickness measurements), and increased subcutaneous abdominal fat (as measured by magnetic resonance imaging).[11] In a smaller study of 27 primarily African American, mother–child pairs, maternal glucose concentration was positively associated with offsprings' lean mass and fat mass, as measured by dual-energy X-ray absorptiometry, independent of their resting energy expenditure, physical activity, and energy intake.[12]

Few previous studies have examined how GDM impacts risk factors for T2D in offspring. The Diabetes in Pregnancy Study evaluated plasma glucose and insulin after a glucose load annually between age 1.5 years and age 16 years in offspring of diabetic mothers and one time in control children aged 10-16 years. The data showed a significantly higher prevalence of impaired glucose tolerance in the offspring of diabetic mothers compared with age- and sex-matched controls.[3] A longitudinal case-control study of 189 mother–daughter pairs, primarily Caucasian, found that GDM offspring at 15 years had a 2-fold increase in prevalence of overweight, a 40% greater risk of central adiposity as measured by waist circumference, higher fasting insulin levels and insulin resistance as measured by Homeostatic Model Assessment–Insulin Resistance, and lower high-density lipoprotein cholesterol levels.[13] Another longitudinal cohort study conducted in Finland on more than 4000 Caucasian adolescents, found more obesity, larger waist circumferences, higher fasting insulin levels, and more insulin resistance at age 16 years in GDM offspring (n = 95) compared with non-GDM offspring (n = 3909). The metabolic results were attenuated after adjusting for BMI, but remained statistically significant.[14] Although the foregoing studies were longitudinal, they all compared adiposity and metabolic variables in GDM and non-GDM offspring in a cross-sectional manner. The present study is the first to assess how GDM impacts changes in adiposity and metabolic variables across puberty, accounting for the intraindividual and interindividual correlations in the adiposity and metabolic measurements over time.

Several animal studies have shown that maternal hyperglycemia during pregnancy leads to impaired glucose tolerance and decreased insulin action and β-cell function in adult offspring.[15,16] Some human studies that directly measured SI and secretion demonstrated an insulin secretory defect in adult GDM offspring.[17,18] Studies examining the impact of GDM on insulin action in children are limited, however. In a cross-sectional study of 21 children aged 5-10 years, Bush et al[7] found an inverse association between maternal glucose concentration and offspring SI, as measured by a liquid meal tolerance test, with the effects independent of adiposity. Maternal gestational glucose concentration was positively associated with static β-cells, the β-cell response to average or

above basal glucose concentrations, but was not significantly associated with DI.[7] In contrast, in the present study, GDM status had no affect on SI in offspring, but was associated with steeper declines in AIR and DI function across puberty. The foregoing results suggest that GDM initially causes declines in SI and subsequent increases in the compensatory response of β-cells in prepubertal children, as seen in the study of Bush et al. However, as during puberty, the GDM offspring appear to have increasing β-cell deterioration and are unable to compensate appropriately in the face of increasing insulin resistance. Taken together, our findings suggest that exposure to hyperglycemia during pregnancy may "program" the developing pancreas in a way that leads to subsequent impaired pancreatic β-cell function.

The present study has several limitations to consider. GDM status was self-reported and was not confirmed by a medical records review; thus, our study could not ascertain GDM severity or treatment modality (ie, insulin vs diet only), or whether the women were screened for diabetes after pregnancy. Our study sample included only overweight Latino children with a family history of T2D, and thus our results are not generalizable to normal-weight Hispanic children and other ethnic populations. We also did not assess maternal or paternal BMI, parity, gestational weight gain, type of delivery, or newborn size for gestational age, all of which play roles in subsequent obesity and risk of metabolic disease in offspring. The sample size for GDM offspring was rather small (n = 47); however, each subject had a minimum of 2 annual visits, with an average of 3 $\pm$ 1 annual visits. Other limitations include the retrospective assessment of breastfeeding up to 13 years later and the dearth of information on breastfeeding collected (ie, breastfeeding status [yes/no] and duration of breastfeeding), which precluded ascertainment of exclusive breastfeeding.

Further research is needed to determine whether the decline in β-cell function in this population actually leads to the progression of T2D. Further research is also needed to determine the impact of GDM on adiposity and insulin action in offspring of normal-weight Hispanic children and other ethnic groups. These results highlight the need for more interventions and public health messages to work with mothers on achieving better glucose control throughout pregnancy. ■

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