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Gestational Diabetes Mellitus, Maternal Obesity, and Adiposity in offspring

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Abstract

Objective—To determine the effects of maternal gestational diabetes mellitus (GDM) on offspring adiposity in a well-characterized cohort of Mexican American mother-child pairs.

Study design—This study included 62 Mexican American mothers and their index offspring. Maternal GDM and normal glucose status during index pregnancy were documented, and mothers were previously matched on age, BMI and parity. Mothers-child pairs were recruited when offspring were between the ages of 5 and 16 years. A medical history was collected and anthropometrics were measured. Main outcome measures were offspring body mass index (BMI), BMI z-scores, BMI percentiles and hip and waist circumferences.

Results—GDM exposed offspring (n=37) had greater measures of BMI (all p < 0.02) and greater waist and hip circumferences (both p=0.002) compared with 25 offspring of non-GDM mothers. Adjustment for offspring age, sex, Tanner Stage, birth weight, months of breastfeeding, maternal pre-pregnancy BMI and pregnancy weight gain attenuated the differences, but BMI z-score and BMI percentile remained significantly greater in the GDM exposed group (p<0.05).

Conclusion—Intrauterine exposure to GDM is associated with greater adiposity in Mexican American children, and this relationship is not mediated by maternal obesity. In contrast to prior reports, this study included only Mexican Americans, thus ethnic variations may influence the contributions of maternal GDM and maternal obesity to offspring adiposity.

Keywords

gestational diabetes; intrauterine exposure to diabetes; childhood obesity; Mexican American

Obesity and its associated co-morbidities are major public health problems and there is a disproportionate prevalence of obesity in people of Hispanic origin. In 2003-2004 over 75% of Mexican American adults were overweight or obese compared with approximately 66% of non-Hispanic whites¹. Although a number of factors likely contribute to the current obesity epidemic, a growing body of evidence suggests that intrauterine exposure to

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gestational diabetes mellitus (GDM) results in an increased risk for obesity later in life ²⁻⁹ [ENREF 9](#). However, some studies have found that the *in utero* effects of GDM on offspring BMI are attenuated when data are adjusted for maternal pre-pregnancy BMI^{3, 6}. Studies also suggest that in addition to maternal obesity, post-partum factors, such as breastfeeding, may also moderate the *in utero* effects of GDM exposure ¹⁰⁻¹². Other factors, including race and ethnic variation, may play a role as well.

Therefore, the aim of this study was to determine the effects of intrauterine exposure to GDM on offspring adiposity in a cohort of well-characterized Mexican American mother-child pairs. We hypothesized that children exposed to GDM *in utero* would have higher body mass index (BMI) and greater adiposity compared with non-exposed ethnicity-matched children, and that GDM exposure effects would remain even after adjustments for maternal pre-pregnancy BMI.

Methods

Participants are the index offspring of probands who participated in our BetaGene Study, which included women with documented GDM and age-, ethnicity-, post-partum BMI-, and parity-matched women with documented normal glucose levels in pregnancy. Details on the original BetaGene Cohort are described by Black et al ¹³. All study participants are self-reported Mexican American, as defined by at least ¾ of grandparents of Mexican descent. Mothers were contacted by phone calls, and mothers-child pairs returned for a follow-up visit when offspring were between the ages of 5 and 16 years old.

Interviews and testing of offspring and mothers were conducted between 2010-2012 at the Clinical Trials Unit of the University of Southern California Keck School of Medicine and at participant's homes. The Institutional Review Board at the University of Southern California Health Sciences Campus approved the study. Informed written consent and assent were obtained from parents and children, respectively, for their participation in the study.

A detailed medical history was collected by interviews with mother-child pairs to determine maternal pre-pregnancy weight and height, maternal weight gain during pregnancy, maternal smoking history during pregnancy, duration of breastfeeding, child's birth weight, and maternal and child medical problems. Pubertal development was assessed by child and mother report with a diagrammatic representation of Tanner staging adapted from Marshall and Tanner ¹⁴.

Offspring and maternal height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, using a portable stadiometer and medical scale. Body mass index (BMI) was calculated as weight in kg divided by height in m². Age- and sex-specific BMI z-scores and BMI percentiles were calculated from CDC growth curves. Waist and hip circumferences were measured in triplicate to the nearest 0.1 cm. Waist circumference was measured at the midpoint between the iliac crest and lower costal margin in the midaxillary line. Hip circumference was measured at the maximum width of the buttocks.

Statistical Analyses

Prior to analyses all data were checked for distributional assumptions. Two-group independent t-tests and Wilcoxon rank sum tests were performed to compare the maternal and offspring characteristics and anthropometrics between GDM and non-GDM groups. Conclusions were similar and results are reported from the t-test. Offspring BMI, BMI z-scores, BMI percentiles, waist and hip circumferences and waist to hip ratios were compared between GDM exposed and non-exposed. We first adjusted for potential confounding due to differences in offspring age, sex, and Tanner Stage (as a continuous variable) (Model 1). We

then assessed the residual confounding due to maternal obesity by additionally adjusting for maternal pre-pregnancy BMI and weight gain during pregnancy (Model 2). The impact of differences in breast-feeding duration and birth weight on the relationship between GDM exposure and offspring anthropometric outcomes were evaluated in Model 3. Multiple linear regression was used for Models 1-3. Data were analyzed with SAS version 9.2 (SAS Institute Inc, Cary, North Carolina), with a significance level set at $p < 0.05$.

Results

Sixty-two mother-child pairs participated in the study, 37 with GDM and 25 without GDM (Table I). During the index pregnancy from which the offspring were born, maternal age was ~1-year lower in the GDM group. Participant reported maternal weight prior to pregnancy, weight gain during pregnancy, and duration of breastfeeding following pregnancy were similar between groups. None of the mothers smoked during the index pregnancy. A higher fraction of infants in the GDM group were males and that group had a marginally lower birth weight than the non-exposed group.

At the follow-up exam, mothers in the GDM and non-GDM groups had the same mean age and similar BMI. Six (16%) of the GDM mothers and 1 (4%) of the control mothers had been diagnosed with diabetes mellitus (Table II). Offspring exposed to GDM were ~1.4 years older and had significantly greater BMI, BMI z-scores, BMI percentiles, waist circumference, and hip circumference compared with GDM non-exposed offspring. Waist to hip ratio was similar in the two groups.

Results of multiple regression analyses appear in Table III. Model 1 shows that measures of adiposity were higher in the GDM exposed offspring after adjusting for child age, sex, and Tanner Stage. Models 2 and 3 show that measures of adiposity remained higher in the GDM exposed offspring after adjusting for maternal pre-pregnancy weight, weight gain during pregnancy, child birth weight and months of breastfeeding. Effects on waist and hip circumference were slightly attenuated and effects on waist to hip ratio more pronounced by these adjustments.

Discussion

We found that offspring of Mexican American mothers with GDM had greater BMI and waist and hip circumferences compared with offspring of non-GDM mothers. The differences were not explained by differences in maternal BMI and likely reflect greater adiposity in the GDM exposed offspring.

Some previous studies have found that adjustments for maternal pre-pregnancy BMI attenuated associations between intrauterine exposure to GDM and childhood adiposity^{3, 6}. In contrast to these reports, we found that adjustments for self-reported maternal pre-pregnancy weight and maternal weight gain during pregnancy did not significantly affect our results. This is not particularly surprising, as GDM and non-GDM mothers were matched for BMI when they enrolled in our BetaGene Study, and BMI remained similar in the subset of the BetaGene cohort who participated in this study. These similarities, together with the similarities of self-reported pre-pregnancy weights and weight gain during pregnancy provide a high level of confidence that maternal BMI was not the cause of intergroup differences in BMI in offspring. Unlike prior reports, the present study included only Mexican Americans, raising the possibility that there may be ethnic variations in the contributions of maternal GDM and maternal obesity to the risk of overweight in offspring.

Breast-feeding status has been shown to attenuate the effects of GDM exposure on offspring risk for obesity¹⁰⁻¹². Mayer-Davis reported a significantly reduced risk of overweight in

children exposed to maternal diabetes *in utero* who were exclusively breast-fed compared with those exclusively formula fed¹⁰. Crume et al reported that breast-feeding for at least six months mitigated the impact of maternal diabetes on BMI and central fat distribution in children ages 6-13¹¹. After controlling for duration of breast-feeding months, we still found a significant effect of GDM exposure on offspring adiposity. This may be due to the fact that average breast-feeding duration was similar in both GDM exposed and non-exposed groups, and on average, children in both groups were breast-fed for >6 months duration. As with maternal BMI, the similarity of duration of breast-feeding between GDM and non-GDM mothers in our cohort strengthens our ability to quantify the impact of GDM on offspring.

A few studies have reported that exposure to GDM is associated with greater levels of abdominal fat^{8, 15, 16} suggesting that intrauterine exposure to diabetes may increase risk for visceral adiposity, which is linked to adverse health consequences including type 2 diabetes and cardiovascular disease¹⁷. In unadjusted analyses, we found that both waist and hip circumference were significantly greater in GDM exposed compared to non-exposed offspring with no significant differences in waist to hip ratio, a marker of greater abdominal fat distribution. However, when we adjusted for covariates, we found that waist to hip ratio was higher in GDM exposed compared with non-exposed offspring. Thus, our findings suggest that the effects of GDM exposure on body fat distribution may also be affected by other factors, including age, sex, and maternal pre-pregnancy weight. Most studies, including our own, used waist and hip circumferences to estimate body fat distribution, and only a few studies have used magnetic resonance imaging (MRI) to quantitate visceral and subcutaneous fat stores in children exposed to maternal diabetes^{15, 18}. Our findings provide a strong rationale for more detailed phenotyping to identify potential differences in body fat storage and distribution between GDM exposed and non-exposed offspring.

Our study has several limitations. The average age of the GDM exposed offspring was ~1.4 yrs older than the average age of non-exposed offspring, and there was a greater percentage of females in the non-exposed group. However, group differences in measures of BMI remained after adjustments for these variables and for Tanner Stage. Other than GDM status, characteristics of the study cohort during the index pregnancy were based on self-report, which holds the potential for error years later. The fact that mothers were matched for postpartum BMI at entry into the BetaGene study combined with the fact that maternal BMI was similar in GDM and non-GDM groups when height and weight were measured for the current study provides evidence for similar maternal BMI between groups on an ongoing basis. Error seems unlikely for smoking, which was denied by all women in the cohort. We are unaware of factors that would lead to systematic differences between groups in recalling duration of breastfeeding, which was obtained by recall in most other studies of long-term impact on offspring¹⁰⁻¹². Tanner stage was based on self-assessment, which is not as accurate as assessments made by physical examination. However, several studies have found a reasonable agreement between self-assessment and physician determination of pubertal development, particularly among females and normal-weight children¹⁹⁻²². It should be noted that we did not study the effects of paternal factors, including paternal weight, on offspring adiposity. Thus, we cannot account for potential contributions of paternal BMI to the observed differences in offspring BMI between GDM exposed and non-exposed groups. Finally, the study sample was relatively small and was limited to Mexican American children; thus the results may not be generalizable to other ethnic groups.

These results highlight the need for obesity prevention strategies that begin early in life, including strategies that aim to prevent the growing number of pregnancies affected by GDM particularly in high-risk ethnic groups.

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Table 1

Characteristics of study cohort during the index pregnancy*

	Non-Exposed N=25	GDM Exposed N=37	p-value
Mothers			
Age (years)	33.1 ± 1.0	32.0 ± 1.2	0.48
Pre-Pregnancy BMI (kg/m ²)	28.3 ± 9.5	28.4 ± 4.0	0.98
Pre-Pregnancy Weight (kg)	70.7 ± 5.2	71.1 ± 2.2	0.95
Weight Gain during Pregnancy (kg)	12.9 ± 1.6	10.5 ± 1.1	0.20
Smoking during pregnancy	0	0	n/a
Breast-feeding duration (months)	7.6 ± 0.8	6.2 ± 0.7	0.24
Offspring			
Female	13 (52.0%)	10 (27.0%)	0.05
Birthweight (g)	3454 ± 79	3186 ± 113	0.08

* Data are presented as mean±SE or N(%)

Table 2

Characteristics of the cohort at the time of testing for the study*

	Non-Exposed	GDM Exposed	p-value
Mothers			
Age (years)	41 ± 1.4	41 ± 1.1	0.83
BMI kg/m ²	29.2 ± 1.1	31.2 ± 0.9	0.14
Diabetes (n,%)	1 (4%)	6 (16%)	0.23
Offspring			
Age (years)	7.9 ± 0.4	9.3 ± 0.4	0.02
Tanner stage	1.2 ± 0.1	1.8 ± 0.2	0.004
BMI (kg/m ²)	16.9 ± 0.6	20.3 ± 0.8	0.001
BMI z-score	0.25 ± 0.2	0.95 ± 0.2	0.02
BMI percentile	52.5 ± 6	73.7 ± 5	0.01
Waist Circumference (cm)	61.3 ± 2	71.5 ± 2	0.002
Hip Circumference (cm)	69.8 ± 2	79.6 ± 2	0.002
Waist:Hip Ratio	0.88 ± 0.01	0.90 ± 0.01	0.28

* data are unadjusted means ± SE

Table 3

Results of multiple linear regression analysis*

Offspring Outcome	Model 1 ^a			Model 2 ^b			Model 3 ^c		
	Beta *	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
BMI (kg/m²)	2.13	−0.20 – 4.47	0.072	1.96	−0.38 – 4.31	0.099	2.11	−0.30 – 4.52	0.085
BMI z	0.66	0.01 – 1.32	0.047	0.63	−0.02 – 1.28	0.058	0.69	0.02 – 1.37	0.043
BMI percentile	17.7	0.8 – 34.6	0.041	17.1	0.32 – 33.9	0.046	18.6	1.32 – 35.9	0.035
Waist (cm)	6.0	−0.5 – 12.6	0.070	5.5	−0.9 – 12.0	0.091	5.8	−0.8 – 12.5	0.085
Hip (cm)	3.8	−1.7 – 9.4	0.17	3.2	−2.3 – 8.8	0.25	3.5	−2.2 – 9.2	0.22
Waist/Hip	0.03	−0.003 – 0.065	0.072	0.03	−0.001 – 0.065	0.058	0.03	−0.001 – 0.067	0.060

* Data are presented as regression coefficients (Beta) associated with GDM exposure for each offspring outcome, 95% CI and p-value

^a Model 1: adjusted for child age, sex, and Tanner stage

^b Model 2: adjusted for covariates in Model 1, maternal prepregnancy BMI and weight gain during pregnancy

^c Model 3: adjusted for covariates in Model 2, birth weight and months of breastfeeding