Treating Gestational Diabetes Reduces Birth Weight but Does Not Affect Infant Adiposity Across the 1st Year of Life

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OBJECTIVE

The continuum of maternal glycemia in pregnancy shows continuous associations with both *1*) neonatal birth weight at delivery and *2*) subsequent adiposity later in childhood. While treating gestational diabetes mellitus (GDM) can lower birth weight and thereby disrupt the former association, it is unclear if such treatment reduces childhood adiposity. Thus, we sought to compare anthropometry across the 1st year of life between infants born to women who were treated for GDM and those with lesser degrees of gestational dysglycemia (untreated).

RESEARCH DESIGN AND METHODS

Anthropometric measurements were performed at 3 months and 12 months of life in 567 infants born to women comprising the following four gestational glucose tolerance groups: *1*) women with normoglycemia on both glucose challenge test (GCT) and oral glucose tolerance test (OGTT) in pregnancy; *2*) women with an abnormal GCT but normal OGTT; *3*) those with mild gestational impaired glucose tolerance; and *4*) women treated for GDM.

RESULTS

Birth weight progressively increased across the three untreated groups but was lowest in women treated for GDM ($P = 0.0004$). Similarly, women treated for GDM had the lowest rate of macrosomia ($P = 0.02$). Conversely, however, there were no differences among the four groups in weight *z* score, length *z* score, weight-for-length *z* score, or BMI *z* score at either 3 months or 12 months (all *P* values = NS). Similarly, there were no differences among the groups in triceps/biceps/subscapular/suprailiac skinfold thickness or sum of skinfolds at either 3 months or 12 months (all *P* values = NS).

CONCLUSIONS

Despite reducing birth weight and macrosomia, the treatment of GDM does not have analogous effects on infant adiposity across the 1st year of life.

There exists a continuous association between maternal glycemia in pregnancy and infant birth weight, reflecting the anabolic effects of glycemia-induced fetal insulin secretion (1). As the most severe element along the continuum of maternal glycemia in pregnancy, gestational diabetes mellitus (GDM) confers an elevated risk of macrosomia and associated complications, including cesarean delivery, shoulder

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dystocia, and birth injury (1). Accordingly, women who are diagnosed with GDM are treated with glucose-lowering therapy (lifestyle modification, oral antidiabetic medication, or insulin) to decrease maternal/fetal hyperglycemia and thereby reduce fetal hyperinsulinemia and its stimulation of fetal overgrowth. Indeed, clinical trials (such as the Australian Carbohydrate Intolerance Study in Pregnant Women [ACHOIS] trial and the Maternal-Fetal Medicine Units [MFMU] Network GDM trial [2,3]) have shown that controlling maternal glycemia in women with GDM can reduce fetal overgrowth and the incidence of adverse outcomes at delivery. Thus, glucose-lowering intervention (whether lifestyle or pharmacologic) has become a standard component of the management of GDM that disrupts the continuous association between maternal glycemia and infant birth weight (4,5).

It is now recognized that the continuum of maternal glycemia shows similar associations with adiposity in the offspring at 10–14 years of age (though this association is attenuated by adjustment for maternal BMI in pregnancy) (6). Indeed, the children of women who had GDM exhibit an increased incidence of childhood overweight and obesity that emerges during school age and beyond (6–10). However, it is not clear if the antepartum glucose-lowering therapy that decreases birth weight in the offspring of GDM pregnancies similarly impacts their adiposity in childhood. Although secondary analyses of the ACHOIS and MFMU Network trials found that GDM treatment had no effect on BMI in the children at 4–5 and 5–10 years, respectively, both analyses were limited by considerable loss to follow-up and anthropometric focus on BMI (11,12). Moreover, little is known about the impact of GDM treatment on adiposity in infancy (i.e., shortly after its effect on birth weight, rather than later in childhood). While this question would be best addressed with a randomized clinical trial of treated versus untreated GDM, it would be difficult to perform such a trial now that glucose-lowering therapy (whether lifestyle or pharmacologic) is standard clinical management for GDM. In the absence of such a trial, we postulated that relevant insight could potentially be obtained from observational data by determining whether the treatment of GDM disrupts the continuous association of maternal glycemia with childhood adiposity (i.e., in the same way as it does for the analogous association with birth weight). Thus, we sought to compare anthropometric measurements across the 1st year of life between infants born to women who were treated for GDM and those with lesser degrees of untreated gestational dysglycemia.

RESEARCH DESIGN AND METHODS

In this secondary analysis of a prospective observational cohort study, women were recruited at the time of screening for GDM in late second trimester, and their infants were subsequently followed with assessments at delivery, 3 months, and 12 months of age. The recruitment strategy was designed to generate a cohort of women reflecting the full spectrum of glucose tolerance in pregnancy, as described in the next section below. The study protocol has been previously described in detail (13–15) and has been approved by the Mount Sinai Hospital Research Ethics Board. All women provided written informed consent for their participation and that of their infant.

Maternal Recruitment in Pregnancy

At our institution, all pregnant women are screened for GDM by 50-g glucose challenge test (GCT) at 24–28 weeks' gestation, followed by oral glucose tolerance test (OGTT) in those in whom the GCT is abnormal (plasma glucose $\geq$7.8 mmol/L at 1 h after ingestion of 50 g glucose). For this study, women were recruited either before or after the GCT. The recruitment of women after an abnormal GCT was a design feature that served to enrich the study population for women with varying degrees of gestational dysglycemia, including GDM (15). For this study, all women completed a 3-h 100-g OGTT whether or not the GCT was abnormal. As previously described (15), the GCT and OGTT enable identification of the following four groups reflecting the full spectrum of gestational glycemia: *1*) women with GDM diagnosed by two or more glucose values on the OGTT meeting National Diabetes Data Group (NDDG) criteria (16); *2*) women with gestational impaired glucose tolerance (GIGT), defined by one glucose value meeting NDDG criteria; *3*) women with an abnormal GCT followed by normal glucose tolerance (NGT) on the OGTT (abnormal GCT NGT); and *4*) women with normoglycemia on both the GCT and the OGTT (normal GCT NGT).

Women who were diagnosed with GDM were referred to the diabetes in pregnancy clinic, where they were treated with lifestyle modification (diet and physical activity) to target fasting glucose $<$5.3 mmol/L and 2-h postprandial glucose $<$6.7 mmol/L on self-monitoring. Women not meeting the targets after 1 week were then treated with insulin therapy, with doses titrated to these glucose targets. Unlike women with GDM, those with GIGT or abnormal GCT NGT received no specific glucose-lowering therapy (either lifestyle counseling or insulin), as per standard clinical practice at our institution.

Infant Anthropometric Measures

Obstetrical outcome data, including birth weight and length of gestation, were obtained from the institutional labor and delivery database. Macrosomia was defined as birth weight $>$4,000 g, and large for gestational age (LGA) was defined as sex-specific birth weight for gestational age $>$90th percentile of Canadian fetal growth curves (17). At both 3 months and 12 months of age, participating infants underwent anthropometric assessment at the clinical investigation unit. Recumbent length was measured with a digital measuring board, and weight was measured by digital pediatric scale. Each of these measurements was performed three times, with the average recorded. Skinfold thickness (SFT) measurements were obtained by Harpenden calipers at the triceps, biceps, subscapular, and suprailiac regions. SFT measurements have been previously validated in infants against body fat assessed by direct measurement, including DEXA (18), though a recent National Institutes of Health workshop noted that measurement errors can be increased in young children due to excessive movement such that the reliability of SFT in children $<$4 years of age ranges between 60 and 70% (19). In the current study, each SFT measurement was performed three times by a single study coordinator. The average of the three repeated measurements was taken for data analysis because the intraobserver correlation coefficient (ICC) for each SFT measurement was indicative of good reproducibility. Specifically, at 3 months, the ICC for biceps, triceps, subscapular, and suprailiac SFT was 0.87, 0.96, 0.88, and 0.90, respectively. At 12 months, the ICC for these measurements was 0.92, 0.94, 0.93, and 0.96, respectively.

Statistical Analyses

All analyses were performed using the Statistical Analysis System (SAS 9.4; SAS Institute, Cary, NC). Infant characteristics

were compared among the four gestational glucose tolerance groups at birth, 3 months, and 12 months, respectively (Table 1). Infant length and weight were used to calculate age- and sex-specific standardized child weight *z* score, length *z* score, and BMI *z* score and to calculate sex-specific weight-for-length *z* score, according to the World Health Organization age- and sex-specific growth reference for children (20). Continuous variables were compared by ANOVA for those that were normally distributed and Wilcoxon rank sum nonparametric test for those with skewed distribution. Categorical variables were compared by χ^2 test.

Since the treatment of GDM reduced birth weight as anticipated, we: *1*) evaluated birth weight by maternal gestational glucose tolerance status after adjustment for infant sex and length of gestation; and *2*) evaluated the changes in weight from birth to 3 months and from 3 to 12 months, respectively, after adjustment for infant sex and age (Fig. 1). On sensitivity analyses, these comparisons were further adjusted for maternal prepregnancy BMI, gestational weight gain up to the antepartum OGTT, and ethnicity, and the postnatal changes in weight were also further adjusted for duration of exclusive breastfeeding. We next evaluated *z* scores of measures of adiposity at each age of 3 months and 12 months, adjusted for maternal/paternal ethnicity and duration of breastfeeding (weight-for-length *z* score was additionally adjusted for age, recognizing that age is incorporated into weight *z* score, length *z* score, and BMI *z* score) (Fig. 2). Similarly, the changes in these *z* scores from 3 months to 12 months were evaluated after adjustment for the same covariates (Supplementary Fig. 1). Finally, we evaluated infant SFT measurements by maternal gestational glucose tolerance status, at each age of 3 months and 12 months, after adjustment for infant age, sex, maternal/paternal ethnicity, and duration of exclusive breastfeeding (Table 2). All comparisons were conducted with multiple linear regression analyses.

RESULTS

Table 1 shows infant characteristics at birth, 3 months, and 12 months stratified into the following four groups based on maternal glucose tolerance status in pregnancy: normal GCT NGT (n = 102); abnormal GCT NGT (n = 194); GIGT (n = 96); and GDM (n = 175). Birth weight progressively increased across the first three groups but was lowest in the infants of women who were treated for GDM (overall P = 0.0004). Rates of macrosomia showed the same pattern (P = 0.02), with the lowest rate (4.6%) in the GDM group. Rates of LGA were also lowest in the GDM group (6.8%) (though this comparison across the groups did not reach statistical significance; P = 0.15). The rate of LGA was significantly lower in women with GDM compared with those without GDM (6.8% vs. 12.9%; P = 0.048). Women treated for GDM delivered at mean 38 ± 1 weeks, while the other groups delivered at mean 39 ± 1 weeks ($P < 0.0001$). After adjustment for infant sex and length of gestation, mean adjusted birth weight showed the same pattern of progressive increase from normal GCT to abnormal GCT to GIGT, followed by a decrease in the infants of women treated for GDM (overall P = 0.027) (Fig. 1*A*). These findings were unchanged after further adjustment for maternal prepregnancy BMI and gestational weight gain up to the antepartum OGTT (normal GCT NGT: mean adjusted birth weight 3,363 ± 43 g [SE]; abnormal GCT NGT: 3,415 ± 32 g; GIGT: 3,480 ± 45 g; GDM: 3,325 ± 35 g; overall P = 0.038). Similarly, these findings were unchanged upon further adjustment for maternal ethnicity (normal GCT NGT: 3,350 ± 46 g; abnormal GCT NGT: 3,404 ± 35 g; GIGT: 3,465 ± 47 g; GDM: 3,310 ± 37 g; overall P = 0.035).

At 3 months (Table 1), the duration of exclusive breastfeeding differed among the groups (P = 0.007), with infants of women with GDM having the shortest duration. Of note, there were no differences among the groups in SFT measurements (triceps, biceps, subscapular, suprailiac, and sum of skinfolds), abdominal circumference, weight *z* score, length *z* score, weight-for-length *z* score, and BMI *z* score. At 12 months, the findings mirrored those at 3 months, with the infants of women with GDM having the shortest duration of exclusive breastfeeding (P = 0.008) and there being no differences among the groups in any of the anthropometric measures.

Since the treatment of GDM reduced birth weight as anticipated, we next evaluated weight parameters across infancy after adjustment for covariates. Unlike birth weight, the mean adjusted change in weight from birth to 3 months showed no difference among the four groups (P = 0.64), after adjustment for infant sex and age (Fig. 1*B*). This finding was unchanged after further adjustment for maternal ethnicity, paternal ethnicity, and duration of exclusive breastfeeding (P = 0.88) (data not shown). Similarly, further adjustment for maternal prepregnancy BMI and gestational weight gain up to the OGTT also did not change this finding (P = 0.94) (data not shown). In contrast, after adjustment for infant sex and age, the mean adjusted change in weight from 3 months to 12 months differed among the four groups (overall P = 0.009), with the infants of women with GDM showing greater weight gain than those of women with lesser degrees of untreated gestational dysglycemia (Fig. 1*C*). These findings were unchanged upon further adjustment for maternal ethnicity, paternal ethnicity, and duration of exclusive breastfeeding (P = 0.0092) (data not shown). Similarly, the findings were unchanged upon further adjustment for maternal prepregnancy BMI and gestational weight gain (P = 0.0089) (data not shown). Thus, taken together, the adjusted analyses in Fig. 1 showed a pattern in which the decrease in birth weight induced by the treatment of GDM (Fig. 1*A*) was mirrored by a comparative increase in weight from 3 months to 12 months in the infants of the women with GDM (Fig. 1*C*).

We next evaluated *z* scores of measures of adiposity adjusted for maternal ethnicity, paternal ethnicity, and duration of breastfeeding (Fig. 2). These analyses showed that, upon adjustment for these covariates, there were no significant differences among the infants of the four groups in weight *z* score, length *z* score, weight-for-length *z* score, or BMI *z* score at either 3 months or 12 months (all P values = NS). These findings were unchanged upon further adjustment for maternal prepregnancy BMI and gestational weight gain (data not shown). There were also no significant differences among the four groups in the changes in these *z* scores from 3 months to 12 months (Supplementary Fig. 1). Finally, at both 3 months and 12 months, there were no differences among the groups in SFT measurements at triceps, biceps, subscapular, suprailiac, and sum of skinfolds, after adjustment for infant age, sex, maternal/paternal ethnicity, and duration of exclusive breastfeeding (Table 2). These findings were unchanged

Table 1—Infant characteristics at birth, 3 months, and 12 months stratified according to maternal glucose tolerance status in pregnancy as follows: *1*) normal GCT NGT, *2*) abnormal GCT NGT, *3*) GIGT, and *4*) GDM

	Normal GCT NGT (*n* = 102)	Abnormal GCT NGT (*n* = 194)	GIGT (*n* = 96)	GDM (*n* = 175)	*P*
At birth					
Male sex, *n* (%)	41 (40.2)	89 (46.4)	56 (58.3)	87 (49.7)	0.07
Weeks' gestation	39 ± 1	39 ± 2	39 ± 1	38 ± 1	<0.0001
Birth weight (g)	3,437 ± 485	3,435 ± 469	3,486 ± 465	3,268 ± 458	0.0004
Macrosomia, *n* (%)	14 (13.7)	25 (13.1)	14 (14.6)	8 (4.6)	0.02
LGA, *n* (%)	10 (10.3)	24 (14.9)	10 (12.2)	10 (6.8)	0.15
Maternal weight					
Prepregnancy BMI (kg/m^2)	23.1 (21.2–26.6)	23.5 (21.2–26.2)	23.1 (21.3–25.9)	24.8 (21.4–29.6)	0.02
Gestational weight gain (kg)*	12.5 (9.8–15.5)	9.1 (7.0–12.3)	10.9 (8.2–14.3)	9.2 (6.4–13.0)	<0.0001
Maternal ethnicity, *n* (%)					0.06
White	77 (75.5)	125 (64.4)	64 (66.7)	106 (60.6)	
Asian	7 (6.9)	28 (14.4)	17 (17.7)	37 (21.1)	
Other	18 (17.6)	41 (21.2)	15 (15.6)	32 (18.3)	
Paternal ethnicity, *n* (%)					0.08
White	75 (74.3)	130 (69.5)	61 (64.2)	115 (68.1)	
Asian	5 (5.0)	21 (11.2)	16 (16.8)	29 (17.2)	
Other	21 (20.7)	36 (19.3)	18 (19.0)	25 (14.7)	
At 3 months					
Age (months)	3.2 ± 0.6	3.5 ± 1.0	3.6 ± 1.0	3.4 ± 0.7	0.02
Exclusively breastfed (months)	3 (2–3)	3 (0–3)	3 (0.4–3)	2 (0–3)	0.007
SFT (mm)					
Triceps	10.5 (8.8–12.0)	10.0 (8.6–11.2)	10.2 (8.9–11.2)	10.0 (8.9–11.5)	0.32
Biceps	7.0 (5.9–8.3)	6.7 (5.8–8.0)	7.2 (6.1–8.6)	7.0 (5.9–8.2)	0.06
Subscapular	7.1 (6.1–8.1)	7.3 (6.2–8.3)	7.4 (6.5–8.5)	7.2 (6.3–8.1)	0.57
Suprailiac	7.6 (6.1–8.9)	7.4 (6.1–8.7)	7.3 (6.3–8.6)	7.4 (6.1–8.6)	0.96
Sum of skinfolds	32.6 (28.0–36.5)	32.2 (28.4–35.1)	32.5 (29.0–35.7)	32.1 (28.7–35.3)	0.60
Abdominal circumference (cm)	40.1 (38.2–41.8)	40.5 (39.2–42.5)	40.8 (39.0–42.8)	40.7 (38.7–42.9)	0.41
Length (cm)	60.7 (59.0–63.0)	61.7 (59.8–63.6)	61.4 (60.0–63.3)	61.4 (59.5–63.0)	0.04
Length *z* score	0.2 ± 1.2	−0.03 ± 1.3	−0.04 ± 1.2	−0.2 ± 1.5	0.09
Weight (kg)	6.1 (5.6–6.9)	6.4 (5.8–7.0)	6.4 (5.8–6.9)	6.3 (5.7–6.7)	0.04
Weight *z* score	0.04 ± 1.1	0 ± 1.0	0.02 ± 1.0	−0.1 ± 1.1	0.69
Weight-for-length *z* score	−0.07 ± 1.2	0.12 ± 1.1	0.2 ± 1.3	0.2 ± 1.1	0.25
BMI (kg/m^2)	16.6 (15.7–17.6)	17.0 (15.8–18.2)	16.7 (15.8–17.6)	16.4 (15.3–17.8)	0.33
BMI *z* score	−0.08 ± 1.2	0.04 ± 1.0	0.07 ± 1.1	0.06 ± 1.0	0.69
At 12 months					
Age (months)	12.7 ± 2.8	12.4 ± 1.7	13.1 ± 2.7	12.5 ± 2.5	0.31
Exclusively breastfed (months)	5 (2–6)	5 (2–6)	5 (0.75–6)	3.75 (0–6)	0.008
SFT (mm)					
Triceps	10.1 (9.0–11.9)	10.0 (8.7–11.1)	10.4 (9.2–11.8)	9.9 (8.8–11.4)	0.38
Biceps	6.0 (5.0–7.3)	6.0 (5.1–7.1)	6.0 (5.0–7.9)	6.0 (5.1–7.4)	0.91
Subscapular	6.5 (5.8–7.7)	6.6 (5.5–7.5)	6.7 (5.7–8.1)	6.5 (5.7–7.8)	0.97
Suprailiac	5.3 (4.6–7.0)	5.2 (4.2–6.7)	5.7 (4.2–6.8)	5.3 (4.6–6.4)	0.90
Sum of skinfolds	28.0 (25.7–33.7)	28.3 (25.1–31.8)	28.6 (25.3–32.4)	27.9 (24.3–32.0)	0.48
Abdominal circumference (cm)	44.6 (42.0–48.0)	44.3 (41.8–46.7)	45.0 (42.8–47.1)	44.5 (42.0–46.7)	0.41
Length (cm)	76.5 (74.1–79.2)	74.9 (72.5–77.2)	75.7 (73.0–77.9)	75.0 (72.7–77.3)	0.03
Length *z* score	0.5 ± 1.2	0.04 ± 2.0	0.1 ± 2.6	−0.2 ± 2.1	0.09
Weight (kg)	9.7 (9.0–10.6)	9.5 (8.6–10.4)	9.8 (9.2–10.5)	9.7 (8.8–10.5)	0.17
Weight *z* score	0.4 ± 1.0	0.2 ± 1.5	0.4 ± 2.0	0.2 ± 1.1	0.79
Weight-for-length *z* score	0.2 ± 0.9	0.2 ± 1.0	0.4 ± 1.1	0.32 ± 1.1	0.57
BMI (kg/m^2)	16.5 (15.8–17.5)	17.1 (15.9–17.9)	16.8 (16.3–18.1)	16.9 (15.7–18.1)	0.19
BMI *z* score	0.09 ± 0.9	0.2 ± 1.2	0.4 ± 1.2	0.3 ± 1.1	0.36

Continuous data are presented as median (interquartile range) (if skewed distribution or if infant anthropometric measurement at 3 or 12 months). Other continuous data are presented as mean ± SD (if normal distribution). Categorical variables are presented as absolute *n* (%). *Maternal weight gain in pregnancy was up to the antepartum OGTT.

upon further adjustment for maternal prepregnancy BMI and gestational weight gain (data not shown). Thus, despite having a lower birth weight, the infants of women with GDM showed no differences in mean adjusted measures of adiposity at 3 months and 12 months of age.

Lastly, we queried whether infant anthropometrics varied according to the type of treatment for GDM that the mother received in pregnancy (i.e., lifestyle modification alone vs. lifestyle modification followed by insulin therapy). There were 116 women with GDM treated with lifestyle alone and 54 women with GDM who

required the further addition of insulin therapy. As shown in Supplementary Table 1, there were no significance differences between these two groups in birth weight or rate of macrosomia (both of which were lower than in women with lesser degrees of untreated gestational glycemia [shown in Table 1]). Of note, there were also no significant differences in infant anthropometric measures between these two groups at either 3 months or 12 months.

CONCLUSIONS

In this study, we show that, although the treatment of GDM led to a decrease in birth weight compared with that of untreated pregnancies with lesser degrees of maternal glycemia, this weight difference did not persist across the 1st year of life. Instead, the reduction in birth weight was balanced by comparatively greater weight gain between 3 months and 12 months in the infants of women with GDM. Overall, the infants of the four groups reflecting varying degrees of gestational dysglycemia showed no significant differences in any of the measures of adiposity at either 3 months or 12 months of life, including BMI *z* scores, weight-for-length *z* scores, and SFT measurements. These data suggest that, while the treatment of GDM can disrupt the continuous association between maternal glycemia in pregnancy and birth weight, it may not affect the analogous association with childhood adiposity.

The ACHOIS and MFMU Network trials have had a profound impact on clinical practice by demonstrating that the treatment of GDM with glucose-lowering therapy (whether lifestyle or pharmacologic) can reduce neonatal birth weight and the incidence of adverse delivery outcomes (2,3). Conversely, secondary analyses of these trials showing that this treatment had little effect on BMI in the children at 4–5 and 5–10 years of age, respectively (11,12), could not offer the same certainty in their findings owing to three factors. First, these follow-up analyses in the children were conducted in only 20% of the ACHOIS study population (199 out of 1,000 pregnancies) and 55% of the eligible offspring from MFMU (500 out of 905). Second, anthropometric measurements in the children focused primarily on BMI, which comprises both lean and fat mass and does not necessarily reflect adiposity. Third, both trials treated women with relatively mild GDM, as defined by the degree of hyperglycemia required for diagnosis. Indeed, the respective investigators of both offspring follow-up analyses (11,12) noted this point when considering that their findings stood in contrast to an earlier observational study (7) in which the graded association between maternal glycemia and childhood obesity at 5–7 years of age appeared to be attenuated in the children of women who had received antepartum treatment for more severe GDM (defined by the stringent NDDG criteria) as compared with those whose mothers were not treated for lesser dysglycemia in pregnancy (although the potential impact of adjustment for maternal prepregnancy BMI was not assessed). Collectively, these conflicting findings raised the possibility that antepartum glucose-lowering therapy might reduce childhood adiposity in only the offspring of women with more severe GDM. Thus, it has remained an open question whether or not maternal treatment of GDM could be a modifiable determinant of offspring adiposity.

The current study sought to address this question during the 1st year of life by comparing the infants of women who were treated for GDM with those of women who had lesser degrees of untreated gestational glycemia. In this study, women were diagnosed with GDM based on NDDG criteria, yielding a treated population with greater severity of glycemia than that of ACHOIS and MFMU, as also evidenced by 31% requiring insulin therapy (compared with 20% and 8% in ACHOIS and MFMU, respectively [11,12]). Accordingly, this treated population was more like that of the earlier observational study that had suggested that the treatment of maternal GDM may impact childhood adiposity (7). Secondly, the anthropometric assessments performed in this study evaluated adiposity with SFT measurements, in addition to weight, weight-for-length, and BMI. Finally, the 567 participants had longitudinal assessments at birth, 3 months, and 12 months, allowing for insight into changes over time across infancy.

With this design, we found that, although the treatment of GDM reduced birth weight and macrosomia, this weight difference did not persist across the 1st year of life. Instead, the reduction in birth weight was balanced by comparatively greater weight gain between 3 months and 12 months in the infants of women who were treated for GDM. There has been limited previous study of the patterns of weight gain across infancy in the offspring of GDM pregnancies, with conflicting findings reported. An earlier report noted slower change in weight-for-length from birth to 6 months in the infants of 35 women with GDM compared with control subjects (21). Conversely, Logan et al. (22) noted a greater increase in adipose tissue volume over the first 10 weeks of life in the infants of 42 women with GDM, as compared with 44 control subjects, but with no differential change in weight among the groups. Against this background, the current study evaluated a much larger population of 567 infants (including 175 whose mothers received treatment for GDM) and found that there were no differences in weight-for-length *z* score or BMI *z* score at either 3 or 12 months or in their respective interval changes between those exposed to treated GDM and those whose mothers had lesser degrees of untreated gestational glycemia.

Our finding of an effect of GDM treatment on birth weight but not on adiposity in infancy is also consistent with other observations. Indeed, in a study of 421 mother–daughter pairs, the association between maternal glycemia in pregnancy and offspring adiposity at ∼10–12 years of age was not mediated by birth weight (8). Similarly, in a recent study comparing intensive lifestyle therapy and standard diet/exercise counseling for the management of GDM in Chinese women, the intensive intervention reduced birth weight but did not impact offspring BMI at 2 years of age (23). Coupled with the current findings showing that the treatment of GDM can disrupt the continuous association of maternal glycemia with birth weight without impacting infant BMI or SFT, the concept that emerges is one of discordance between the determinants of birth weight and childhood adiposity. While it has been suggested that postnatal factors such as offspring diet and physical activity could contribute to such discordance (11), this explanation is likely less applicable during infancy, particularly after the current adjustment for exclusive breastfeeding. Instead, these data potentially may be more supportive of a model in which fetal programming secondary to the altered intrauterine environment that predates the diagnosis of GDM (and hence the treatment thereof) contributes to offspring adiposity but may be unaffected by

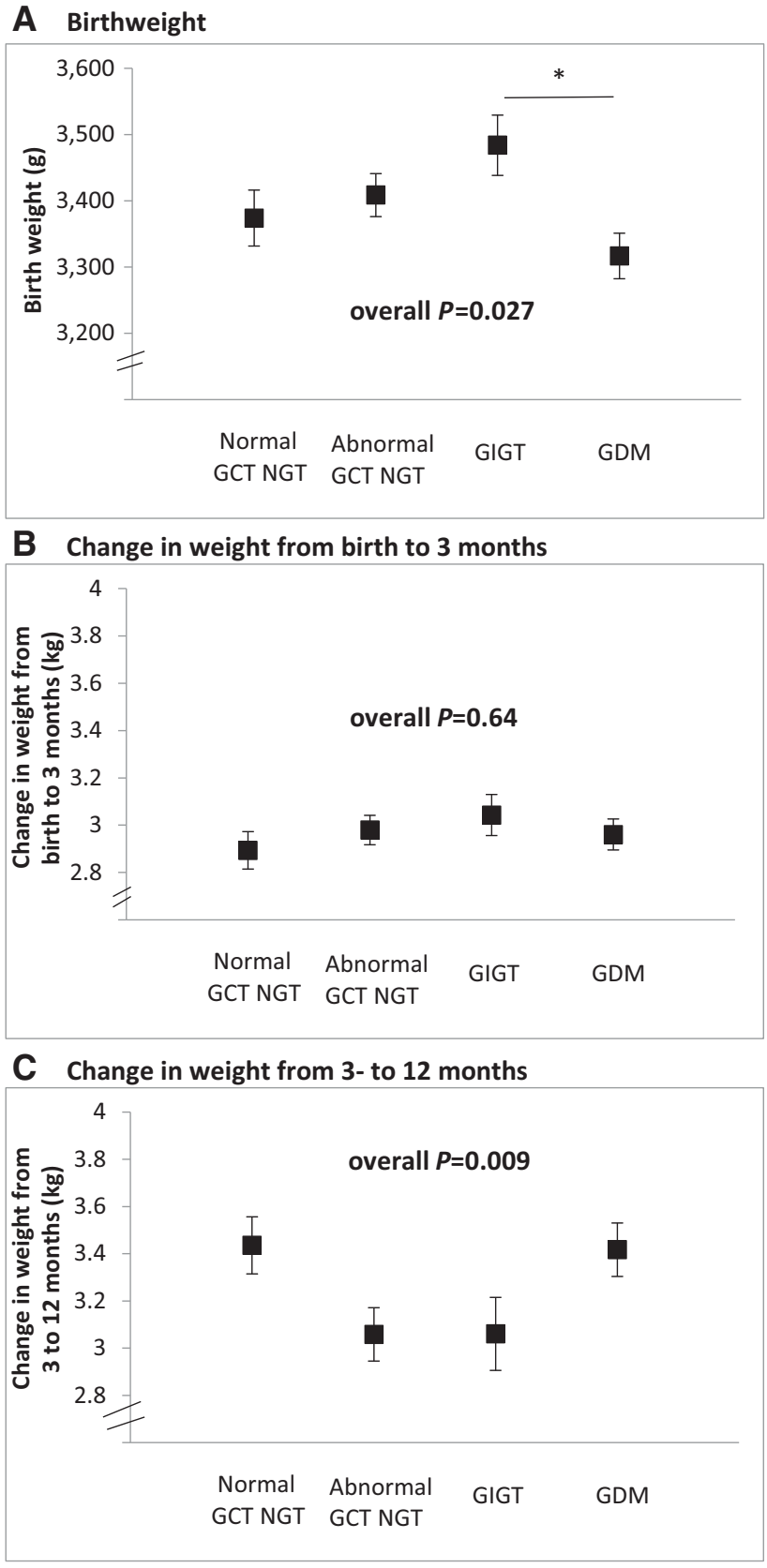

Figure 1—Mean adjusted infant anthropometric outcomes by maternal gestational glucose tolerance status: birth weight (*A*); change in weight from birth to 3 months (*B*); and change in weight from 3 to 12 months (*C*) (*A* is adjusted for infant sex and length of gestation: *B* and *C* are adjusted for infant sex and age). Data shown are adjusted mean and SE. *Pairwise comparison $P < 0.05$.

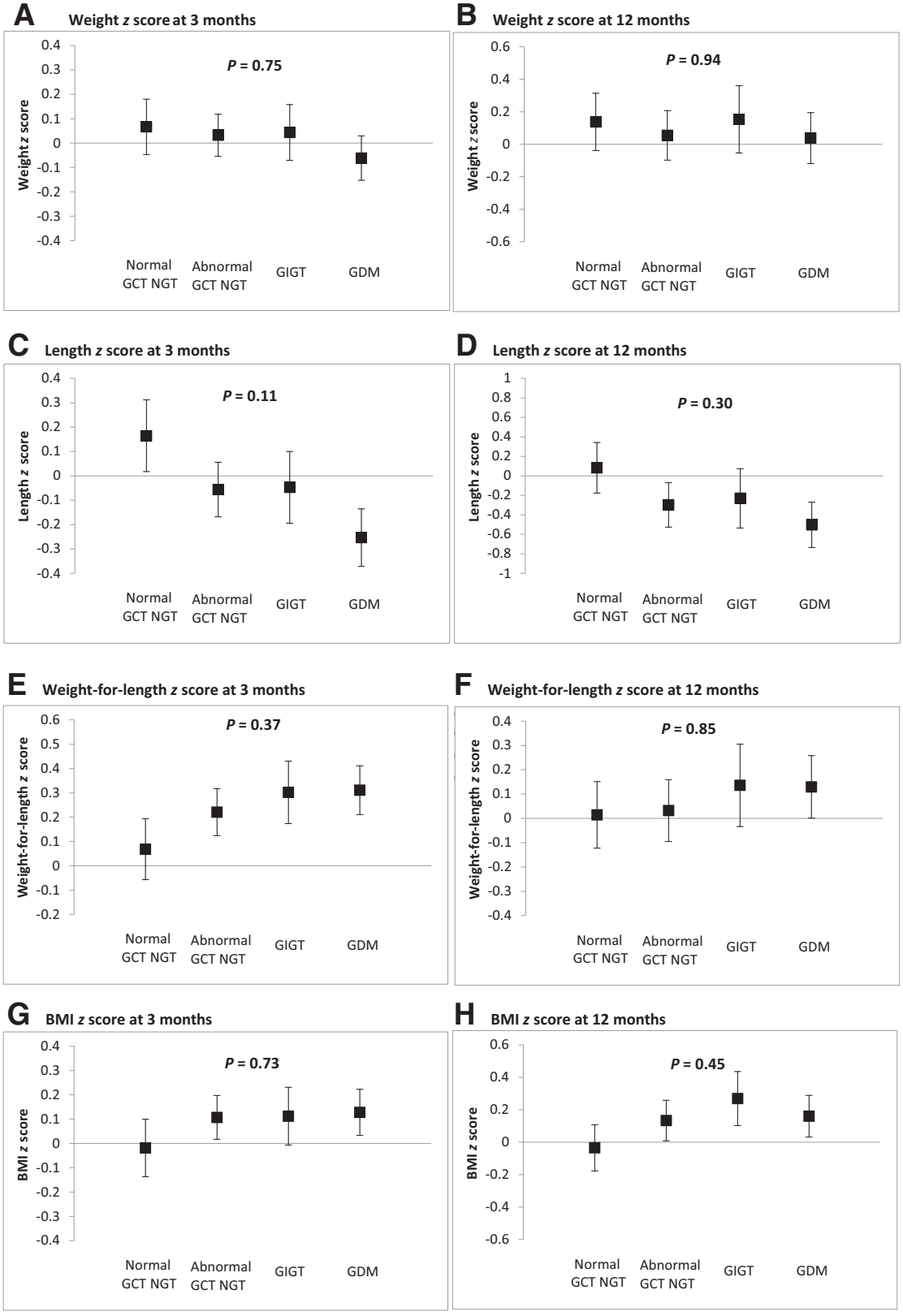

Figure 2—Mean adjusted infant anthropometric outcomes by maternal gestational glucose tolerance status: weight *z* score at 3 months (*A*), weight *z* score at 12 months (*B*), length *z* score at 3 months (*C*), length *z* score at 12 months (*D*), weight-for-length (WFL) *z* score at 3 months (*E*), WFL *z* score at 12 months (*F*), BMI *z* score at 3 months (*G*), and BMI *z* score at 12 months (*H*). All *z* scores are adjusted for maternal ethnicity, paternal ethnicity, and duration of exclusive breastfeeding (WFL *z* score is additionally adjusted for age). Data shown are adjusted mean and SE.

Table 2—Mean adjusted infant SFT measurements at 3 months and 12 months by maternal gestational glucose tolerance status, adjusted for infant age, sex, maternal ethnicity, paternal ethnicity, and duration of exclusive breastfeeding

	Normal GCT NGT	Abnormal GCT NGT	GIGT	GDM	*P*
At 3 months					
Triceps skinfold (mm)	10.8 ± 0.2	10.3 ± 0.2	10.2 ± 0.2	10.5 ± 0.2	0.081
Biceps skinfold (mm)	7.4 ± 0.2	7.0 ± 0.1	7.5 ± 0.2	7.2 ± 0.1	0.067
Subscapular skinfold (mm)	7.6 ± 0.2	7.8 ± 0.1	7.8 ± 0.2	7.6 ± 0.1	0.72
Suprailiac skinfold (mm)	8.0 ± 0.2	7.8 ± 0.2	7.8 ± 0.2	7.9 ± 0.2	0.86
Sum of skinfolds (mm)	33.8 ± 0.6	32.8 ± 0.4	33.3 ± 0.6	33.2 ± 0.5	0.49
At 12 months					
Triceps skinfold (mm)	10.1 ± 0.3	9.7 ± 0.3	10.1 ± 0.4	9.9 ± 0.3	0.56
Biceps skinfold (mm)	6.5 ± 0.3	6.5 ± 0.2	6.5 ± 0.3	6.5 ± 0.2	0.99
Subscapular skinfold (mm)	7.0 ± 0.2	6.8 ± 0.2	6.8 ± 0.3	6.9 ± 0.2	0.93
Suprailiac skinfold (mm)	6.1 ± 0.2	5.7 ± 0.2	6.1 ± 0.3	5.8 ± 0.2	0.47
Sum of skinfolds (mm)	29.6 ± 0.8	28.6 ± 0.7	28.9 ± 1.0	28.1 ± 0.8	0.49

the impact of glucose-lowering therapy on fetal growth and birth weight. This model also underscores the importance of the sensitivity analyses adjusting for maternal prepregnancy BMI and gestational weight gain. While this model remains speculative, it could reconcile the observed discordance between the impact of GDM treatment on neonatal birth weight and infant adiposity across the 1st year of life.

A limitation of the current study is that measures such as neonatal recumbent length and SFT measurements were not performed at birth, which could have provided further insight into longitudinal changes during infancy. An additional concern is the reproducibility of the OGTT (24), which could yield misclassification of maternal glucose tolerance. However, while this limitation applies to most GDM studies, it may be comparatively less problematic in the current study in which the observation of greatest interest is the juxtaposition of: *1*) the disruption of the continuous association between maternal glycemia and infant birth weight induced by the treatment of GDM; and *2*) the lack of such disruption in the analogous association with infant adiposity (since any misclassification would apply similarly to both of these associations). An additional limitation is that the gestational weight gain variable in this study tracked maternal weight gain in pregnancy up to the antepartum OGTT but not from the OGTT to delivery. However, since the treatment of GDM was precipitated by the OGTT and maternal weight gain is a likely factor in the causal pathway by which this treatment impacts birth weight, the adjustment for gestational weight gain up to the OGTT may be the more appropriate variable for adjustment of the birth weight outcome. Another limitation is the observational design, which precludes definitive attribution of causality when considering the effects of GDM treatment. However, the evidence base at this time makes the future implementation of a trial of treated versus untreated GDM an unlikely proposition. In this context, the comparison of anthropometric measurements between the offspring of women who were treated for GDM and those whose mothers had lesser degrees of untreated glycemia in pregnancy offers a workable model for addressing this question within the setting of an observational study design.

A caveat to note is that the apparent lack of impact on infant adiposity of treating GDM diagnosed by NDDG criteria does not rule out the possibility that treating women with GDM diagnosed by less stringent criteria (reflecting a lesser degree of maternal hyperglycemia) might affect infant adiposity. Conversely, however, follow-up of both the ACHOIS and MFMU Network trials found that treating comparatively milder GDM had no effect on childhood BMI at 4–5 and 5–10 years of age, respectively (11,12). Moreover, the earlier observational study (7) showing that the treatment of GDM diagnosed by NDDG criteria appeared to attenuate the graded association between maternal glycemia and childhood obesity at 5 to 7 years of age provided additional rationale for addressing the current study question in women diagnosed by NDDG criteria.

Another caveat to consider is that Silverman et al. (25) have previously reported that the infants of women with either GDM or preexisting diabetes had greater weight-for-length than their peers at birth but showed no significant difference in weight-for-height at 1 year of age. Accordingly, even if the treatment of GDM were to have long-term effects on offspring adiposity, it is possible that such effects may not be apparent in the 1st year of life. Indeed, when inferring effects of GDM treatment on offspring adiposity, one also needs to consider the potential importance of critical windows of development. For example, in the Hyperglycemia and Adverse Pregnancy Outcome cohort, the associations of maternal glycemia with adiposity that were observed in neonates (26) were not apparent in toddlers at 2 years of age (27), before reemerging later in childhood at 10–14 years of age (6). Thus, the absence of an observed impact of GDM treatment on adiposity in infancy cannot fully rule out the possibility of an effect emerging later in childhood/adolescence.

In conclusion, the treatment of GDM can reduce neonatal birth weight compared with that of untreated pregnancies with lesser degrees of maternal glycemia. However, this effect does not persist during infancy, in which no significant differences were observed in any measures of adiposity, including BMI *z* scores, weight-for-length *z* scores, and SFT measurements, at either 3 months or 12 months of age. It thus emerges that, while the treatment of GDM can disrupt the continuous association between maternal glycemia in pregnancy and birth weight, this treatment does not have analogous effects on infant adiposity across the 1st year of life.

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