



# Mild Gestational Diabetes Mellitus and Long-Term Child Health

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## OBJECTIVE

To evaluate whether treatment of mild gestational diabetes mellitus (GDM) confers sustained offspring health benefits, including a lower frequency of obesity.

## RESEARCH DESIGN AND METHODS

Follow-up study of children (ages 5–10) of women enrolled in a multicenter trial of treatment versus no treatment of mild GDM. Height, weight, blood pressure, waist circumference, fasting glucose, fasting insulin, triglycerides, and HDL cholesterol were measured.

## RESULTS

Five hundred of 905 eligible offspring (55%) were enrolled. Maternal baseline characteristics were similar between the follow-up treated and untreated groups. The frequencies of BMI  $\geq$ 95th (20.8% and 22.9%) and 85th (32.6% and 38.6%) percentiles were not significantly different in treated versus untreated offspring ( $P = 0.69$  and  $P = 0.26$ ). No associations were observed for BMI z score, log waist circumference, log triglycerides, HDL cholesterol, blood pressure, or log HOMA-estimated insulin resistance (HOMA-IR). The effect of treatment was different by sex for fasting glucose and log HOMA-IR ( $P$  for interaction = 0.002 and 0.02, respectively) but not by age-group (5–6 and 7–10 years) for any outcomes. Female offspring of treated women had significantly lower fasting glucose levels.

## CONCLUSIONS

Although treatment for mild GDM has been associated with neonatal benefits, no reduction in childhood obesity or metabolic dysfunction in the offspring of treated women was found. However, only female offspring of women treated for mild GDM had lower fasting glucose.

Gestational diabetes mellitus (GDM), defined as carbohydrate intolerance first recognized during pregnancy, affects up to 14% of pregnancies and appears to be increasing in frequency in concert with the rising prevalence of adult obesity (1). Childhood obesity has also become a major public health problem as evidenced by a nearly fourfold increase over a 30-year period ending in 2000 (2). Freinkel (3) first suggested that even the mildest forms of diabetes complicating pregnancy could have long-range effects on offspring by affecting behavioral, anthropometric, and metabolic functions. Emerging evidence suggests that the intrauterine environment of maternal diabetes can have significant influence on health in later life. Longitudinal studies of the offspring of women with diabetes during pregnancy demonstrate a link between maternal hyperglycemia and the development of obesity and altered carbohydrate metabolism during childhood and adolescence that is

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independent of both maternal obesity and birth weight (4,5). In utero exposure to hyperglycemia as measured by amniotic fluid insulin levels has been found to be a strong predictor of insulin resistance during childhood (6), and these effects of maternal diabetes on offspring appear to extend into adult life (7). Thus, fetal programming in the setting of maternal diabetes affecting fetal islet function can lead to the development of subsequent obesity, diabetes, and insulin resistance, which may create an intergenerational cycle of diabetes (8).

After decades of uncertainty, results from randomized treatment trials now confirm that treatment of mild GDM is associated with immediate benefits, including reductions in birth weight, macrosomia, and neonatal fat mass, among other outcomes (9,10). There is, however, insufficient evidence regarding whether treatment confers long-term metabolic benefit in offspring. The results of an observational study and limited follow-up from one treatment trial remain inconsistent about whether treatment of GDM is a modifiable risk factor for childhood obesity (11,12). Because of concerns about potential long-term effects of maternal diabetes on the developing fetus, we conducted a follow-up study of the offspring from a randomized treatment trial for mild GDM to determine whether treatment influences child health outcomes.

## RESEARCH DESIGN AND METHODS

Between February 2012 and September 2013, we conducted an unplanned follow-up study of the offspring of women who participated in a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network randomized clinical trial (RCT) for mild GDM (10). Mild GDM was defined as a fasting glucose <95 mg/dL and two of three timed measurements that exceeded established thresholds (1 h, 180 mg/dL; 2 h, 155 mg/dL; 3 h, 140 mg/dL). Eligibility for the follow-up study included enrollment in the RCT at a center still participating in the MFMU Network at the time of the follow-up study (12 of 16 centers; 94% of the original RCT patients). Following mother informed consent and child assent, when appropriate, children ages 5–10 years of the index pregnancy were enrolled in the follow-up

study. At the study visit, trained nursing personnel obtained height and weight measurements using a calibrated scale and stationary stadiometer. Blood pressure measurements were performed in the sitting position using standardized methodology. In addition, waist circumference measurements were obtained at the position horizontal to the uppermost lateral border of the right ilium of the pelvis per the National Health and Nutrition Examination Survey anthropometry procedures manual (13). The study visit took place after an overnight fast, and blood samples were collected and sent to the Northwest Lipid Metabolism and Diabetes Research Laboratories for fasting glucose, insulin, HDL cholesterol, and triglyceride levels. The mothers were administered a questionnaire concerning demographic information, breast-feeding history, child health, diet, and physical activity. Mothers were asked whether their child showed any signs of pubertal changes using drawings and descriptions of the five Tanner stages (14), and their responses were coded as no (Tanner = 1) or yes for any (Tanner >1) without requiring the mothers to specify the stage. The study was approved by the institutional review board of all participating centers.

The primary outcome of the study was defined as a BMI  $\geq$ 95th percentile for child age and sex per 2000 Centers for Disease Control and Prevention growth charts (15). Secondary outcomes were waist circumference  $\geq$ 90th percentile for age, sex, and race/ethnicity (16); BMI  $\geq$ 85th percentile for child age and sex; diabetes defined as fasting glucose  $\geq$ 126 mg/dL or impaired fasting glucose of 100–125 mg/dL (17); elevated triglyceride levels  $\geq$ 100 mg/dL in the children aged 5–9 years and  $\geq$ 130 mg/dL in the children aged 10 years (18); low HDL cholesterol <40 mg/dL (18); and hypertension  $\geq$ 95th percentile for child age, sex, and height (19). These outcomes were also assessed as continuous outcomes, as was HOMA-estimated insulin resistance (HOMA-IR) calculated as (fasting glucose [mmol/L]  $\times$  fasting insulin [ $\mu$ U/mL]) / 22.5 (20). Continuous variables were assessed to determine whether they were normally distributed and log-transformed when appropriate; BMI percentile for child age and sex was converted to a z score.

Estimation of the required sample size for the follow-up study was based on a two-sided type I error of 5%. Given the race/ethnicity distribution of the children eligible for this study and the reported prevalence of BMI  $\geq$ 95th percentile (21), we estimated that 20% of the treated offspring would be obese. Assuming a one-third reduction in obesity (30% untreated vs. 20% treated), a sample size of  $\sim$ 600 was required for 80% power. If the children of the mild GDM-treated group were one-half as likely to be obese (e.g., 20% in the untreated and 10% in the treated), a sample size of  $\sim$ 550 would provide 90% power.

Because we previously reported sex differences in neonatal outcomes from the original trial (22), we assessed whether the association between treatment and childhood outcomes varied by sex. Furthermore, we assessed whether the associations varied by age and neonatal adiposity.

The  $\chi^2$  and Wilcoxon rank sum tests were used to assess differences between treatment groups and baseline characteristics and birth outcomes as well as to assess differences in baseline characteristics and birth outcomes between those eligible who did and did not participate in the follow-up study. When examining the primary and secondary binomial outcomes, we used multivariable log-binomial regression to estimate relative risks and 95% CIs, adjusting for race/ethnicity and log maternal baseline BMI. For continuous outcomes, we used multivariable generalized least squares to estimate adjusted means and 95% CIs. Tests for interaction between treatment group and age (5–6 years, 7–10 years) and between treatment group and sex were determined a priori and assessed by including an interaction term in the multivariable model. Post hoc analyses also assessed the association between treatment group and child BMI by neonatal adiposity. SAS statistical software (SAS Institute, Cary, NC) was used for the analyses. All tests were two-tailed, and  $P < 0.05$  was used to define statistical significance without adjustment for multiple comparisons. No imputation for missing data was performed.

## RESULTS

### Baseline Characteristics

A total of 666 of 905 eligible women (74%) from the RCT were successfully

contacted, and 500 (55%) consented to have their children enrolled in the follow-up study; 390 children provided fasting blood samples for glucose, insulin, and lipid measurements. A comparison of maternal baseline characteristics between treated and untreated groups revealed no difference in 50-g glucose screening value, diagnostic oral glucose tolerance test results, BMI, or gestational age at entry into the trial (Table 1). Treatment was associated with lower birth weight, fat mass >90th percentile, frequency of large-for-gestational age (LGA), and birth weight >4,000 g. However, these associations were observed only in male offspring (Table 2). The maternal baseline characteristics and birth outcomes were generally similar in eligible children who did and did not participate in the follow-up study, although some differences were observed (Supplementary Tables 1 and 2). For example, a higher percentage of the children of non-Hispanic white women participated in the follow-up study. Among those who participated in the follow-up study, and similar to the full trial cohort, the maternal glucose values during the intervention in the treated group indicated that target glycemic thresholds were achieved (Supplementary Table 3).

### Follow-up Data

In the cohort of enrolled children overall, no significant difference was found between treated and untreated groups in terms of sex (53.0% vs. 51.3% males,  $P = 0.69$ ), frequency of breast-feeding

>1 month (72.4% vs. 72.5%,  $P = 0.98$ ), Tanner stage >1 (20.5% vs. 26.3%,  $P = 0.12$ ), or age at follow-up ( $7.0 \pm 1.3$  vs.  $7.2 \pm 1.4$  years,  $P = 0.40$ ). Additionally, no differences were noted among offspring of treated versus untreated women with respect to reported diet or physical activity levels (data not shown).

Overall, 21.8% of the children were obese, and 6.4% had impaired fasting glucose; none had diabetes. We found no difference in the primary outcome, as 20.8% vs. 22.9% ( $P = 0.69$ ) of offspring of treated compared with untreated mothers were found to have a BMI  $\geq 95$ th percentile at follow-up (Table 3). Additionally, no significant differences existed with respect to any secondary measures of obesity or metabolic dysfunction between the treatment groups (Tables 3 and 4).

Significant interaction was observed between treatment group and sex for fasting glucose and log HOMA-IR ( $P$  for interaction 0.007 for impaired fasting glucose, 0.002 for fasting glucose, and 0.02 for log HOMA-IR). No treatment group-by-sex interaction was observed for measures of obesity (Tables 3 and 4). Female offspring of treated women had a decreased frequency of impaired fasting glucose, lower fasting glucose, lower log HOMA-IR, but higher diastolic blood pressure than female offspring of untreated women. However, lipid levels were similar between treatment groups (Tables 3 and 4). In male offspring, mean fasting glucose and log HOMA-IR were

not significantly affected by treatment. No interaction was observed between treatment group and age for any of the outcomes.

Supplementary Fig. 1 shows the relationship between treatment group and childhood BMI z score stratified by neonatal adiposity. In the high neonatal adiposity stratum, treatment was associated with a significantly lower childhood BMI z score in female offspring (Supplementary Fig. 1B) but not in male offspring (Supplementary Fig. 1A).

### CONCLUSIONS

In this follow-up study of the offspring of women participating in an RCT for the treatment of mild GDM, we observed no difference in the overall frequency of obesity or metabolic dysfunction at ages 5–10 years according to whether treatment was undertaken. We did, however, observe sex-specific differences according to treatment with respect to childhood blood glucose levels. Mild GDM treatment was associated with a decreased frequency of impaired fasting glucose, lower fasting glucose, and lower log HOMA-IR in female offspring at ages 5–10 years but not in male offspring.

This follow-up study represents the largest of its kind in offspring from a randomized treatment trial for mild GDM. The follow-up rate of 55% in those eligible from the original RCT was accomplished despite this being an unplanned study at the time we conducted the RCT. However, enrollment of 500 children fell short of our goal of 600 needed to observe at least a one-third reduction in childhood obesity with treatment with 80% power, which means that we were underpowered to observe a more modest treatment effect. Although the study also included assessment of several metabolic outcomes in addition to measures of childhood obesity, a limitation of this study was the use of BMI as the primary measure of obesity. Furthermore, although we collected anthropometric data, more-precise measures of body composition, such as DEXA or air densitometry, may have more accurately assessed relative obesity. We also limited glucose measurements to the fasting state such that the full spectrum of carbohydrate intolerance in the offspring could not be assessed. Thus, a greater number of children with carbohydrate intolerance

**Table 1—Maternal baseline characteristics by mild GDM treatment group**

Characteristic	Treated ( $n = 264$ )	Untreated ( $n = 236$ )	$P$ value†
Age (years)	29.2 $\pm$ 5.2	28.7 $\pm$ 5.5	0.31
Glucose after 50-g glucose-loading test (mg/dL)	158.2 $\pm$ 15.3	158.4 $\pm$ 15.4	0.90
Glucose in 3-h OGTT (mg/dL)			
Fasting glucose	86.9 $\pm$ 5.7	86.5 $\pm$ 5.6	0.30
1-h OGTT	191.0 $\pm$ 21.2	192.9 $\pm$ 19.1	0.13
2-h OGTT	172.5 $\pm$ 21.4	172.5 $\pm$ 18.5	0.79
3-h OGTT	138.2 $\pm$ 29.1	133.7 $\pm$ 31.6	0.15
BMI at entry ( $\text{kg}/\text{m}^2$ )	30.2 $\pm$ 5.1	30.6 $\pm$ 5.4	0.44
Gestational age at entry (weeks)	28.8 $\pm$ 1.6	29.0 $\pm$ 1.4	0.34
Race/ethnicity			0.53
Non-Hispanic black	28 (10.6)	27 (11.4)	
Non-Hispanic white	84 (31.8)	65 (27.5)	
Hispanic	144 (54.6)	132 (55.9)	
Other	8 (3.0)	12 (5.1)	

Data are mean  $\pm$  SD and  $n$  (%). OGTT, oral glucose tolerance test. †Based on the  $\chi^2$  test for categorical variables and Wilcoxon rank sum test for continuous variables.

**Table 2—Birth outcomes by mild GDM treatment group, overall and by sex**

Outcome	Overall			Male		Female		P value†
	Treated (n = 264)	Untreated (n = 236)	P value†	Treated (n = 140)	Untreated (n = 121)	Treated (n = 124)	Untreated (n = 115)	
Gestational age at delivery (weeks)	38.9 ± 1.8	39.0 ± 1.7	0.30	38.8 ± 1.9	39.2 ± 1.7	39.1 ± 1.6	38.9 ± 1.7	0.33
Birth weight (g)	3,283.2 ± 491.4	3,468.3 ± 546.4	<0.001	3,285.5 ± 507.2	3,557.6 ± 532.5	3,280.6 ± 475.0	3,375.0 ± 547.5	0.08
Macrosomia (>4,000 g)	12 (4.6)	32 (13.6)	<0.001	7 (5.0)	21 (17.5)	5 (4.0)	11 (9.6)	0.09
Fat mass (g)	421.3 ± 173.3	482.9 ± 210.2	<0.001	407.3 ± 152.7	502.0 ± 213.8	437.1 ± 193.3	463.3 ± 205.6	0.16
Fat mass >90th percentile	9 (3.8)	36 (16.7)	<0.001	1 (0.8)	20 (18.4)	8 (7.2)	16 (15.1)	0.06
Cord C-peptide (units)	1.2 ± 0.9	1.4 ± 1.5	0.06	1.1 ± 0.7	1.4 ± 1.8	1.3 ± 1.0	1.3 ± 1.0	0.48
Cord C-peptide >95th percentile	35 (14.8)	48 (22.4)	0.04	15 (12.0)	25 (22.3)	20 (17.9)	23 (22.6)	0.39
Size for gestational age			0.003					0.35
Small	16 (6.1)	9 (3.8)		10 (7.1)	4 (3.3)	6 (4.8)	5 (4.4)	
Appropriate	231 (87.5)	189 (80.4)		123 (87.9)	95 (79.2)	108 (87.1)	94 (81.7)	
Large	17 (6.4)	37 (15.7)		7 (5.0)	21 (17.5)	10 (8.1)	16 (13.9)	

Data are mean ± SD and n (%). †Based on the  $\chi^2$  or Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

might have been identified if a glucose tolerance test had been performed.

A large prospective analysis of mother-infant pairs enrolled in the National Collaborative Perinatal Project revealed that infants of GDM mothers were more likely to have a higher BMI z score at 7 years of age (23). In contrast, a retrospective cohort study of 2,093 women-and-toddler pairs demonstrated that the risk for childhood obesity was not associated with GDM but was associated with higher maternal prepregnancy BMI and LGA birth weight status (24). These authors suggested that because their GDM population was well controlled, GDM management could be a modifiable risk factor for childhood obesity. Whether treatment of GDM is a determinant of offspring outcomes can only be assessed from follow-up studies of treatment trials. Both the MFMU Network GDM and the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trials demonstrated a reduction in birth weight and macrosomia with treatment of mild GDM (9,10). These combined results led the U.S. Preventive Services Task Force to acknowledge for the first time that treatment of GDM is beneficial (25). To date, however, there has been a paucity of information regarding whether treatment of GDM conveys long-term benefits to offspring (12,26). Gillman et al. (12) reported follow-up data on 199 (or ~20%) 4–5-year-olds who participated in the ACHOIS trial. Unlike the present study in which specific study follow-up visits occurred, the ACHOIS follow-up was limited to preschool height-and-weight measurements obtained through data linkage analysis. These investigators found no difference in the BMI z score or frequency of BMI >85th percentile in the intervention group compared with the control group (12). A smaller and underpowered follow-up study of 89 children aged 9 years from an unblinded RCT for the treatment of GDM revealed an overall greater-than-expected rate of impaired glucose tolerance with no difference in treated versus control subjects (26). There were fewer children with BMI >85th percentile in the group treated for GDM; however, this difference was not significant.

Notwithstanding the concern that some researchers have raised regarding the inconsistent evidence of an

association of GDM and childhood obesity due to failure to consider important factors such as maternal and paternal obesity, there may be several explanations for the results of the present study (27). Of note, the present study included women with mild GDM (fasting glucose <95 mg/dL) of whom only 7% required insulin therapy. Inclusion of women with more-pronounced hyperglycemia during pregnancy might have demonstrated a long-term treatment effect on obesity in their offspring. Alternatively, although treated women met conventional glucose targets for control, these maternal glucose levels may actually exceed those required to affect later outcomes, such as childhood obesity.

The appropriate offspring follow-up period for assessing the effects of maternal diabetes is debatable. An analysis of the Hypoglycemia and Adverse Pregnancy Outcomes study in offspring 2 years of age found no relationship between maternal glucose levels and child obesity (28). We followed children ages 5–10 years, yet the emergence of both obesity and metabolic dysfunction in the offspring of diabetic women may not occur until adolescence or early adulthood (6,29). Overweight infants of diabetic mothers may have normalization of their weight in the first few years of life and then develop obesity later in childhood. Crume et al. (29) reported that the effects of maternal diabetes on offspring BMI may not be apparent until age 9 or until puberty. Because most of the children in the present study were prepubertal (average age 7 years), we acknowledge that the development of obesity and any potential treatment benefit may not yet be apparent in this cohort. A follow-up study of Indian children born to GDM mothers also revealed that differences in adiposity compared with control subjects diminished during infancy and then increased through childhood (30).

Social and environmental factors could also be significant confounders affecting the results of a childhood follow-up study for which obesity is an outcome. Breast-feeding, for example, may be associated with a reduction in childhood obesity in offspring of diabetic women (29). We collected data on physical activity and nutrition, including breast-feeding practices, and did not observe significant differences between groups.

**Table 3—Follow-up outcomes (binomial) by mild GDM treatment group, overall and by sex**

Outcome	Overall		Male		Female	
	Treated	Untreated	Treated	Untreated	Treated	Untreated
BMI ≥95th percentile for age and sex	55 (20.8)	54 (22.9)	35 (25.0)	30 (24.8)	20 (16.1)	24 (20.9)
BMI ≥85th percentile for age and sex	86 (32.6)	91 (38.6)	49 (35.0)	46 (38.0)	37 (29.8)	45 (39.1)
Waist circumference >90th percentile for age, sex, and race/ethnicity	31 (11.7)	27 (11.4)	18 (12.9)	15 (12.4)	13 (10.5)	12 (10.4)
Impaired fasting glucose ≥100 mg/dL†	12 (5.7)	13 (7.2)	9 (8.4)	2 (2.2)	3 (2.9)	11 (12.1)
Elevated triglycerides ≥100 mg/dL 4–9 years; ≥130 mg/dL 10 years	38 (18.2)	29 (16.0)	18 (16.8)	11 (12.2)	20 (19.6)	18 (19.8)
Low HDL cholesterol <40 mg/dL	27 (13.0)	22 (12.2)	13 (12.2)	8 (8.9)	14 (13.9)	14 (15.4)
Hypertension ≥95th percentile or age, sex, and height	30 (11.5)	23 (9.8)	20 (14.7)	13 (10.7)	10 (8.1)	10 (8.7)
		Adjusted RR (95% CI)*		Adjusted RR (95% CI)*		Adjusted RR (95% CI)*
		0.94 (0.68–1.28)		1.04 (0.70–1.55)		0.79 (0.48–1.33)
		0.88 (0.71–1.10)		0.94 (0.70–1.27)		0.81 (0.59–1.13)
		1.05 (0.65–1.69)		1.06 (0.56–2.00)		1.02 (0.49–2.13)
		0.76 (0.36–1.62)		3.50 (0.78–15.7)		0.24 (0.07–0.82)‡
		1.11 (0.71–1.72)		1.31 (0.66–2.62)		0.99 (0.56–1.75)
		1.03 (0.61–1.76)		1.31 (0.57–3.00)		0.88 (0.45–1.73)
		1.23 (0.74–2.05)		1.41 (0.74–2.71)		0.97 (0.42–2.23)

Data are n (%) unless otherwise indicated. RR, relative risk. \*All models adjusted for race/ethnicity and log maternal baseline BMI, except waist circumference >90th percentile for age, sex, and race/ethnicity was adjusted only for log maternal baseline BMI. The data presented by child sex are based on multivariable adjusted models that included treatment group, sex, and a treatment group-by-sex interaction term. †P = 0.007 for interaction between treatment group and sex. ‡P = 0.02.

**Table 4—Follow-up outcomes (continuous) by mild GDM treatment group, overall and by sex**

Outcome	Adjusted mean (95% CI)					
	Overall		Male		Female	
	Treated	Untreated	Treated	Untreated	Treated	Untreated
BMI z score based on BMI percentile for age and sex	0.33 (0.15–0.51)	0.36 (0.17–0.55)	0.36 (0.12–0.60)	0.34 (0.09–0.60)	0.30 (0.05–0.56)	0.37 (0.10–0.64)
Waist circumference (cm)*	57.28 (56.30–58.27)	57.56 (56.54–58.60)	57.69 (56.40–59.02)	58.02 (56.65–59.43)	56.87 (55.52–58.26)	57.10 (55.68–58.57)
Fasting glucose (mg/dL)†	88.41 (87.33–89.50)	88.67 (87.56–89.78)	89.64 (88.25–91.04)	87.71 (86.25–89.18)	87.11 (85.65–88.57)	89.62 (88.12–91.12)‡
HOMA-IR*§	1.05 (0.94–1.17)	1.10 (0.99–1.24)	1.06 (0.92–1.22)	0.95 (0.81–1.10)	1.05 (0.90–1.22)	1.30 (1.11–1.52)¶
Triglycerides (mg/dL)*	58.91 (54.82–63.30)	57.38 (53.33–61.73)	57.99 (52.83–63.67)	54.85 (49.73–60.51)	60.15 (54.57–66.31)	60.20 (54.45–66.56)
HDL cholesterol (mg/dL)	54.35 (52.42–56.28)	55.10 (53.16–57.05)	55.06 (52.60–57.53)	56.65 (54.05–59.26)	53.42 (50.81–56.04)	53.43 (50.77–56.09)
Systolic BP (mmHg)	100 (98–101)	100 (98–101)	101 (99–103)	100 (98–102)	99 (97–101)	99 (97–101)
Diastolic BP (mmHg)	60 (59–61)	59 (58–60)	60 (59–62)	60 (59–62)	61 (59–62)	58 (57–60)¶

All models adjusted for race/ethnicity and log maternal baseline BMI; log waist circumference also adjusted for child's sex (overall model) and child's age in months; log triglycerides also adjusted for child's age in months; and systolic and diastolic BPs also adjusted for child's sex (overall model), child's age in months, and child's height. The data presented by child sex are based on multivariable adjusted models that included treatment group, sex, and a treatment group-by-sex interaction term. BP, blood pressure. \*Back transformation of the log value. †P = 0.002 for interaction between treatment group and sex. ‡P = 0.01. §Calculated as (fasting glucose [mmol/L] × fasting insulin [μU/mL]) / 22.5 (20). ||P = 0.02 for interaction between treatment group and sex. ¶P = 0.04.

Because metabolic differences exist between male and female neonates, differing sensitivities to hyperglycemia in utero may also result in long-term sex-specific programming (31). We previously reported that male offspring of treated women from this RCT had lower birth weight and neonatal fat mass, which was not apparent in female offspring (22). In agreement with these findings, Lingwood et al. (31) also reported that males appear more immediately sensitive to maternal glycemia as it relates to the development of neonatal adiposity. In contrast, female offspring may be more likely to exhibit the effects of in utero exposure to maternal diabetes later in childhood. At 5 years of age, female offspring of diabetic mothers exhibited increased skinfold thicknesses and higher insulin concentrations and were more likely to develop impaired glucose tolerance than control subjects (30). The present follow-up metabolic data further support the concept of sex-specific programming because we found higher glucose levels and a trend toward increased insulin resistance in untreated female offspring. Females have been shown to have similar cord glucose to males yet increased insulin levels at birth. Together with lower birth weight and increased neonatal adiposity compared with males, in females, this might suggest increased insulin resistance (32). In female offspring, the present results indicate that the development of such insulin resistance might be modifiable with treatment of mild GDM. We found no evidence of such an effect in males. Because neonatal adiposity has been determined to be predictive of subsequent childhood obesity, we stratified subjects according to neonatal fat mass percentile in our analysis and found a relationship with subsequent BMI. In female offspring exhibiting the highest neonatal fat mass, treatment of mild GDM was associated with a lower childhood BMI z score. Infants with the greatest degree of fat accumulation in utero in the untreated arm might represent those most susceptible to the effects of maternal hyperglycemia, which might be particularly true in the setting of mild maternal hyperglycemia found in subjects participating in the present RCT. The long-term offspring effects of maternal diabetes may be partly mediated by neonatal

body composition. Whereas the development of childhood obesity has been reported to be increased across the spectrum of birth weight in offspring of GDM women, Boney et al. (33) reported that only LGA offspring of diabetic mothers are at significant risk for the development of childhood metabolic syndrome.

In conclusion, although this study did not demonstrate an overall effect on childhood obesity with treatment of mild GDM, our observations with respect to the metabolic differences according to sex among the offspring remain intriguing. The association between neonatal adiposity and childhood obesity in this study is also apparent, and a potential treatment effect was suggested in female offspring with the highest neonatal fat mass. Thus, the possibility that fetal programming of metabolic function in GDM can have an intergenerational effect that may in turn be modified by treatment remains open to question. Larger follow-up studies of pregnancy randomized trials are necessary to provide evidence that the vicious cycle of intergenerational diabetes and obesity can in fact be interrupted.

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**Author Contributions.** M.B.L. contributed to the study concept, protocol development, data collection, and writing of the manuscript. M.M.R. contributed to the protocol development, supervision of the statistical analysis, methods and results, and review and editing of the manuscript. M.W.V., B.M.C., R.J.W., D.J.R., J.R.B., J.M.T., E.K.C., G.S., A.M.P., and S.C.B. contributed to the protocol development, data collection, and review and editing of the manuscript. U.M.R. contributed to the study oversight and review and editing of the manuscript. J.P.V. contributed to the protocol development and review and editing of the manuscript. M.M.R. is the guarantor of this study and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The final study design was approved by the MFMU Network Steering Committee. The data were held and analyzed by the data coordinating center at the George Washington University Biostatistics Center.

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