Gestational Diabetes and the Risk of Offspring Obesity

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ABSTRACT. *Background.* **Intrauterine exposure to the metabolic alterations of maternal diabetes may increase the risk of later obesity. We determined whether offspring of mothers with diet-treated, gestational diabetes mellitus (GDM) have an increased risk of childhood obesity and examined the relationship between childhood obesity and metabolic markers of GDM.**

Methods. **At a health maintenance organization in Seattle, WA, we reviewed medical records to obtain the life-time height and weight measurements of 524, 8- to 10-year-old children whose mothers had been screened for GDM. Maternal plasma glucose and triglyceride levels were obtained in midgestation 1 hour after ingestion of 50 g of glucose. Those with glucose screening levels ≥7.77 mmol/L (140 mg/dL) underwent a 3-hour, 100-g, oral glucose tolerance test to determine GDM status. Cord serum insulin levels also were obtained at birth. Obesity was defined as an average body mass index between 5 and 10 years of age at or above the 85th percentile for age and sex.**

Results. **The prevalence of obesity was 19% in the 58 offspring of mothers with diet-treated GDM and 24% in the 257 offspring of mothers with negative glucose screen values. There also was no difference in mean body mass index (adjusted for age and sex) between these two groups of offspring. Among all 524 offspring, there was no significant increase in the rate of offspring obesity according to the quartile of maternal screening glucose, triglyceride, oral glucose tolerance test, or cord serum insulin level.**

Conclusion. **Prenatal exposure to the metabolic effects of mild, diet-treated GDM does not increase the risk of childhood obesity.** ***Pediatrics*** **1998;101(2). URL: http://www.pediatrics.org/cgi/content/full/101/2/e9;** ***pregnancy in diabetes, obesity, fetus, child, body mass index.***

ABBREVIATIONS. IDDM, insulin-dependent diabetes mellitus; GDM, gestational diabetes mellitus; NIDDM, noninsulin-dependent diabetes mellitus; GHC, Group Health Cooperative of Puget Sound; HMO, health maintenance organization; OGTT, oral glucose tolerance test; BMI, body mass index.

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Children born to mothers with insulin-dependent diabetes mellitus (IDDM) have an increased risk of later obesity.[1–5] These children may be programmed in utero for later obesity by exposure to excess metabolic substrate at a sensitive period in development.[6–8] Gestational diabetes mellitus (GDM), that is, diabetes with onset or first recognition during pregnancy,[9] affects 3% to 5% of all pregnancies.[10,11] GDM is far more common in pregnant women than is existing IDDM or noninsulin-dependent diabetes mellitus (NIDDM). Previous studies suggest that GDM also increases the risk for later obesity in the offspring.[12–15] Each of these studies, however, contained a mixture of subjects with GDM and either IDDM or NIDDM. No study has ever compared childhood obesity rates in offspring of mothers with and without GDM. Therefore, we tested the hypothesis that offspring from pregnancies affected by GDM have an increased risk of childhood obesity. To suggest a possible mechanism by which the intrauterine environment affects later obesity risk, we also examined the association between childhood obesity and the metabolic markers of GDM measured during gestation.

METHODS

The study was conducted at Group Health Cooperative of Puget Sound (GHC), a staff-model, health maintenance organization (HMO) in Washington state. In 1985 and 1986, 977 pregnant women at GHC participated in a study of screening tests for GDM.[16,17] The offspring of these pregnancies, followed up at 5 to 10 years of age, are the subjects of the current study. The study was approved by the Human Subjects Review Committees both at the University of Washington and at GHC.

GDM Screening Study

At between 24 and 32 weeks' gestation, plasma glucose and triglyceride levels were obtained from each mother 1 hour after a 50-g, oral glucose load. Those with glucose screening values ≥7.77 mmol/L (140 mg/dL) were recalled for a 3-hour, 100-g, oral glucose tolerance test (OGTT). At delivery, an attempt was made to obtain serum insulin levels from the cord blood of all infants.

All 3517 women who enrolled for prenatal care at the two main GHC prenatal clinics between January 1985 and May 1986 were potentially eligible for the GDM screening study (Fig 1). A total of 2019 women without known diabetes consented to participate. Of these, 1477 had a normal glucose screen value, 456 had an abnormal screen value, and 86 were excluded for reasons such as twin gestation or delivery at a non-GHC hospital. A control group of 521 mothers was selected randomly from those 1477 with a normal glucose screen value. The 456 mothers with an abnormal glucose screen value were placed in one of three other groups based on the OGTT result. GDM was diagnosed in 101 mothers, based on any two of the four OGTT values exceeding the criteria published by Carpenter and Coustan[18]; 264 had a normal OGTT result, and 91 refused to undergo the OGTT. All with GDM were generally prescribed a 7560 to 9240 J (1800- to 2200-kcal) diet low in oligo-

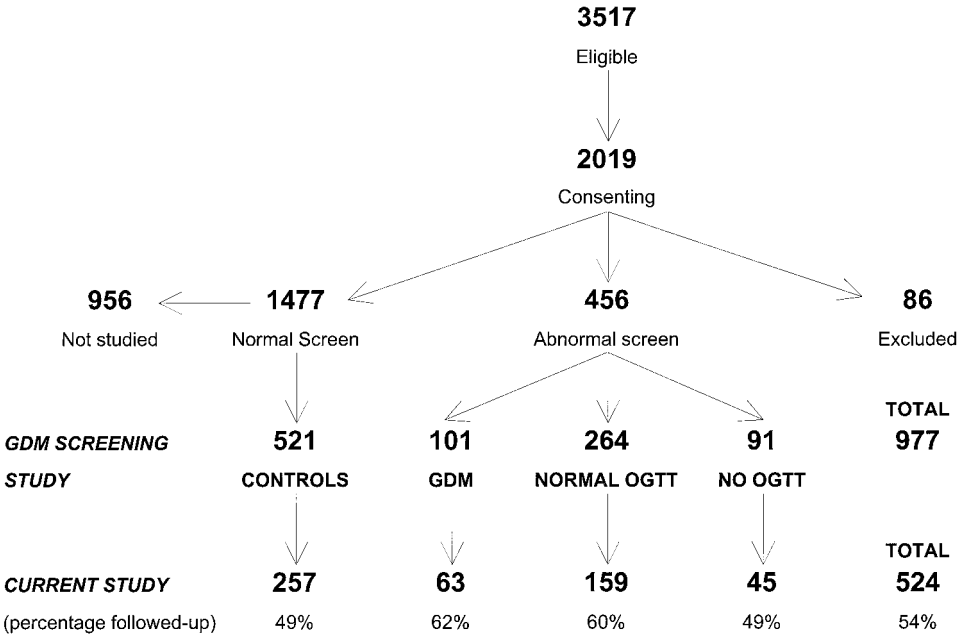

Fig 1. Selection of the mothers for the original GDM screening study and the follow-up rates of their offspring in the current study.

saccharide, and they were instructed in home glucose monitoring. Women began to receive insulin if they had fasting glucose values >5.9 mmol/L (105 mg/dL) and/or 2-hour postprandial glucose values >6.7 mmol/L (120 mg/dL) on two or more occasions within a 2-week period. Of those mothers with GDM, only 5 were treated with insulin. Two of these five were begun on insulin therapy based on elevated glucose screening values (9.3 mmol/L [168 mg/dL] and 11.0 mmol/L [198 mg/dL]) and did not have an OGTT.[16]

Offspring Follow-up Study

Most offspring of mothers in the GDM screening study received subsequent health care at GHC, and childhood growth measurements were available in their outpatient medical charts. Because our hypotheses related to childhood obesity, offspring were eligible for this follow-up study only if their chart contained at least one height and weight measurement, recorded on the same day, on or after their fifth birthday. For eligible offspring, we obtained all height and weight measurements recorded before January 1, 1996, in the outpatient medical chart (unless from an emergency department visit). We excluded six children with conditions having a major impact on stature and/or adiposity (eg, cancer), and three offspring were stillborn.

Outcome Measures

We used body mass index (BMI) (weight [kilograms] divided by height [meters] squared) to assess fatness. Although BMI does not measure fatness directly, it is an acceptable surrogate measure of childhood fatness among indices derived from height and weight measurements.[19,20] BMI in children is correlated with direct measures of adiposity,[21] blood pressure,[22] and serum lipid[23] and insulin concentrations.[24]

BMI points (height and weight measurement recorded on the same day) were standardized for age and sex by conversion to a z score. This standardization was required because children were measured at different ages and because BMI varies with age. To standardize BMI, we used z scores rather than percentiles, because z scores are more normally distributed and because z scores more clearly convey the magnitude of BMI difference between any two measurements at the extremes of the BMI distribution. The z score was calculated as (BMI − mean)/SD, where the mean and SD of BMI were from a reference population of the same age and sex as the subject. For points after 3 years of age, we used as a reference the combined data from National Health and Nutrition Examination Surveys I and II,[25] and for points before 3 years of age, we used data from the Fels Longitudinal Study (S. Guo, personal communication, September 20, 1995). Means and SD values of BMI for specific ages (eg, 6.2 years) were found by linear interpolation between discrete ages (eg, 6 years and 7 years) given in the reference data.

For each subject, we calculated the average BMI z score between 5 and 10 years of age. For subjects with two or more BMI points between 5 and 10 years of age, we estimated the average BMI z score by interpolating data linearly between available points and extrapolating the first and last points out to the ends of the 5- to 10-year interval. The formula used for the average was therefore,

$$\sum_{i=1}^{K+1} \frac{1}{2}(\text{BMI } z(t_i) + \text{BMI } z(t_{i-1}))(t_i - t_{i-1})/(t_{K+1} - t_0),$$

where the ages at which BMI points were measured were $t_1, \ldots t_K$ *and where the endpoints of the time interval were* $t_0 = 5$ and $t_K + 1 = 10$. The formula can also be rewritten to show that it computes a weighted average with BMI points closely spaced in time receiving relatively less weight than widely spaced points. This weighting ensures that the average is not unduly influenced by multiple observations clustered close together in time.

Although there is no established BMI cut-point to define childhood obesity,[26] subjects were classified as obese if, between 5 and 10 years of age, their average BMI z score was ≥1.036, which corresponds to the 85th percentile of a normal distribution. We also calculated the average BMI for age intervals before 5 years and the BMI at birth to demonstrate, using a consistent measure across ages, how offspring fatness changed from birth through age 10 years. Weight for height is an alternative surrogate measure of fatness in children, especially at younger ages. However, this measure could not be calculated for a number of subjects at the older ages because the National Center for Health Statistics weight-for-height charts do not use data for males taller than 145 cm or females taller than 137 cm.[27] Birth–weight ratio was calculated as another surrogate measure of birth size, because the ratio provides a continuous measure of birth weight adjusted for gestational age and sex. The birth–weight ratio was calculated by dividing the offspring birth weight by the median birth weight for gestational age and sex (based on a reference population of non-Hispanic white newborns).[28] Infants were considered large for gestational age if they had a birth–weight ratio ≥1.15, ie, a birth weight ≥115% of reference weight for gestational age and sex. This cut-point is equal to ~4000 g for infants born at 40 weeks' gestation.

Predictor Measures

Because there were only five insulin-treated mothers, we excluded them from our primary analysis. The main comparison of interest was between the offspring of mothers with GDM (treated

with diet alone) and the offspring of control mothers (those with a normal glucose screen value). Among all offspring with available data, we also examined the relationship between offspring obesity in childhood and four metabolic markers of GDM. Three markers (maternal screening plasma glucose, triglyceride, and glucose tolerance) are indirect measures of the maternal metabolic substrate available to the fetus. The fourth marker, serum insulin from the offspring cord blood, is an indirect measure of the fetal hyperinsulinemia induced by the increased transplacental transfer of maternal glucose.[29,30] The OGTT results were summarized for each mother as the area under the OGTT curve, with a larger area indicating greater glucose intolerance. The laboratory measurement of all specimens and the calculation of the area under the OGTT curve were described previously.[16,17]

Maternal obesity before pregnancy and paternal obesity at offspring delivery were the covariates considered. Maternal prepregnant BMI was based on self-reported prepregnant weight and the measured height, both recorded at the first prenatal visit. Paternal BMI at offspring delivery was estimated from the available height and weight measurements in the father's GHC medical record. If paternal height was available in the medical record, then BMI points were calculated for the recorded paternal weight measurements. The paternal BMI on the day of offspring delivery was estimated by linear interpolation between paternal BMI points before and after the delivery date. Parent obesity was defined as a BMI ≥27.8 in fathers and ≥27.3 in mothers.[31]

Statistical Analysis

Rates of obesity and mean BMI *z* scores in GDM and control offspring were compared with χ^2 and Wilcoxon rank sum tests, respectively. Offspring were divided into quartiles by the value for each of the four metabolic markers of interest. We tested the association between quartiles of each metabolic marker and offspring obesity using logistic regression with likelihood ratio tests. Multivariable logistic regression analyses of obesity rates also were performed, controlling for the effects of parental obesity.

RESULTS

Of the original 977 offspring, 524 (54%) met criteria for follow-up. Figure 1 shows follow-up rates by maternal GDM screening group. The majority of those not followed-up had disenrolled from GHC before 5 years of age (62%) or had no health care visits to GHC after 5 years of age despite being enrolled (16%). Fifty-one percent of the eligible offspring were boys, 94% were non-Hispanic whites, and 93% were born to married mothers. Subjects had a median of 2 BMI points recorded after 5 years of age (range, 1 to 17 points), with the most recent BMI point at a median age of 8.0 years. The age distribution of BMI points was similar in GDM and control offspring (data not shown). Table 1 describes the offspring and their parents. Twenty percent of the children were obese between 5 and 10 years of age, which is consistent with current US trends.[32] The obesity rate was higher in the fathers than in the mothers.

The offspring of diet-treated mothers with GDM tended to have lower obesity rates and BMI *z* scores than offspring of control mothers, but neither difference was statistically significant (Table 2). Even when we used a higher BMI cut-point to define obesity (average BMI *z* score ≥1.645 or approximately the 95th percentile of BMI for age and sex), there still was no significant difference in obesity rates between GDM and control offspring (12.1% vs 11.7%; $P = .93$). Three of the five offspring of insulin-treated mothers were obese. When these five offspring were combined with the offspring of diet-treated mothers, there still was no increased risk of obesity (or no higher mean BMI *z* score) in offspring of mothers with GDM compared with offspring of controls (22% vs 24%; $P = .75$). The OGTT criteria for the diagnosis of GDM, which were established by the National Diabetes Data Group,[9] are more stringent than those we used. When these stricter criteria were applied to our cohort, there were 37, rather than 58, offspring of diet-treated mothers with GDM. The rate of obesity in this group of 37 offspring of mothers with GDM was 27% and still was not significantly greater than the rate of 24% among controls ($P = .70$).

There was a significantly higher obesity rate in children whose mothers or fathers were obese (Table 2). Because parent obesity is a strong risk factor for childhood obesity,[33] and because maternal obesity also is a risk factor for GDM,[11] we evaluated all associations of childhood obesity and maternal GDM status while controlling for parent obesity. In these adjusted analyses, the risk of obesity was no higher in the offspring of mothers with GDM than in offspring of control mothers. Offspring of mothers with a normal glucose screen (plasma glucose <7.77 mmol/L [140 mg/dL]) had a higher rate of obesity than offspring of mothers with an abnormal screen (controls). After adjusting for parent obesity, however, the difference in childhood obesity rates be-

TABLE 1. Characteristics of Study Cohort

Measurement	*N*	Mean	SD
Offspring childhood weight (age 5–10 years)			
BMI *z* score*	524	0.38	0.98
Obese† (%)	524	20	
Offspring characteristics at birth			
Birth weight (g)	524	3617	530
Birth length (cm)	519	50.9	2.2
Birth–weight ratio‡	524	1.06	0.13
Gestational age§ (weeks)	524	39.6	1.6
Parental characteristics			
Maternal age (years)	524	31.1	4.6
Maternal prepregnant BMI	517	22.8	3.9
Maternal obesity‖ (%)	517	11	
Paternal age (years)	490	33.6	5.4
Paternal BMI	359	25.5	3.8
Paternal obesity‖ (%)	359	22	
Pregnancy-related characteristics			
Pregnancy weight gain¶ (kg)	514	15.7	4.85
Multiparous (%)	524	55	
Metabolic markers of GDM			
Maternal triglyceride (mmol/L)#	522	1.95	0.67
Maternal glucose (mmol/L)#	524	7.60	1.56
Maternal glucose tolerance** (mmol/L)	217	22.4	3.4
Cord serum insulin (pmol/L)	352	111	95

* BMI = body mass index (weight[kg]/height[m]^2); see text for method of *z* score calculation.
† Obese defined as average BMI *z* score ≥1.036 between age 5 and 10 years.
‡ See text for method of calculation.
§ Gestational age calculated from first day of last menstrual period; eight offspring had gestational age <36 weeks.
‖ Parental obesity defined as BMI ≥27.3 for mothers and ≥27.8 for fathers.
¶ Based on the difference between self-reported prepregnant weight and the recorded weight at last prenatal visit.
# Plasma level 1 hour after 50-g, oral glucose load at 24–32 weeks' gestation.
** Area under OGTT curve (see reference 17 for explanation of calculation).

TABLE 2. Comparison of Offspring BMI *z* Scores and Obesity Rates at Age 5 to 10 Years by Maternal GDM Screening Group and Parent Obesity Status

	Mean BMI *z* (SD)	No. Obese/No. Studied	% Obese	Group Comparison	*P* Value* (Adjusted *P* Value)
GDM screening group					
Controls	0.45 (0.93)	62/257	24		
GDM (diet-treated)	0.39 (0.94)	11/58	19	vs controls	.40 (.53)†
Abnormal screen, normal OGTT	0.24 (0.93)	22/159	14		
Abnormal screen, no OGTT	0.34 (1.22)	7/45	16		
All abnormal screens‡	0.28 (0.98)	40/262	15	vs controls	.01 (.26)†
Parental obesity‡					
Mother nonobese	0.31 (0.95)	80/461	17		
Mother obese	0.91 (0.99)	21/51	41	vs nonobese	<.001 (.006)§
Father nonobese	0.28 (0.91)	41/279	15		
Father obese	0.71 (1.02)	25/78	32	vs nonobese	<.001 (.002)§

* *P* values are for comparison of obesity rates between groups and are based on χ^2 test.
† Adjusted *P* value controls for the effects of maternal and paternal obesity using logistic regression.
‡ Analysis excludes five insulin-treated mothers with GDM.
§ Adjusted *P* value controls for obesity of the other parent using logistic regression analysis and vice-versa.

tween these two groups was not statistically significant.

We also compared the offspring obesity rates and BMI *z* scores before 5 years of age (Table 3). Offspring of mothers with GDM were larger at birth with a greater proportion classified as large for gestational age by birth–weight ratio ($P = .02$) or birth BMI ($P = .06$). Between 6 and 12 months of age, however, these differences not only disappeared, but there was a suggestion that offspring of mothers with GDM were leaner.

Women in the higher quartiles of screening glucose level had offspring with lower obesity rates (Table 4). However, after adjustment for parent obesity, the differences in childhood obesity rates were no longer statistically significant. There were no significant differences in the rate of childhood obesity across quartiles of maternal glucose tolerance, maternal triglyceride, or cord serum insulin. When these four metabolic measures were each examined as continuous variables and correlated to offspring BMI *z* scores, there were no significant correlations. The five offspring with insulin-treated mothers were excluded from the analyses in Table 4, but the overall results were unchanged when these five cases were included.

Our sample size was adequate to detect a clinically relevant association between maternal GDM and offspring obesity in childhood. Given the prevalence of obesity in the control group (24%) and the number of offspring available for follow-up ($n = 58$ for GDM; $n = 257$ for controls), our study had 85% power ($\alpha = 0.05$) to detect a relative risk of 1.8 for obesity in the offspring of mothers with GDM.

We explored the possibility that differential follow-up in the GDM and control groups masked an association between GDM and offspring obesity (Table 5). In the GDM group, those offspring followed-up tended to have mothers with lower prepregnancy BMI and obesity rates. In contrast, for the control group, those offspring followed-up tended to have mothers with higher prepregnancy BMI and obesity rates. These differences could have biased our results toward the finding of no difference in obesity rates between offspring of control mothers and offspring of mothers with GDM, but when we controlled our analyses in Table 2 for maternal obesity, our conclusions were unchanged.

DISCUSSION

We observed no increased risk of childhood obesity in offspring of mothers with mild, diet-treated GDM and found no association between the metabolic markers of GDM and childhood obesity. Our conclusions apply to the population we studied, namely, the offspring of medically insured, non-Hispanic white mothers with diet-treated GDM. The GDM prevalence in the HMO population from

TABLE 3. Comparison of GDM and Control Offspring BMI *z* Scores and Obesity Rates by Age*

Age Interval	Sample Size		% Obese			BMI *z* Score		
	GDM	Controls	GDM	Controls	*P* Value§	GDM	Controls	*P* Value‖
Birth†	58	257	40	24	.02	1.10	1.06	.10
Birth‡	58	255	38	25	.06	0.63	0.53	.63
1–6 Months	55	238	27	22	.38	0.40	0.27	.32
6–12 Months	49	224	2	12	.04	−0.22	−0.15	.81
1–2 Years	49	230	14	17	.65	−0.26	−0.06	.31
2–5 Years	50	230	12	20	.17	0.21	0.38	.33
5–10 Years	58	257	19	24	.71	0.39	0.45	.58

* Analysis excludes five offspring of insulin-treated GDM mothers.
† Fatness at birth assessed by birth–weight ratio with large for gestational age (or obese) defined as birth–weight ratio ≥1.15.
‡ Fatness at birth assessed by birth BMI with large for gestational age (or obese) defined as BMI *z* score ≥1.036. At all other ages, fatness is assessed by average BMI *z* score over the age interval with obesity defined as BMI *z* score ≥1.036.
§ *P* value for χ^2 tests.
‖ *P* value for Wilcoxon rank sum test.

TABLE 4. Comparison of Offspring BMI *z* Score and Obesity Rates by Quartile of Metabolic Measures From Pregnancy and by Parental Obesity*

	Mean BMI Score *z*	No. Obese/No. Studied	% Obese	*P* Value† (Adjusted *P* Value)‡
Maternal glucose				
1st Quartile	0.42	27/129	21	.05 (.54)
2nd Quartile	0.48	35/128	27	
3rd Quartile	0.32	19/127	15	
4th Quartile	0.26	21/135	16	
Maternal OGTT				
1st Quartile	0.09	4/53	8	.22 (.30)
2nd Quartile	0.38	11/54	20	
3rd Quartile	0.26	7/53	13	
4th Quartile	0.34	10/54	19	
Cord serum insulin				
1st Quartile	0.41	17/86	20	.65 (.49)
2nd Quartile	0.33	12/78	15	
3rd Quartile	0.25	16/89	18	
4th Quartile	0.31	16/98	16	
Maternal triglyceride				
1st Quartile	0.34	20/129	16	.12 (.16)
2nd Quartile	0.33	20/128	16	
3rd Quartile	0.34	29/128	23	
4th Quartile	0.48	33/132	25	

* Analysis excludes offspring of five insulin-treated mothers with GDM.
† *P* values are from likelihood ratio tests for importance of the entire set of quartile indicator variables.
‡ Adjusted *P* values for associations with metabolic measures are calculated using logistic regression models controlling for maternal and paternal obesity.

TABLE 5. Comparison of GDM and Control Groups by Follow-up Status

	GDM Followed Up $n = 58$	GDM Not Followed Up $n = 37$	*P* Value	Controls Followed Up $n = 257$	Controls Not Followed Up $n = 262$	*P* Value
Maternal BMI	23.2	24.8	.07	22.6	22.4	.08
Mother obese* (%)	7/57 (12.3)	8/36 (22.2)	.18	22/255 (8.6)	19/260 (7.3)	.58
Birth–weight ratio	1.10	1.09	.76	1.06	1.05	.22
Maternal triglyceride (mmol/L)	2.32	2.23	.70	1.89	1.84	.22
Maternal glucose (mmol/L)	9.48	9.57	.83	6.33	6.22	.07
Cord serum insulin (pmol/L)	167.4	122.2	.11	105.1	109.0	.33

* A total of six offspring across these categories were missing the data on maternal prepregnant BMI that were used to classify obesity status.

which the study cohort was derived[16] was very similar to prevalence estimates in other populations of non-Hispanic whites. However, the cohort may have had less severe glucose intolerance at presentation or after diagnosis than in populations with poorer access to health care or higher rates of either GDM or maternal obesity.[10,34] It is possible that intrauterine exposure to more severe maternal diabetes may increase the risk of childhood obesity. Although meaningful statistical comparisons cannot be made with our subgroup of five insulin-treated mothers, these five women represented a minority of the GDM cases identified in the population-based sample of 2019 women who were screened.

All previous studies of childhood obesity in the offspring of mothers with GDM also have included mothers with known IDDM[12,14,15,35] or NIDDM.[13] A Swedish study, the only to report results separately for offspring of mothers with GDM, showed no association between GDM and childhood obesity.[35] The other studies, grouping all mothers with diabetes, reported an overall association between maternal diabetes during pregnancy and offspring obesity. In one report from the Northwestern Diabetes in Pregnancy Study, BMI in the offspring of mothers with diabetes was compared with that in a control group.[15] Mean BMI values at an average age of 12 years were higher in the 88 offspring of mothers with diabetes than in the 80 control offspring (22.8 vs 20.3). This finding is difficult to interpret, because the offspring of mothers with GDM were not examined separately; the control group was not matched on markers of social status; and the BMI values were not adjusted for age, sex, stage of sexual maturity, or maternal BMI. Adjusting for maternal obesity is necessary to determine whether the offspring obesity risk is from the effects of an altered intrauterine environment or from obesity genes inherited from the mother. Effects from the intrauterine environment are potentially modifiable by interventions to improve glucose control during pregnancy.

Pettitt and colleagues, studying the Pima Indians in Arizona, compared obesity rates in a large cohort of offspring from diabetic and nondiabetic pregnancies.[13] The risk of obesity (>140% of median weight for height) was two to three times higher in childhood and adolescence among the offspring of mothers with diabetes. This increased risk was present independent of both maternal obesity and birth weight.[36] However, the high underlying genetic pre-

disposition to obesity and diabetes in the Pima[37] makes the findings from this population difficult to generalize, and these reports do not indicate what proportion of mothers with diabetes had known NIDDM before pregnancy.[38]

Our study focused on obesity in children between 5 and 10 years of age. Data from the previous studies suggest that it is not until after ~5 years of age that the weights of offspring of diabetic mothers begin to differ from the growth reference[14,39] or from controls.[12] Thus, differences between offspring of mothers with GDM and offspring of control mothers may have been diminished in our study by averaging BMI over the ages of 5 to 10 years. However, when only those subjects with measurements between 8 and 10 years of age were compared (33 GDM vs 133 control offspring), there still was no significant difference in obesity rates (18% vs 19%; $P = .93$) or in mean BMI z score (0.38 versus 0.30; $P = .80$) at 8 to 10 years of age.

Our study provided an ideal control group. The screening criteria used on the mothers to establish GDM or control status were identical, and all mothers were enrolled at the same time. Furthermore, because the control mothers and mothers with GDM were all insured by the same HMO, this minimized differences in socioeconomic status and access to medical care that may be related to both glucose control in pregnancy and offspring obesity risk. Race and ethnicity, which also are important factors in both GDM risk[10] and childhood obesity risk[40] were not confounding variables in this study. We had incomplete follow-up of this cohort, but we were able to adjust our analyses for baseline differences in maternal obesity, and this adjustment did not affect our conclusions.

Our findings indicate that mothers with mild, diet-treated GDM do not have metabolic alterations that affect the intrauterine environment sufficiently to increase the risk of childhood obesity in their offspring. It is possible that any effects of GDM on the intrauterine environment that increase childhood obesity risk are obscured by the greater impacts of diet and physical activity patterns during childhood. Our results, together with those of previous studies, suggest that the risk of childhood obesity in offspring from diabetic pregnancies may depend on the form and severity of maternal diabetes. Future studies must examine separately mothers with IDDM, NIDDM, and GDM. To delineate further the possible relationship between diabetes during pregnancy and offspring obesity, these studies must examine prospectively fat and carbohydrate metabolism and body fat distribution both in pregnant mothers and in their offspring.

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REFERENCES

1. White P, Koshy P, Duckers J. The management of pregnancy complicating diabetes and of children of diabetic mothers. *Med Clin North Am.* 1953;37:1481–1496
2. Farquhar JW. Prognosis for babies born to diabetic mothers in Edinburgh. *Arch Dis Child.* 1969;44:36–47
3. Cummins M, Norrish M. Follow-up of diabetic mothers. *Arch Dis Child.* 1980;55:259–264
4. Breidahl HD. The growth and development of children born to mothers with diabetes. *Med J Aust.* 1966;1:268–270
5. Hagbard L, Olow I, Reinand T. A follow-up study of 514 children of diabetic mothers. *Acta Paediatr.* 1959;48:184–197
6. Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes.* 1980;29:1023–1035
7. Lucas A. Programming by early nutrition in man. In: Bock GR, Whelan J, eds. *The Childhood Environment and Adult Disease*. Chichester, NY: Wiley; 1991:38–55
8. Whitaker RC, Dietz WH. The role of the prenatal environment in the development of obesity. *J Pediatr*. In press
9. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes.* 1979;28: 1039–1057
10. Dooley SL, Metzger BE, Cho N, Liu K. The influence of demographic and phenotypic heterogeneity on the prevalence of gestational diabetes mellitus. *Int J Gynaecol Obstet.* 1991;35:13–18
11. Jacobson JD, Cousins L. A population-based study of maternal and perinatal outcome in patients with gestational diabetes. *Am J Obstet Gynecol.* 1989;161:981–986
12. Vohr BR, Lipsitt LP, Oh W. Somatic growth of children of diabetic mothers with reference to birth size. *J Pediatr.* 1980;97:196–199
13. Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med.* 1983;308:242–245
14. Silverman BL, Rizzo T, Green OC, et al. Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes.* 1991;40(suppl 2):121–125
15. Silverman BL, Metzger BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinism. *Diabetes Care.* 1995;18:611–617
16. Magee MS, Walden CE, Benedetti TJ, Knopp RH. Influence of diagnostic criteria on the incidence of gestational diabetes and perinatal morbidity. *JAMA.* 1993;269:609–615
17. Knopp RH, Magee MS, Walden CE, Bonet B, Benedetti TJ. Prediction of infant birth weight by GDM screening tests: importance of plasma triglyceride. *Diabetes Care.* 1992;15:1605–1613
18. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol.* 1982;144:768–773
19. Kraemer HC, Berkowitz RI, Hammer LD. Methodological difficulties in studies of obesity. I. Measurement issues. *Ann Behav Med.* 1990;12: 112–118
20. Rolland-Cachera MF, Sempe M, Guilloud-Bataille M, Patois E, Pequignot-Guggenbuhl F, Fautrad V. Adiposity indices in children. *Am J Clin Nutr.* 1982;36:178–184
21. Roche AF, Siervogel RM, Chumlea WC, Webb P. Grading body fatness from limited anthropometric data. *Am J Clin Nutr.* 1981;34:2831–2838
22. Gutin B, Basch C, Shea S, et al. Blood pressure, fitness and fatness in 5- and 6-year-old children. *JAMA.* 1990;264:1123–1127
23. Laskarzewski P, Morrison JA, Mellies MJ, et al. Relationships of measurements of body mass to plasma lipoproteins in schoolchildren and adults. *Am J Epidemiol.* 1980;111:395–406
24. Ronnemaa T, Knip M, Lautala P, et al. Serum insulin and other cardiovascular risk indicators in children, adolescents and young adults. *Ann Med.* 1991;23:67–72
25. Frisancho AR. *Anthropometric Standards for the Assessment of Growth and Nutritional Status.* Ann Arbor, MI: University of Michigan Press; 1990
26. Robinson TN. Defining obesity in children and adolescents: clinical approaches. *Crit Rev Food Sci Nutri.* 1993;33:313–320
27. Hamill PV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr.* 1979;32:607–629
28. Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M. Fetal growth and perinatal viability in California. *Obstet Gynecol.* 1982;59:624–632
29. Sosenko IR, Kitzmiller JL, Loo SW, Blix P, Rubenstein AH, Gabbay KH. The infant of the diabetic mother: correlation of increased cord C-

peptide levels with macrosomia and hypoglycemia. *N Engl J Med.* 1979;301:859–862
30. Metzger BE. Biphasic effects of maternal metabolism on fetal growth: quintessential expression of fuel-mediated teratogenesis. *Diabetes.* 1991; 40(suppl 2):99–105
31. National Institutes of Health Consensus Development Panel on the Health Implications of Obesity. Health implications of obesity: National Institutes of Health Consensus Development Conference Statement. *Ann Intern Med.* 1985;103:147–151
32. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. Overweight prevalence and trends for children and adolescents: National Health and Nutrition Examination Surveys, 1963 to 1991. *Arch Pediatr Adolesc Med.* 1995;149:1085–1091
33. Garn SM, Clark DC. Trends in fatness and the origins of obesity. *Pediatrics.* 1976;57:443–456
34. Dooley SL, Metzger BE, Cho NH. Gestational diabetes mellitus: influence of race on disease prevalence and perinatal outcome in a U.S. population. *Diabetes.* 1991;40(suppl 2):25–29
35. Persson B, Gentz J, Moller E. Follow-up of children of insulin dependent (type I) and gestational diabetic mothers. *Acta Paediatr Scand.* 1984;73: 778–784
36. Pettitt DJ, Knowler WC, Bennett PH, Aleck KA, Baird HR. Obesity in offspring of diabetic Pima Indian women despite normal birth weight. *Diabetes Care.* 1987;10:76–80
37. Knowler WC, Pettitt DJ, Saad MF, et al. Obesity in the Pima Indians: its magnitude and relationship with diabetes. *Am J Clin Nutr.* 1991;53: 1543s–1551s
38. Pettitt DJ, Nelson RG, Saad MF, Bennett PH, Knowler WC. Diabetes and obesity in the offspring of Pima Indian women with diabetes during pregnancy. *Diabetes Care.* 1993;16(suppl 1):310–314
39. Silverman BL, Landsberg L, Metzger BE. Fetal hyperinsulinism in offspring of diabetic mothers: association with the subsequent development of childhood obesity. *Ann NY Acad Sci.* 1993;699:36–45
40. Campaigne BN, Morrison JA, Schumann BC, et al. Indexes of obesity and comparisons with previous national survey data in 9- and 10-year-old black and white girls: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr.* 1994;124:675–680

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