Effect of Treatment of Gestational Diabetes Mellitus on Obesity in the Next Generation

MATTHEW W. GILLMAN, MD, SM[1]
HELENA OAKEY, PHD[2]
PETER A. BAGHURST, PHD[3]
ROBERT E. VOLKMER, BA[4]
JEFFREY S. ROBINSON, FRANZCOG[2]
CAROLINE A. CROWTHER, FRANZCOG[2]

OBJECTIVE — Gestational diabetes mellitus (GDM) may cause obesity in the offspring. The objective was to assess the effect of treatment for mild GDM on the BMI of 4- to 5-year-old children.

RESEARCH DESIGN AND METHODS — Participants were 199 mothers who participated in a randomized controlled trial of the treatment of mild GDM during pregnancy and their children. Trained nurses measured the height and weight of the children at preschool visits in a state-wide surveillance program in the state of South Australia. The main outcome measure was age- and sex-specific BMI *Z* score based on standards of the International Obesity Task Force.

RESULTS — At birth, prevalence of macrosomia (birth weight ≥4,000 g) was 5.3% among the 94 children whose mothers were in the intervention group, and 21.9% among the 105 children in the routine care control group. At 4- to 5-years-old, mean (SD) BMI *Z* score was 0.49 (1.20) in intervention children and 0.41 (1.40) among controls. The difference between treatment groups was 0.08 (95% CI −0.29 to 0.44), an estimate minimally changed by adjustment for maternal race, parity, age, and socio-economic index (0.08 [−0.29 to 0.45]). Evaluating BMI ≥85th percentile rather than continuous BMI *Z* score gave similarly null results.

CONCLUSIONS — Although treatment of GDM substantially reduced macrosomia at birth, it did not result in a change in BMI at age 4- to 5-years-old.

Diabetes Care **33:964–968, 2010**

In animal models, experimentally induced gestational diabetes mellitus (GDM) causes increased offspring adiposity. If the offspring is female, she is likely to develop GDM herself when she becomes pregnant, perpetuating an intergenerational vicious cycle of diabetes and obesity (1,2). Given that obesity and diabetes are epidemic in the developed world and emerging rapidly as primary threats to health in the developing world (3), this sequence—if it also occurs in human populations—could have major adverse effects on health for some time to come. Interrupting the cycle would be a public health imperative.

The extent to which these influences actually operate in human populations, however, is not known. Evaluating whether GDM causes obesity in even one subsequent generation is challenging. Observational studies showing that diabetes during pregnancy is associated with higher offspring BMI emanate predominantly from populations with high prevalences of obesity and diabetes (4,5). General population samples, in which the average severity of GDM is milder, typically yield more modest or null associations (6,7). One hypothesis for these differences across studies is that effective treatment of mild GDM reduces the risk of obesity in the child. In a U.S. managed care population, Hillier et al. (8) found an almost twofold increased risk of elevated weight at 5- to 7-years-old among children whose mothers had untreated GDM, whereas the association with treated GDM was weaker, similar to that of the milder impaired glucose tolerance.

While observational studies can raise the hypothesis that treatment of GDM mitigates an otherwise high risk of child obesity, only a randomized controlled trial can address this hypothesis in an unconfounded manner. No such studies exist. The aim of this study was to examine the effect of the treatment of GDM on the BMI of 4- to 5-year-old children whose mothers participated in a randomized controlled trial of treatment for mild GDM in pregnancy. To achieve this aim, we took advantage of the temporal and geographic co-existence of a randomized controlled trial and a child height/weight surveillance system. Given that the randomized intervention resulted in lower weight at birth, and that lower birth weight is associated with lower BMI in childhood (9), we hypothesized that the intervention would also result in lower BMI at age 4- to 5-years-old.

RESEARCH DESIGN AND METHODS

Subjects and measurements

The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) was a multi-center randomized controlled trial of treatment of mild GDM. From 1993 to 2003, the investigators randomly allocated women who had mild GDM between 24 and 34 weeks' gestation to an intervention group consisting of dietary advice, blood glucose monitoring, and insulin therapy if necessary, or to a routine care control group. Approximately 20% of the intervention participants received insulin. The intervention reduced serious perinatal complications from 4 to 1%, and it reduced the prevalence of macrosomia (birth weight ≥4,000 g) from 21 to 10% (10). Just over half of the 1,000 mothers who participated in the trial lived in the state of South Australia.

South Australia's Children, Youth and Women's Health Service (CYWHS

From the [1]Obesity Prevention Program, Department of Population Medicine, Harvard Medical School/Harvard Pilgrim Health Care Institute, Boston, Massachusetts; the [2]Discipline of Obstetrics and Gynaecology, Australian Research Centre for the Health of Women and Babies, University of Adelaide, Adelaide, Australia; the [3]Discipline of Paediatrics and Public Health, Australian Research Centre for the Health of Women and Babies, University of Adelaide, Adelaide, Australia; and the [4]Children, Youth, and Women's Health Service, Public Health Research Unit, Adelaide, Australia.
Corresponding author: Matthew W. Gillman, matthew_gillman@hms.harvard.edu.
Received 2 October 2009 and accepted 26 January 2010. Published ahead of print at http://care.diabetesjournals.org on 11 February 2010. DOI: 10.2337/dc09-1810.

See accompanying articles, p. 1080, 1115, and 1146.

and called Child and Youth Health until 2004) provides a range of health and social services and programs for parents, children, and young people across the state. As part of these services, child and family health nurses have performed health checks on 4- to 5-year-old children at all kindergartens and preschool centers since 1995. During these visits, they have used a standard protocol to measure height with a fixed tape and weight of children dressed in underwear, and they have recorded the data electronically (11). From 1997 through 2007, the period of child follow-up in this study, the average participation rate was ~65% of South Australian children. To merge the ACHOIS trial data with the CYWHS surveillance data, we used the child's date of birth, sex, name, and address as the linking variables. We required an exact match for all four variables.

There were 526 mothers of 542 children from South Australia that participated in the ACHOIS trial. Two stillbirths occurred in this group leaving 524 mothers of 540 children for follow-up. Given that CYWHS nurses measured preschool height and weight on ~65% of the children in the state, ~351 (65% of 540) were eligible for inclusion in this study. Through the linking process, we obtained height and weight data at 4- to 5-years-old on 241 children, among whom 29 weight measurements were missing and 1 (162 kg) was implausible. We further excluded the 6 pairs of twins leaving a sample for analysis of 199 mothers and their singleton children representing ~60% of eligible children. Figure 1 shows participant flow by treatment group.

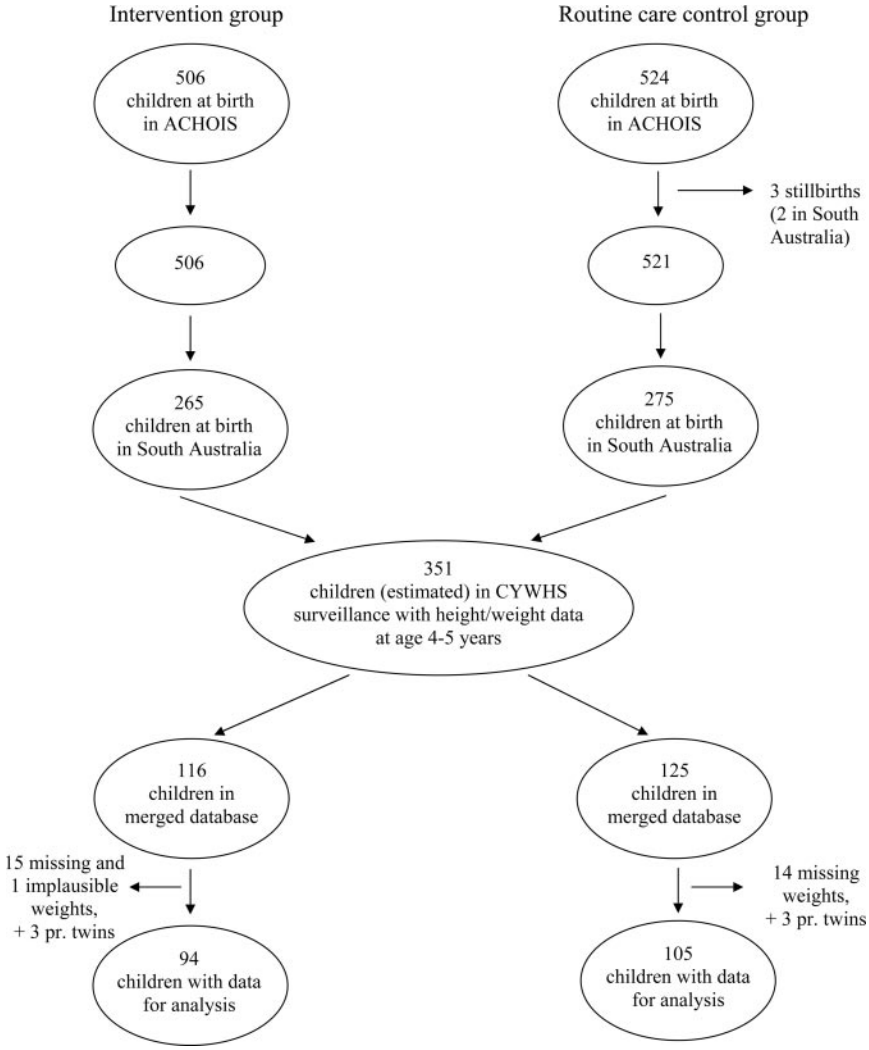

Figure 1—*Participants in a study assessing BMI among 4- to 5-year-old children whose mothers participated in a randomized controlled trial of treatment of mild gestational diabetes.*

Data analysis

The outcome variable was BMI, calculated as child's weight (kg) divided by the square of height (m). We expressed BMI as continuous *Z* score based on age- and sex-specific standards of the International Obesity Task Force (12). We first examined simple differences in BMI-*Z* by treatment group, then used multiple linear regression analysis to adjust for potentially confounding maternal and child covariates. In secondary analyses, we used multivariable log binomial regression to examine the effects of treatment on a dichotomous outcome, BMI at or exceeding the age- and sex-specific 85th percentile. We reported regression estimates or prevalence risk ratios (relative risk) along with 95% CIs. We used SAS version 9.2 (Cary, NC).

Ethics

Through the linkage of the two data sources, we created a de-identified dataset. The Human Research Ethics Committee of CYWHS approved the protocol. The researchers were independent of the funders. The sponsors of the study had no roles in study design; collection, analysis, and interpretation of data; writing the article; or the decision to submit it for publication.

RESULTS — Among the 199 participating mothers, the distributions of factors according to treatment group at trial baseline were similar to those among the 524 eligible South Australians and all 1,000 mothers recruited into ACHOIS (Table 1). At birth, prevalence of macrosomia was 5.3% among the 94 children whose mothers were in the intervention group and 21.9% among the 105 in the routine care control group. A similar contrast was evident among all South Australian and all ACHOIS subjects (Table 1).

At 4- to 5-years-old, mean (SD) BMI *Z* score was 0.49 (1.20) among intervention children and 0.41 (1.40) in the routine care group (Table 2); 33.0 and 27.6%, respectively, had BMI at or exceeding the 85th percentile. Because the participants' mothers had relatively high BMI themselves, these estimates were higher than the prevalence of 15.9–20.1% among the over 100,000 children in the CYWHS surveillance database for the years 1997-2007 (13) (and unpublished CYWHS data).

For child BMI *Z* score, the unadjusted difference between treatment groups was 0.08 (95% CI −0.29 to 0.44). After adjustment for maternal race, parity, age, and socio-economic index, the estimate was minimally changed (0.08 [−0.29 to

Table 1—*Characteristics of participants at trial baseline in pregnancy and at birth*

	This study		All South Australian subjects in ACHOIS		All subjects in ACHOIS	
n (children)	199		540		1,030	
	I	C	I	C	I	C
n	94	105	265	275	506	524
Maternal characteristics at trial baseline			Mean			
Age (years)	30.3	28.9	30.0	29.4	30.9	30.1
Results from oral glucose tolerance test						
Fasting glucose (mmol/l)	4.9	4.8	4.9	4.9	4.8	4.8
			Median			
BMI (kg/m^2)	27.7	25.3	27.4	26.5	26.8	26.0
Gestational age at entry (week)	29.5	29.7	29.4	29.7	29.1	29.2
Results from oral glucose tolerance test						
2-h glucose	8.4	8.6	8.5	8.6	8.6	8.5
			%			
Race						
White	85.1	89.5	82.1	87.6	72.7	77.6
Asian	11.7	8.6	12.1	9.0	18.8	14.1
Aboriginal/other	3.2	1.9	5.8	3.4	8.6	8.2
Socio-economic index						
Overseas					4.7	4.5
Low	48.9	34.3	45.5	39.3	31.2	24.7
Low-mid	11.7	22.9	17.5	24.0	21.6	25.1
Mid-high	26.6	22.9	23.3	21.7	21.8	22.4
High	12.8	20.0	13.6	15.0	20.6	23.3
Primiparous	44.7	43.8	48.2	46.4	43.3	49.2
Child characteristics at birth			Mean			
Birth weight (bw), g	3,346	3,585	3,290	3,468	3,335	3,482
			%			
SGA (bw <10th percentile)	9.6	6.7	9.1	7.3	6.5	7.3
LGA (bw >90th percentile)	10.6	22.9	10.2	21.1	13.4	21.9
Macrosomia (bw > 4,000 g)	5.3	21.9	7.5	18.5	9.7	21.0
Sex (male)	50.0	52.4	52.1	52.7	51.4	49.8

This study comprised singleton pregnancies. In the original ACHOIS study, however, because of twin pregnancies, the number of participating mothers (524 in South Australia, 1,000 overall) was lower than the number of children. C, routine care control group; I, intervention group; LGA, large for gestational age, percentiles from general population reference; SGA, small for gestational age, percentiles from general population reference.[12]

0.45]). We found similar null results for BMI exceeding the 85th percentile. For this outcome, the multivariable adjusted relative risk for treated versus untreated GDM was 1.17 (0.77–1.78), which was marginally different from the unadjusted estimate (Table 2).

Data on maternal BMI at trial entry in early pregnancy were available for a total of 178 mother-child pairs. Additional adjustment for this variable did not materially change the estimates for the treatment effects on either child outcome, BMI *Z* score, or BMI ≥85th percentile (data not shown).

CONCLUSIONS — In this follow-up study of children whose mothers participated in a randomized controlled trial, we did not find that treatment of mild GDM during pregnancy reduced BMI in 4- to 5-year-olds even though macrosomia at birth was substantially lower in the intervention group than the control group. Statistical power was adequate. The multivariable-adjusted effect estimate for BMI *Z* score was 0.08 with a lower 95% confidence limit of −0.29. Thus we effectively ruled out any reduction in BMI greater than one-fourth to one-third of SD, which equates to only 0.3–0.4 kg/m^2 (also about 0.3–0.4 kg) for the average 4- to 5-year-old boy or girl whose BMI is in the range of 16–17 kg/m^2.

Given that animal experiments and many observational studies suggest that GDM may cause offspring obesity, it is natural to wonder why the results of this study were null. Observational studies may overestimate treatment effects because of confounding; minimizing confounding is the principal reason for doing randomized trials. Because all mothers in ACHOIS had mild GDM, we could not assess the effect of treatment of more severe GDM, which might be necessary to

Table 2—*Effect of treatment of mild gestational diabetes on child BMI at age 4- to 5-years*

	Intervention group	Routine care control group	Unadjusted treatment effect	Adjusted* treatment effect
	Mean (SD)			
Age at measurement (years)	4.7 (0.2)	4.7 (0.4)	Regression estimate (95% CI)	
Weight (kg)	19.1 (2.9)	19.4 (4.2)	−0.31 (−1.33 to 0.70)	−0.37 (−1.40 to 0.66)
Height (cm)	107.9 (4.6)	108.5 (5.8)	−0.61 (−2.08 to 0.86)	−0.66 (−2.16 to 0.85)
BMI *Z* score†	0.49 (1.20)	0.41 (1.40)	0.08 (−0.29 to 0.44)	0.08 (−0.29 to 0.45)
	N (%)		Relative risk (95% CI)	
BMI > 85th percentile†	31 (33.0)	29 (27.6)	1.19 (0.78–1.82)	1.17 (0.77–1.78)

Data from 199 mother-child pairs from South Australia.*Adjusted for maternal race, parity, age, and socio-economic index; †calculated from standards of the International Obesity Task Force.[12]

program offspring obesity. Another possibility is that postnatal factors that determine a child's height and weight, such as diet and physical activity, overwhelm any effects of treating GDM during pregnancy. We did not have data on child behaviors to assess this possibility.

Alternatively, the long-term effect of GDM on childhood obesity and its reduction through treatment may not appear until later in childhood. In studies based in a specialty clinic, Metzger and colleagues (5) observed that children of diabetic mothers were heavier than population control subjects at birth, but not at ages 1, 2, or 3 years. Only in school age did the excess weight reappear. Likewise, in a study of Pima Indian sib-pairs, associations of GDM with higher offspring BMI were apparent from age 9 years through early adulthood, but not at 6–9 years of age (4). Consistent with these observations, in the pre-birth cohort study Project Viva, we recently reported that children of mothers with GDM had less rapid weight gain in the first 6 months of life than children of nondiabetic mothers (14). The explanation for the age-associated disappearance and re-emergence of the association of GDM with higher child weight status is unknown. One possibility is that GDM has differential effects on lean and fat mass in the early years of life. In the Hyperglycemia and Adverse Pregnancy Outcomes Study, higher maternal glucose levels were associated with the sum of skinfold thicknesses at birth (a direct measure of adiposity) (15). Among 3-year-old children in Project Viva, GDM was associated with increased systolic blood pressure and the sum of skinfold thicknesses (a direct measure of adiposity) but not with BMI, which comprises both lean and fat mass (16). Unfortunately, we could not directly evaluate whether mild GDM caused higher BMI in later childhood in the present analysis because the CYWHS surveillance of the height and weight of the children does not extend past 5 years of age.

A less likely explanation for null results is selection bias. We obtained outcome data on fewer than half of South Australian ACHOIS subjects. However, differences according to treatment group at baseline and in the newborn period were similar among participants and nonparticipants, and adjustment for a range of covariates did not materially change effect estimates. These observations suggest that loss to follow-up did not substantially bias the results.

Inaccurate outcome measurement is also unlikely to explain the null results. Child and family health nurses measured height and weight with standard protocols. Moreover, while nondifferential error in exposure measurement can bias estimates toward the null value, noise in measurement of the outcome merely makes estimates less precise but does not introduce bias.

It is also unlikely that the observed effects of the ACHOIS intervention on infant outcomes were the result of chance, and that further child follow-up revealed the fallacy. The intervention reduced the risk of several newborn morbidities in addition to macrosomia, including the primary outcomes of fetal and neonatal death and birth injuries (10). Also, recent data from a U.S.-based randomized trial of the treatment of mild GDM showed reductions in macrosomia (6 vs. 14%), newborn fat mass, caesarean section, and shoulder dystocia, although a composite neonatal end point was not demonstrably different in the intervention versus control group (17). Consistency across these two studies suggests a real effect of GDM treatment on important infant health outcomes.

To conduct this study, we recognized that routine surveillance offered a low-cost way to obtain outcome data for research studies. This type of collaboration has the potential to increase knowledge and improve health by combining research studies, public health programs, and surveillance activities.

Measuring health outcomes among children whose mothers participated in randomized trials during pregnancy is not only the most direct way of confirming animal experiments of prenatal programming, but also may reveal how to improve child and adult health outcomes by intervening at early stages of human development. In this study, however, we did not substantiate our hypothesis that treatment of mild GDM during pregnancy reduces BMI in preschool-age children. Studies are needed that involve longer follow-up of children whose mothers participated in completed randomized trials of GDM treatment. Moreover, any newly designed trials of treatment or prevention of GDM would benefit from funding to follow the children long term with measures of body composition.

Acknowledgments— Funding for this study was provided by the U.S. National Institutes of Health (HL 68041), the Australian National Health and Medical Research Council (NHMRC Project Grants 950096 and 157914), and the Harvard Medical School and the Harvard Pilgrim Health Care Foundation. M.W.G. is a recipient of the Australia-Harvard Fellowship from the Harvard Club of Australia.

No potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in poster form at the 27th Annual Scientific Meeting of

The Obesity Society, Washington, D.C., 24–28 October 2009.

We thank Libby Roughead for introducing the investigators to the CYWHS surveillance system; Chris Miller, database administrator; and Kristyn Willson, statistician responsible for the original ACHOIS analyses.

References

1. Aerts L, Van Assche FA. Animal evidence for the transgenerational development of diabetes mellitus. Int J Biochem Cell Biol 2006;38:894–903
2. Plagemann A, Harder T, Dudenhausen JW. The diabetic pregnancy, macrosomia, and perinatal nutritional programming. Nestle Nutr Workshop Ser Pediatr Program 2008;61:91–102
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
4. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, Knowler WC. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000;49:2208–2211
5. Silverman BL, Rizzo T, Green OC, Cho NH, Winter RJ, Ogata ES, Richards GE, Metzger BE. Long-term prospective evaluation of offspring of diabetic mothers. Diabetes 1991;40:121–125
6. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. Pediatrics 2003;111:e221–e226
7. Whitaker RC, Pepe MS, Seidel KD, Wright JA, Knopp RH. Gestational diabetes and the risk of offspring obesity. Pediatrics 1998;101:e9
8. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. Diabetes Care 2007;30:2287–2292
9. Oken E, Gillman MW. Fetal origins of obesity. Obes Res 2003;11:496–506
10. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–2486
11. Children, Youth, and Women's Health Services, Health Surveillance in Child and Family Health Division, Government of South Australia. CYWHS Nursing and Midwifery Clinical Standard. *Measurement and assessment of the length/height of infants and children, and measurement and assessment of weight in infants and children*. 2007 (Document cs2007-505). Available from the Clinical Governance, Education, and Research intranet. Accessed 22 February 2009
12. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240–1243
13. Vaska V, Volkmer R. Increasing prevalence of obesity in South Australian 4-year-olds: 1995–2002. J Paediatr Child Health 2004;40:353–355
14. Parker M, Rifas-Shiman SL, Belfort MB, Taveras EM, Oken E, Gillman MW. Pre- and peri-natal predictors of weight gain in early infancy. Pediatric Academic Societies' Annual Meeting, 2–5 May 2009, Baltimore Maryland
15. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes 2009;58:453–459
16. Wright CS, Rifas-Shiman SL, Rich-Edwards JW, Taveras EM, Gillman MW, Oken E. Intrauterine exposure to gestational diabetes, child adiposity, and blood pressure. Am J Hypertens 2009;22:215–220
17. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Thorp JM Jr, Sciscione A, Catalano P, Harper M, Saade G, Lain KY, Sorokin Y, Peaceman AM, Tolosa JE, Anderson GB, Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339–1348