Intrauterine Exposure to Diabetes Conveys Risks for Type 2 Diabetes and Obesity

A Study of Discordant Sibships

Dana Dabelea, Robert L. Hanson, Robert S. Lindsay, David J. Pettitt, Giuseppina Imperatore, Momin M. Gabir, Janine Roumain, Peter H. Bennett, and William C. Knowler

Intrauterine exposure to diabetes is associated with an excess of diabetes and obesity in the offspring, but the effects of intrauterine exposure are confounded by genetic factors. To determine the role of the intrauterine diabetic environment per se, the prevalence of diabetes and the mean BMI were compared in siblings born before and after their mother was recognized as having diabetes. Nuclear families in which at least one sibling was born before and one after the mother was diagnosed with type 2 diabetes were selected. Consequently, the siblings born before and after differed in their exposure to diabetes in utero. A total of 58 siblings from 19 families in which at least one sibling had diabetes were examined at similar ages (within 3 years). The risk of diabetes was significantly higher in siblings born after the mother developed diabetes than in those born before the mother's diagnosis of diabetes (odds ratio 3.7, $P = 0.02$). In 52 families, among 183 siblings without diabetes, the mean BMI was 2.6 kg/m^2 higher in offspring of diabetic than in offspring of nondiabetic pregnancies ($P = 0.003$). In contrast, there were no significant differences in risk of diabetes or BMI between offspring born before and after the father was diagnosed with diabetes. Intrauterine exposure to diabetes per se conveys a high risk for the development of diabetes and obesity in offspring in excess of risk attributable to genetic factors alone. *Diabetes* 49:2208–2211, 2000

Type 2 diabetes has strong genetic and environmental risk factors. Previous studies have shown greater transmission of type 2 diabetes to offspring from mothers than from fathers (1–3), and a significantly higher prevalence of diabetes in offspring of women with diabetes during pregnancy than in offspring of nondiabetic and prediabetic women (2). Intrauterine exposure to diabetes is also associated with a higher prevalence of impaired glucose tolerance in adolescence (4) and with an excess of obesity, especially during the first 20 years of life (5–7). Nevertheless, the effects of intrauterine exposure to diabetes may be confounded by genetic factors. For example, women who develop diabetes at an earlier age might carry more diabetes-susceptibility genes than those who develop diabetes later. Hence, they might transmit greater genetic susceptibility to their offspring.

The Pima Indians of Arizona have the world's highest incidence and prevalence of type 2 diabetes (8,9). Both genetic and environmental risk factors contribute to the high rate of diabetes in the Pimas. In Pima Indian children aged 5–19 years, the strongest single risk factor for type 2 diabetes was exposure to diabetes in utero (10). To determine the role of intrauterine diabetic environment, which is in addition to genetic transmission of susceptibility, a sibship study was designed to compare the prevalence of type 2 diabetes and the BMI in Pima Indian siblings born before and after their mother was diagnosed with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data were taken from the longitudinal study of diabetes and its complications conducted since 1965, among the Pima Indian residents of the Gila River Indian Community in central Arizona (8). Standardized biennial examinations included measurements of venous plasma glucose 2 h after a 75-g oral glucose load, height, weight, and blood pressure. Medical history was recorded and data on family relationships were collected. BMI was calculated as weight (kg) divided by height (m) squared. Diabetes was diagnosed according to the 1985 World Health Organization criteria (11).

Nuclear families were selected in which at least one sibling was born before and at least one after the mother was diagnosed with type 2 diabetes. The siblings had the same mother and father; consequently, a major difference between those born before and after was in exposure to intrauterine diabetes. Exposure to diabetes in utero was considered present if the mother had type 2 diabetes diagnosed before the delivery of the child and absent if diabetes was diagnosed after delivery.

For the analysis of diabetes, 19 nuclear families were identified with two or more siblings in which at least one sibling had diabetes and one did not and with at least one sibling born before and at least one born after the mother was diagnosed with diabetes. Because the prevalence of diabetes is age dependent, data from examinations of siblings at similar ages were used. For each sibship, sets of siblings examined within a 3-year age interval (i.e., 6 to <9 years and 9 to <12 years) were selected. When sets of siblings could be selected from more than one such age interval, only the set with the most information regarding diabetes prevalence was selected. The relative risk of type 2 diabetes in offspring, as a function of exposure to diabetes in utero, was estimated by logistic regression analysis, conditional on sibship, allowing variable numbers of matched case and control subjects (12). Families in which either none or all of the siblings examined within an age interval were diabetic were not informative for this analysis and thus were not included.

For the analysis of BMI, 52 families were selected in which at least one sibling was born before and at least one was born after the mother was diagnosed with diabetes. From each sibship, siblings were selected who had been examined when nondiabetic and within a 3-year age interval. When more than one

From the Diabetes and Arthritis Epidemiology Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Phoenix, Arizona.

Address correspondence to William C. Knowler, MD, Diabetes and Arthritis Epidemiology Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 1550 E. Indian School Rd., Phoenix, AZ 85014. E-mail: knowler@nih.gov.

Received for publication 20 December 1999 and accepted in revised form 22 August 2000.

TABLE 1
Characteristics of families informative for diabetes in the offspring

	Families defined by prediabetic and diabetic	
	Mother	Father
Number of families	19	24
Mother's age at diagnosis of diabetes (years)	29	37*
Father's age at diagnosis of diabetes (years)	40†	33
Offspring of prediabetic parent (n)	36	49
Age of mother at birth of offspring (years)	24	24
Age of father at birth of offspring (years)	33	31
Age of offspring at exam (years)	24	23
Offspring of diabetic parent (n)	22	35
Age of mother at birth of offspring (years)	33	29
Age of father at birth of offspring (years)	39	35
Age of offspring at exam (years)	22	22

Data are n or means. *Mother's age at diagnosis known in 21 of these 24 families; †father's age at diagnosis is known in 12 of these 19 families.

set of examinations from a sibship were available, the set that maximized the number of siblings examined was used. If the same number of siblings was available from more than one age interval, the younger set was used. The effect of intrauterine diabetes exposure on BMI in offspring was estimated by analysis of variance with control for sibship.

To determine whether the sibling differences were specifically due to differences in maternal diabetes during pregnancy rather than to some other correlate of birth order, similar analyses were performed in other families selected to have siblings born before and after the father was diagnosed with diabetes.

RESULTS

Nineteen nuclear families with 58 siblings (36 born to prediabetic mothers and 22 to diabetic mothers) were informative for the analysis of diabetes in sibships discordant for maternal diabetes (Table 1). Table 1 shows mean ages at diagnosis of diabetes in each parent, of the parents at birth of the offspring, and of the offspring at examination. These data are also shown for the 24 families with 84 siblings studied for the analysis of diabetes in sibships discordant for paternal diabetes. By design, ages at examination of the offspring born before or after the parent developed diabetes were similar, but, by necessity, the parents were older at the birth of the offspring born after the parent developed diabetes. Similar data are shown in Table 2 for the 52 families studied for the analysis of BMI in sibships discordant for maternal diabetes and 56 discordant for paternal diabetes.

TABLE 2
Characteristics of families informative for BMI in the offspring

	Families defined by prediabetic and diabetic	
	Mother	Father
Number of families	52	56
Mother's age at diagnosis of diabetes (years)	29	40*
Father's age at diagnosis of diabetes (years)	41†	34
Offspring of prediabetic parent (n)	121	147
Age of mother at birth of offspring (years)	25	26
Age of father at birth of offspring (years)	30	31
Age of offspring at exam (years)	13	13
Offspring of diabetic parent (n)	62	79
Age of mother at birth of offspring (years)	32	31
Age of father at birth of offspring (years)	37	37
Age of offspring at exam (years)	13	13

Data are n or means. *Mother's age at diagnosis known in 44 of these 56 families; †father's age at diagnosis is known in 26 of these 52 families.

Table 3 shows, in each of the 19 families discordant for maternal diabetes in pregnancy, the number of siblings with diabetes born before and after the mother was diagnosed with type 2 diabetes. In 15 of the sibships, diabetes was more common in the offspring born after the mother's diagnosis of type 2 diabetes, whereas in 4 sibships it occurred only in those born to mothers before diabetes was recognized. The summary odds ratio, from logistic regression analysis conditional on sibship, was 3.7, 95% CI 1.3–11.3, $P = 0.02$. Similar results were found when controlled for sex differences among siblings. In contrast, among 84 siblings from 24 families of diabetic fathers the risk for type 2 diabetes was similar in siblings born after and before the father's diagnosis of type 2 diabetes (odds ratio 1.1, 95% CI 0.3–2.5, $P = 0.8$). Similar results were found when controlled for maternal diabetes and sex.

In 52 families, 183 nondiabetic siblings born either before or after their mother was diagnosed with diabetes had measurements of BMI. The mean BMI in siblings exposed and not exposed to intrauterine diabetes is shown in Fig. 1. The mean BMI was significantly higher in the 62 siblings who were exposed than in the 121 siblings not exposed to diabetes in utero (mean difference [95% CI] 2.6 kg/m^2 (0.9–4.3), $P = 0.003$, controlled for sibship by analysis of variance). In contrast, in 56 families of diabetic fathers, there was no significant dif-

TABLE 3
Number of siblings with diabetes and total number of siblings born before and after mother's diabetes diagnosis, in each family

Family	Number born before/total	Number born after/total
1	0/1	1/1
2	0/1	1/1
3	1/1	0/1
4	0/1	1/1
5	0/1	1/1
6	0/1	1/1
7	0/1	1/1
8	0/1	1/1
9	2/4	1/1
10	1/1	0/1
11	0/1	1/1
12	0/1	2/3
13	0/2	1/1
14	1/3	1/1
15	2/5	1/1
16	3/7	0/1
17	1/2	1/1
18	0/1	1/1
19	1/1	0/2

Summary odds ratio = 3.7 kg/m^2 (95% CI 1.3–11.3).

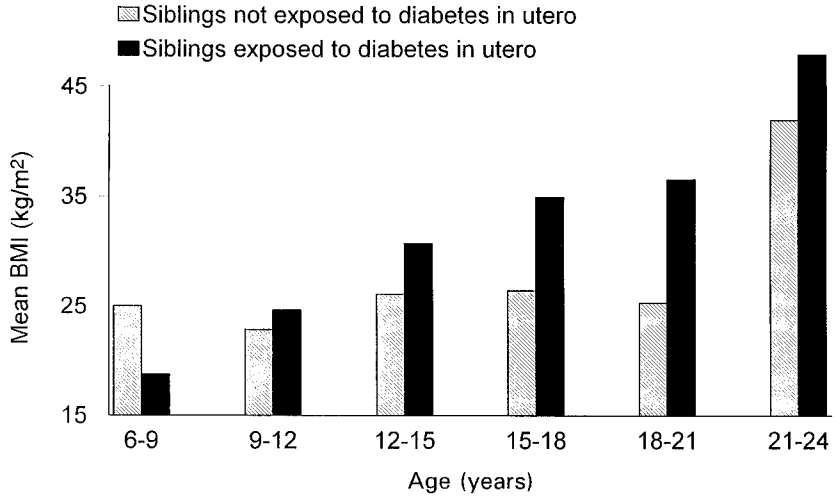

FIG. 1. Mean BMI in siblings exposed and not exposed to diabetic intrauterine environment separated into 3-year age intervals. Siblings exposed have a significantly higher BMI than those unexposed (P = 0.003, controlled for sibship by analysis of variance).

ference in mean BMI between the 79 offspring born after and the 147 offspring born before the father was diagnosed with type 2 diabetes (mean difference 0.4 kg/m^2 [95% CI –0.9 to 1.7], P = 0.5).

DISCUSSION

Type 2 diabetes shows strong familial aggregation, and susceptibility genes have been proposed to explain the increased risk of diabetes in the offspring of diabetic parents. Previous studies in the Pima Indians have shown a much higher prevalence of both type 2 diabetes and obesity in offspring of women who developed diabetes before or during pregnancy than in the offspring of nondiabetic women or the offspring of women who developed diabetes after delivery (prediabetic women) (2,5). This finding is consistent with the greater frequency of diabetes found in offspring of type 2 diabetic mothers than of type 2 diabetic fathers in Pima Indians (2) and in other populations (13,14). These data suggest that exposure to the intrauterine diabetic environment is an important determinant of type 2 diabetes and obesity in adolescence and young adulthood, in addition to the genetic predisposition presumably present in the offspring of both diabetic and prediabetic women (15). An alternative explanation for these earlier observations is that women who develop diabetes at an early age and whose offspring are more frequently exposed to diabetes in utero transmit a greater number of diabetes-susceptibility genes to their offspring than women who develop diabetes later and whose offspring are born before the mother develops the disease. Thus, the greater frequency of diabetes in the offspring of diabetic pregnancies might be due to greater genetic susceptibility in such offspring.

The present study shows that within the same family, offspring born after the mother's diagnosis of diabetes have a much greater risk of developing diabetes and of being obese at an early age than offspring born before the mother is diagnosed with diabetes. In such families, offspring born before and after diabetes develops carry the same risk of inheriting the same susceptibility genes. Consequently, differences in risk among those born before and after the mother develops diabetes are not likely to be due to genetic differences but reflect the effect of intrauterine exposure to diabetes per se. Because some of the prediabetic mothers might have had undiagnosed diabetes during the pregnancy, the analyses were repeated after excluding families of prediabetic mothers who did not undergo glucose tolerance testing during the third trimester. The results were similar, although the differences between the offspring of prediabetic and diabetic mothers were not significant in this much smaller sample (data not shown).

It has been previously shown that the prevalence of diabetes and the prevalence and the degree of obesity have increased over time in Pima Indians (10,16,17) and that there is little effect of maternal age at the offspring's birth on subsequent obesity in the offspring (6). Because there were no significant differences in diabetes or BMI between offspring born before and after the father was diagnosed with type 2 diabetes, it is unlikely that the present findings reflect cohort or birth order effects due to factors other than maternal diabetes.

A higher frequency of maternal than of paternal transmission of diabetes has also been demonstrated in GK rats (18). Furthermore, studies in rats injected with streptozotocin or infused with glucose have demonstrated that hyperglycemia in the mother during the pregnancy leads to impairment of glucose tolerance, impaired insulin secretion, and increased insulin resistance in the adult offspring (19–25). Thus, our findings in the Pima Indians are consistent with the animal studies and show a distinct effect of the intrauterine diabetic environment on the risk of diabetes and obesity in offspring. The mechanisms by which exposure to the diabetic intrauterine environment increases the risk for type 2 diabetes in humans remain unknown, but recent data suggest that it may program the pancreas to secrete less insulin during the early phase of insulin secretion (26).

Is the situation different in type 1 diabetes? The possibility that fuel metabolism in a pregnant woman might have long-term effects on several developmental parameters was suggested 20 years ago (27). In a cohort of adolescent offspring of diabetic mothers, the predisposition to impaired glucose tolerance was associated with maternal hyperglycemia, regardless of whether it was caused by gestational diabetes or pre-existing type 1 or type 2 diabetes (4). However, the

degree to which diabetes is differentially transmitted from mother or father appears to be different in type 1 as opposed to type 2 diabetes. There is a two- to fivefold greater risk of type 1 diabetes in offspring of fathers than mothers with type 1 diabetes (28). Whether this is the consequence of a true maternal protection against subsequent type 1 diabetes in offspring, as suggested by Warram et al. (29), or of increased perinatal mortality of babies who inherited the susceptibility for type 1 diabetes from their mothers, remains to be seen. Current data suggest that effects of maternally transmitted diabetes genes may be modified by environmental intrauterine contributions in both type 1 and type 2 diabetes, although with a possibly different impact. The recent report of an association between paternal, but not maternal, type 2 diabetes, low birth weight, and diabetes in offspring (30) also supports this hypothesis.

Within Pima Indian families, offspring born after their mothers were diagnosed with diabetes are at greater risk for type 2 diabetes and have higher BMI than those born before. These findings provide strong evidence that the intrauterine diabetic environment conveys a high risk for the development of diabetes and obesity in offspring, in addition to any effect that is transmitted genetically. It remains to be seen if a degree of glycemic control can be achieved throughout pregnancy that would decrease the degree and prevalence of obesity and type 2 diabetes in future generations.

ACKNOWLEDGMENTS

We thank the members of the Gila River Indian Community for making this study possible and the Diabetes and Arthritis Epidemiology Section for conducting this study.

REFERENCES

1. Dorner G, Mohnike A: Further evidence for a predominantly maternal transmission of maturity-onset type diabetes. *Endokrinologie* 68:121–124, 1976
2. Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC: Congenital susceptibility to NIDDM: role of intrauterine environment. *Diabetes* 37:622–628, 1988
3. Thomas F, Balkau B, Vauzelle-Kervroedan F, Papoz L, the CODIAB-INSERM-ZENECA Study Group: Maternal effect and familial aggregation in NIDDM: the CODIAB Study. *Diabetes* 43:63–67, 1994
4. Silverman BL, Metzger BE, Cho NH, Loeb CA: Impaired glucose tolerance in adolescent offspring of diabetic mothers. *Diabetes Care* 18:611–617, 1995
5. 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* 308:242–245, 1983
6. Pettitt DJ, Knowler WC, Bennett PH, Aleck KA, Baird HR: Obesity in offspring of diabetic Pima Indian women despite normal birth weight. *Diabetes Care* 10:76–80, 1987
7. Silverman BL, Rizzo TH, Green OG, Cho NH, Winter RJ, Ogata ES, Richards GE, Metzger BE: Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes* 40 (Suppl. 2):121–125, 1991
8. Bennett PH, Burch TA, Miller M: Diabetes mellitus in American (Pima) Indians. *Lancet* 2:125–128, 1971
9. Knowler WC, Bennett PH, Hamman RF, Miller M: Diabetes incidence and prevalence in Pima Indians: a 19-fold greater incidence than in Rochester Minnesota. *Am J Epidemiol* 108:497–504, 1978
10. Dabelea D, Hanson RL, Bennett H, Roumain J, Knowler WC, Pettitt DJ: Increasing prevalence of type II diabetes in American Indian children. *Diabetologia* 41:904–910, 1998
11. World Health Organization: *Diabetes Mellitus: Report of a WHO study group.* Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
12. Breslow NE, Day NE: Conditional logistic regression for matched sets. In *Statistical Methods In Cancer Research.* Vol. 1. Lyon, France, International Agency for Research Cancer Scientific Publications, 1980, p. 248–279 (no. 32)
13. Alcolado JC, Alcolado R: Importance of maternal history of non-insulin-dependent diabetic patients. *Br Med J* 302:1178–1180, 1991
14. Hales CN, Barker DJP: Type II (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 35:595–601, 1992
15. Pettitt DJ: Diabetes in subsequent generations. In *Diabetes and Pregnancy: An International Approach to Diagnosis and Management.* Dornhust A, Hadden DR, Eds. John Wiley & Sons, New York, 1996, p. 367–376
16. Knowler WC, Pettitt DJ, Saad MF, Bennett PH: Diabetes mellitus in Pima Indians: incidence, risk factors and pathogenesis. *Diabetes Metab Rev* 6:1–27, 1990
17. Knowler WC, Pettitt DJ, Saad MF, Charles MA, Nelson RG, Howard BV, Bogardus C, Bennett PH: Obesity in the Pima Indians: its magnitude and relationship with diabetes. *Am J Clin Nutr* 53:1543S–1551S, 1991
18. Gauguier D, Nelson I, Bernard C, Parent V, Marsac C, Cohen D, Froguel P: Higher maternal than paternal inheritance of diabetes in GK rats. *Diabetes* 43:220–224, 1994
19. Bihoreau MT, Ktorza A, Kinebanyan MF, Picon L: Impaired glucose homeostasis in adult rats following intrauterine exposure to mild hyperglycemia during late gestation. *Diabetes* 35:979–984, 1986
20. Gauguier D, Bihoreau MT, Ktorza A, Berthault MF, Picon L: Inheritance of diabetes mellitus as consequence of gestational hyperglycemia in rats. *Diabetes* 39:734–739, 1990
21. Gauguier D, Bihoreau MT, Picon L, Ktorza A: Insulin secretion in adult rats following intrauterine exposure to mild hyperglycemia during late gestation. *Diabetes* 40 (Suppl. 2):109–114, 1991
22. Aerts L, Van Assche FA: Is gestational diabetes an acquired condition? *J Dev Physiol* 1:219–225, 1979
23. Aerts L, Van Assche FA: Endocrine pancreas in the offspring of rats with experimentally induced diabetes. *J Endocrinol* 88:81–88, 1981
24. Aerts L, Sodoyez-Goffaux F, Sodoyez JC, Mallaisse WJ, Van Assche FA: The diabetic intrauterine milieu has a long-lasting effect on insulin secretion by B cells and on insulin uptake by target tissues. *Am J Obstet Gynecol* 259: 1287–1292, 1988
25. Grill V, Johansson B, Jalkanen P, Eriksson UJ: Influence of severe diabetes mellitus early in pregnancy in the rat: effects on insulin sensitivity and insulin secretion in the offspring. *Diabetologia* 34:373–378, 1991
26. Wilson CA, Weyer C, Knowler WC, Pratley RE: Acute insulin secretion is impaired in adult offspring of diabetic pregnancies (Abstract). *Diabetes* 48 (Suppl. 1):A300, 1999
27. Freinkel N: Banting lecture 1980: of pregnancy and progeny. *Diabetes* 29:1023–1035, 1980
28. Warram JH, Krolewski AS, Gottlieb MS, Kahn CR: Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. *N Engl J Med* 311:149–152, 1984
29. Warram JH, Krolewski AS, Kahn CR: Determinants of IDDM and perinatal mortality in children of diabetic mothers. *Diabetes* 37:1328–1334, 1988
30. Lindsay RS, Dabelea D, Roumain J, Hanson RL, Bennett PH, Knowler WC: Type 2 diabetes and low birth weight: the role of paternal inheritance in the association of low birth weight and diabetes. *Diabetes* 49:445–449, 2000