Intrauterine Exposure to Maternal Diabetes Is Associated With Higher Adiposity and Insulin Resistance and Clustering of Cardiovascular Risk Markers in Indian Children

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OBJECTIVE — To test the hypothesis that maternal gestational diabetes increases cardiovascular risk markers in Indian children.

RESEARCH DESIGN AND METHODS — Anthropometry, blood pressure, and glucose/insulin concentrations were measured in 514 children at 5 and 9.5 years of age (35 offspring of diabetic mothers [ODMs], 39 offspring of diabetic fathers [ODFs]). Children of nondiabetic parents were control subjects.

RESULTS — At age 9.5 years, female ODMs had larger skinfolds ($P < 0.001$), higher glucose (30 min) and insulin concentrations, and higher homeostasis model assessment (HOMA) of insulin resistance and systolic blood pressure ($P < 0.05$) than control subjects. Male ODMs had higher HOMA ($P < 0.01$). Associations were stronger than at age 5 years. Female ODFs had larger skinfolds and male ODFs had higher HOMA ($P < 0.05$) than control subjects; associations were weaker than for ODMs. Associations between outcomes in control subjects and parental BMI, glucose, and insulin concentrations were similar for mothers and fathers.

CONCLUSIONS — The intrauterine environment experienced by ODMs increases diabetes and cardiovascular risk over genetic factors; the effects strengthen during childhood.

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Offspring of diabetic mothers (ODMs) are at an increased risk for obesity/adiposity, glucose intolerance, and increased blood pressure even during childhood (1–4). These risks are higher compared with offspring of diabetic fathers (ODFs), suggesting intrauterine programming by maternal hyperglycemia (1). Even in nondiabetic pregnancies, higher maternal glycaemia is associated with neonatal and postnatal adiposity (5,6). In a cohort of 5-year-old Indian children, maternal gestational diabetes (GDM), but not paternal diabetes, was associated with increased adiposity and insulin concentrations in the female offspring (7). The children were reexamined at 9–10 years of age.

RESEARCH DESIGN AND METHODS

During 1997–1998, 630 women who completed an oral glucose tolerance test at 30 ± 2 weeks' gestation delivered live, normal babies at the Holdsworth Memorial Hospital, Mysore, India (7); 41 women had GDM (Carpenter-Coustan criteria) (8).

At age 5 and 9.5 years, weight (Salter, Kent, U.K.), height (Microtoise; CMS Instruments, Cambridge, U.K.), mid–upper-arm circumference, and triceps and subscapular skinfolds (Harpenden calipers; CMS Instruments) were measured in 514 children available for follow-up (35 ODMs). Systolic and diastolic blood pressure were measured in the left arm (Dinamap; Criticon). Blood samples were collected fasting and 30 and 120 min after a 1.75 g/kg body wt glucose load, after an overnight fast.

Plasma glucose, triglycerides, and HDL cholesterol concentrations were measured by standard enzymatic methods (Alcyon 3000 autoanalyzer; Abbott Laboratories). Insulin was measured using a time-resolved, fluoroimmunoassay (DELFIA) method (PerkinElmer Life 186 and Analytical Sciences, Wallac Qy, Turku, Finland). Interassay coefficients of variations were 12.5% at <45 pmol/l and <10% at ≥45 pmol/l.

Paternal diabetes status was assessed using fasting glucose at the 5-year follow-up. Offspring of non-GDM mothers and diabetic fathers were designated ODFs ($n = 39$). Offspring of nondiabetic parents were designated control subjects ($n = 381$). During 6–10 years of age, physical activity was measured in 408 children using Actigraph accelerometers (AM7164/GT1M; MTI) that measure movement in the vertical plane as counts. Detailed methodology is described elsewhere (9). Pubertal growth was assessed at age 9.5 years, using breast development in girls and testicular volume in boys (10). The hospital ethical committee approved the study; the parents and children gave informed consent/assent.

Statistical methods

Insulin resistance was estimated using the homeostasis model assessment (HOMA) equation (11). Maternal plasma glucose area under the curve (GAUC) and insulin area under the curve (IAUC) were calculated using the trapezoid rule (12). Offspring BMI, subscapular skinfolds, insulin concentrations, and HOMA were log transformed to normality. Differences between ODMs, ODFs, and control subjects were assessed using *t* tests. Adjust-

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ments for parental BMI were performed using multiple regression. Parental BMI, insulin, and glucose variables, expressed as SD scores were used in linear regression models to test the associations in control children.

RESULTS — At age 9.5 years, female ODMs were larger in all anthropometric measurements, except height, than control subjects (Table 1), even after adjusting for maternal BMI ($P < 0.05$). The difference in skinfold measurement between ODMs and control female subjects increased with age (online appendix Fig. A1, available at http://care.diabetesjournals.org/cgi/content/full/dc09-1393/DC1). Plasma 30-min glucose concentrations, insulin concentrations at all time points, HOMA, and systolic blood pressure were higher in female ODMs, and male ODMs had higher fasting insulin and HOMA, than control subjects. The differences were greater at age 9.5 years than at age 5 years (Table 1). Associations with 0-min and 120-min insulin concentrations, HOMA, and systolic blood pressure in girls became nonsignificant after adjusting for current BMI. The interaction term sex × maternal GDM status was statistically significant for skinfold measurements and 30-min insulin ($P < 0.05$).

Physical activity counts were lower in ODMs than control children (Table 1) ($P = 0.01$, sexes combined). They also spent less time vigorously active (≥3,000 counts/min; $P = 0.03$, sexes combined). Female ODMs were more likely to be in the second and third stages of breast development (43% [$n = 10$] vs. 24% [$n = 45$] in control girls; $P = 0.01$), but among boys, testicular volume was similar in all groups.

Female ODFs had larger subscapular skinfolds, and male ODFs had higher fasting insulin concentrations and HOMA than control children at age 9.5 years (Table 1). These differences became nonsignificant in male subjects after adjusting for paternal BMI. There were no significant sex interactions.

In the control children at age 9.5 years, maternal (gestational) and paternal BMI (5-year follow-up) were positively related to subscapular skinfolds ($\beta = 0.08$ [95% CI 0.05–0.12] and $\beta = 0.09$ [0.06–0.12], respectively; $P < 0.001$ adjusted for age and sex) and HOMA ($\beta = 0.09$ [0.03–0.15]; $P < 0.01$). Maternal IAUC was positively re-

Table 1—*Anthropometry, glucose, insulin, and lipid concentrations and blood pressure in ODMs, control subjects, and ODFs, at the age of 5 and 9.5 years*

	Girls					Boys				
	Follow-up at 9.5 years					Follow-up at 9.5 years				
	ODMs ($n = 23$)	P_1	Control subjects ($n = 191$)	P_2	ODFs ($n = 19$)	ODMs ($n = 12$)	P_1	Control subjects ($n = 190$)	P_2	ODFs ($n = 20$)
Anthropometry										
Height (cm)	132.2 ± 6.3	0.2	130.4 ± 5.9	0.6	129.7 ± 6.1	130.8 ± 6.3	0.8	131.3 ± 5.5	0.4	132.3 ± 5.6
BMI (kg/m^2)	16.4 (14.8–17.8)	<0.001	14.3 (13.3–15.4)	0.9	14.3 (13.1–15.6)	15.2 (13.8–16.6)	0.07	14.2 (13.4–15.4)	0.4	14.8 (13.9–15.5)
MUAC (cm)	20.1 ± 2.3	<0.001	17.9 ± 2.0	0.8	18.0 ± 1.9	19.1 ± 1.9	0.04	17.9 ± 2.0	0.4	18.3 ± 1.6
Triceps (mm)	14.9 ± 4.7	<0.001	10.5 ± 3.1	0.2	11.4 ± 2.7	10.3 ± 3.6	0.1	8.8 ± 3.2	0.9	8.9 ± 2.2
Subscapular (mm)	14.1 (8.2–17.3)	<0.001	7.6 (6.2–9.4)	0.006	8.4 (7.5–12.9)	7.15 (5.8–8.8)	0.2	6.0 (5.3–7.9)	0.7	6.3 (5.4–8.1)
Glucose/insulin										
Glucose^0 (mmol/l)	4.6 ± 0.4	0.7	4.7 ± 0.4	0.3	4.8 ± 0.5	4.7 ± 0.4	0.6	4.7 ± 0.4	0.9	4.7 ± 0.5
Glucose^{30} (mmol/l)	7.7 ± 1.0	0.002	6.9 ± 1.3	0.2	6.5 ± 1.2	6.8 ± 1.3	0.9	6.7 ± 1.3	0.5	6.5 ± 1.6
Glucose^{120} (mmol/l)	5.4 ± 0.9	0.2	5.2 ± 0.9	0.8	5.1 ± 0.8	5.1 ± 0.7	0.9	5.0 ± 1.0	0.999	5.0 ± 1.2
Insulin^0 (pmol/l)	35 (25–48)	0.003	25 (18–37)	0.95	26 (18–34)	32.1 (26.3–40.1)	0.001	17 (11–27)	0.01	22 (15–34)
Insulin^{30} (pmol/l)	432 (302–597)	<0.001	261 (167–418)	0.6	246 (157–380)	197 (124–392)	0.99	194 (118–338)	0.9	162 (137–342)
Insulin^{120} (pmol/l)	172 (101–244)	0.006	118 (80–176)	0.3	116 (78–150)	95 (45–174)	0.6	78 (52–130)	0.3	108 (67–158)
Cardiovascular disease risk factors										
Insulin resistance (HOMA)	1.2 (0.8–1.6)	0.006	0.9 (0.63–1.30)	0.95	0.9 (0.6–1.2)	1.1 (0.9–1.4)	0.002	0.6 (0.36–0.94)	0.03	0.8 (0.5–1.2)
Triglycerides (mmol/l)	1.1 ± 0.5	0.2	1.0 ± 0.4	0.5	0.9 ± 0.4	0.8 ± 0.3	0.6	0.8 ± 0.3	0.9	0.9 ± 0.3
HDL cholesterol (mmol/l)	1.0 ± 0.2	0.2	1.1 ± 0.2	0.4	1.0 ± 0.2	1.2 ± 0.3	0.4	1.1 ± 0.2	0.7	1.1 ± 0.2
Systolic blood pressure (mmHg)	103.8 ± 8.0	0.02	99.4 ± 8.5	0.8	100.0 ± 8.3	106 ± 12.0	0.2	101.9 ± 8.9	0.8	102.5 ± 7.3
Diastolic blood pressure (mmHg)	59.8 ± 4.8	0.09	57.9 ± 6.6	0.9	57.8 ± 6.6	60.3 ± 7.6	0.4	58.6 ± 6.9	0.9	58.4 ± 7.5
Physical activity										
Total counts (n)	388,977 ± 91,730	0.3	415,458 ± 126,925	0.7	399,763 ± 135,255	443,025 ± 87,648	0.3	482,348 ± 126,790	0.4	514,960 ± 212,854
Vigorous activity (min)	15.8 ± 11.3	0.2	19.1 ± 12.5	0.8	19.9 ± 15.1	20.9 ± 10.9	0.2	27.2 ± 14.2	0.4	30.9 ± 18.9
	Follow-up at 5 years					Follow-up at 5 years				
Triceps skinfold (cm)	10.1 (7.8–10.6)	0.007	8.0 (6.8–9.3)	0.6	8.3 (7.2–9.3)	7.2 (5.9–8.4)	0.7	7.0 (6.2–8.1)	0.2	7.6 (6.7–8.7)
Subscapular skinfold (cm)	7.8 (5.8–8.7)	0.005	5.9 (5.0–7.5)	0.7	6.0 (5.3–7.9)	5.2 (4.6–6.2)	0.9	5.2 (4.7–6.1)	0.3	5.6 (5.0–6.7)
Glucose^{120} (mmol/l)	6.1 ± 1.2	0.2	5.8 ± 0.9	0.4	6.0 ± 1.0	6.0 ± 0.6	0.9	6.0 ± 1.0	0.006	5.3 ± 1.1
Insulin^{30} (pmol/l)	217 (154–300)	0.01	172 (104–228)	0.4	164 (126–233)	168 (84–242)	0.8	117 (73–207)	0.5	157 (88–255)
Insulin^{120} (pmol/l)	114 (74–192)	0.049	92 (63–131)	0.1	83 (36–129)	85 (63–156)	0.5	80 (53–118)	0.01	50 (26–80.0)
Insulin resistance (HOMA)	1.1 (0.6–1.3)	0.2	0.8 (0.5–1.2)	0.7	0.8 (0.6–1.2)	1.0 (0.4–1.1)	0.5	0.7 (0.4–1.0)	0.2	0.7 (0.4–1.3)
Systolic blood pressure (mmHg)	99.0 ± 8.2	0.08	95.8 ± 8.1	0.8	95.4 ± 9.4	101.2 ± 8.7	0.1	97.2 ± 8.9	0.6	98.2 ± 6.1

Data are means ± SD or median (interquartile range). P_1 for the difference between ODMs and control subjects; P_2 for the difference between ODFs and control subjects.

lated to subscapular skinfolds (β = 0.10 [0.06–0.14]; $P < 0.001$), HOMA (β = 0.09 [0.02–0.16]), and systolic blood pressure (β =1.17 [0.18–2.16]; $P = 0.02$). Paternal fasting insulin was related to subscapular skinfolds (β = 0.07 [0.03–0.11]) and HOMA (β = 0.11 [0.04–0.17]). Maternal GAUC and paternal fasting glucose were unrelated to offspring adiposity and HOMA.

CONCLUSIONS — In a sample of normal children in India, ODMs, particularly girls, were more adipose and had higher systolic blood pressure and insulin resistance compared with control children at age 9.5 years. Our findings are consistent with earlier studies among Pima Indian and Caucasian children (1–4). The differences between ODMs and control subjects were greater at age 9.5 years than at age 5 years. Physical activity was lower in the ODMs, and female ODMs were at an advanced pubertal stage than control subjects at age 9.5 years. Sedentary behavior and advanced maturity may be aggravating factors.

The different associations in boys and girls may be related to fewer boys than girls in our ODM group. Alternatively, female subjects may be more susceptible to adverse lifestyle behaviors in a shared environment due to their proximity to mothers in this population.

Though paternal diabetes was associated with higher offspring adiposity and insulin resistance, associations with maternal diabetes were stronger and related to more outcomes, suggesting that intrauterine exposure to hyperglycemia has additional effects apart from those related to genetic predisposition. The associations between child outcomes and parental BMI, glucose, and insulin concentrations in the absence of diabetes were similar for mothers and fathers; these could be mediated by genes or by shared family lifestyle/environment. Thus, our study does not suggest an additional independent effect of intrauterine exposure to higher maternal glycemia in the nondiabetic range.

Maternal diabetes is a strong determinant of adiposity and clustering of cardiovascular risk factors in Indian children. Since GDM now affects 5–20% of urban Indian pregnant women (7,13), this may contribute to the escalating prevalence of type 2 diabetes in this region.

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

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