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 (Centers for Disease Control and Prevention criteria) (8).

At age 5 and 9.5 years, weight (Salter, Kent, U.K.), height (Micromed; CAM, Cambridge, U.K.), midupper-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 trapezoidal 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-
### 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

#### Boys

| Metric                        | ODFs (n = 20) | ODMs (n = 22) | ODFs (n = 23) | ODMs (n = 22) | ODFs (n = 23) | ODMs (n = 22) | P     |
|-------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|------|
| Subscapular skinfold (cm)     | 7.8 (5.8–8.7)| 5.9 (5.0–7.5)| 6.0 (5.3–7.9)| 5.2 (4.7–6.2)| 5.6 (5.0–6.7)|              |      |
| Triceps skinfold (cm)         | 10.1 (7.8–10.6)| 8.0 (6.8–10.1)| 8.3 (7.2–9.3)| 7.2 (5.9–8.4)| 7.0 (6.2–8.1)|              |      |
| Waist-to-height ratio         |              |              |              |              |              |              |      |
| MUAC (cm)                     | 20.1          |              |              |              |              |              |      |
| Blood pressure (mmHg)         |              |              |              |              |              |              |      |
| Glucose (mmol/l)              |              |              |              |              |              |              |      |
| Insulin (pmol/l)              |              |              |              |              |              |              |      |
| Triglycerides (mmol/l)        |              |              |              |              |              |              |      |

#### Girls

| Metric                        | ODFs (n = 20) | ODMs (n = 22) | ODFs (n = 19) | ODMs (n = 22) | ODFs (n = 23) | ODMs (n = 22) | P     |
|-------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|------|
| Subscapular skinfold (cm)     | 6.6 (5.3–8.7)| 5.0 (4.6–6.2)| 5.6 (5.0–6.7)| 4.7 (4.4–6.1)| 5.6 (5.0–6.7)|              |      |
| Triceps skinfold (cm)         | 9.4 (7.6–11.0)| 7.6 (5.9–9.3)| 7.8 (6.2–9.3)| 7.0 (5.9–8.4)| 7.6 (6.7–8.7)|              |      |
| Waist-to-height ratio         |              |              |              |              |              |              |      |
| MUAC (cm)                     | 18.0          |              |              |              |              |              |      |
| Blood pressure (mmHg)         |              |              |              |              |              |              |      |
| Glucose (mmol/l)              |              |              |              |              |              |              |      |
| Insulin (pmol/l)              |              |              |              |              |              |              |      |
| Triglycerides (mmol/l)        |              |              |              |              |              |              |      |

#### Comparison

- Female ODFs had larger subscapular skinfolds than male ODFs.
- Female ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.
- Female ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.
- Female ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.

### RESULTS

At age 5 years, female ODFs were taller in all anthropometric parameters, and female ODFs had higher fasting insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.

- Female ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.
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- Female ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.

### Discussion

The differences in insulin and control concentrations were observed in the second phase of the study, even after adjusting for current BMI. The interaction term sex was significant in all groups.

- Male ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.
- Male ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.
- Male ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.

### Conclusion

Female ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs. The differences in insulin and control concentrations were observed in the second phase of the study. The interaction term sex was significant in all groups.

- Female ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.
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- Female ODFs had higher insulin concentrations and HOMA, and higher HOMA and insulin concentrations than male ODFs.

- **DISCLAIMER:** The statistical analysis was performed using multiple regression models. Potential BMI, age, and sex effects were controlled for in the analysis. The results are based on a sample of 50 participants, with 25 in each group. The study was conducted over a period of 12 months, with follow-up visits at 6 months. The main outcomes were linear associations between variables and insulin and control concentrations.

- **Figure 1:** Available at [http://care.diabetesjournals.org](http://care.diabetesjournals.org)
Maternal hyperglycemia and offspring risks

...ted 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 diabes 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 glycermia 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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