Glucose Intolerance and Cardiometabolic Risk in Adolescents Exposed to Maternal Gestational Diabetes

A 15-year follow-up study

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OBJECTIVE — Adolescent offspring of women with a history of gestational diabetes (GD) were evaluated for their cardiometabolic risks at a mean age of 15 years.

RESEARCH DESIGN AND METHODS — One hundred and twenty-nine adolescents who were assessed for their cardiometabolic risks at 8 years of age were reassessed at 15 years of age.

RESULTS — Adolescent offspring of mothers with GD had similar blood pressure, plasma lipid profile, and a rate of abnormal glucose tolerance as control subjects. In utero hyperinsulinaemia was associated with a 17-fold increase in metabolic syndrome and a 10-fold increase in lipid profile, and a rate of abnormal glucose tolerance as control subjects. In utero hyperinsulinaemia, irrespective of the degree of maternal GD, was associated with increased risk of overweight and metabolic syndrome during early adolescence in the offspring.

CONCLUSIONS — In utero environment of hyperinsulinaemia, irrespective of the degree of maternal GD, was associated with increased risk of overweight and metabolic syndrome during early adolescence in the offspring.

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Received 23 December 2009 and accepted 28 February 2010. Published ahead of print at http://care.diabetesjournals.org on 9 March 2010. DOI: 10.2337/dc09-2343.

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Statistical analyses

Statistical analysis was performed using the SPSS 17.0 (SPSS, Chicago, IL). Between-group differences were compared by Student t and Mann-Whitney U tests for continuous variables, and χ² or Fisher
exact tests for categorical variables as appropriate. Multivariable logistic regression analysis was used to obtain adjusted odds ratios (ORs) of in utero hyperinsulinemia (either umbilical cord insulin level ≥90th percentile [Ins90] or C-peptide level ≥90th percentile [Cpep90] based on the reference ranges of the original 942 cohort) for abnormal glucose tolerance, overweight, and metabolic syndrome, with forced entry of subject’s birth weight, Tanner’s stage, maternal GD status during pregnancy, and maternal BMI at follow-up evaluation. Model fit was assessed using the Hosmer and Lemeshow Goodness-of-Fit test. A P value <0.05 was considered significant.

RESULTS — A total of 129 adolescent offspring of 87 mothers with NGT and 42 mothers with GD completed both the physical examination and the laboratory investigations. Among the mothers with GD, only six required dietary treatment investigations. Among the mothers with GD, only six required dietary treatment during the index pregnancy based on our previous treatment criteria. The age, sex and anthropometric parameters at the 8-year follow-up evaluation, birth weight, and maternal GD status during index pregnancy were similar between participants and nonresponders at this 15-year follow-up evaluation (data not shown).

There were no statistical differences in the age, Tanner stage, anthropometric parameters, BP, plasma lipid levels, and the rate of AGT between the offspring of mothers with NGT and those of mothers with GD (Table 1). AGT includes diabetes, impaired glucose tolerance, and impaired fasting glucose using the American Diabetes Association criteria. A total of 14 adolescents were diagnosed as having AGT (1 DM, 12 impaired glucose tolerance, and 1 impaired fasting glucose) at the 15-year evaluation. The latter group was more obese (BMI: 23.1 [4.4] vs. 20.8 [3.7] kg/m²; P = 0.03) and had greater adiposity (percentage of fat: 27.4 [7.3] vs. 22.6 [7.3]; P = 0.02) than those with NGT.

Both Ins90 (OR 7.66 [95% CI 1.32–44.5], P = 0.023) and Cpep90 (10.8 [1.69–69.2], P = 0.012) significantly increased the risk of adolescent overweight after adjustment for birth weight, Tanner staging, maternal GD status, and maternal BMI at follow-up evaluation. However, only Cpep90 but not Ins90 was found to increase the risk for MetS after adjustment (17.6 [1.32–235], P = 0.03). Both Ins90 and Cpep90 were not found predictive of offspring’s AGT after adjustment of birth weight, age, sex, Tanner stage, and maternal DM at follow-up evaluation.

CONCLUSIONS — Our results suggest that in utero hyperinsulinemic environment in GD mothers, irrespective of its severity, is associated with offspring’s increased risk of being overweight and developing MetS during early adolescence, similar to that demonstrated previously among offspring of pregestational diabetic mothers (11,12).

Earlier study has shown that the effect of maternal GD on offspring’s insulin resistance and MetS in childhood appeared to be limited to those born large for gestational age (13) By contrast, our results showed that the effect of hyperinsulinemia on MetS and overweight was independent of the offspring’s own birth weight and remained significant after controlling for the mother’s BMI.

Nonetheless, the present study was limited by a small sample size and is underpowered to detect the effect of maternal GD on offspring’s AGT and other cardiometabolic risks at adolescence. A large prospective study extending from

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**Table 1—Demographic characteristics and cardiometabolic status of the offspring of mothers with NGT and GD after 15 years of follow-up**

|                  | NGT     | GD      | P    |
|------------------|---------|---------|------|
| n                | 87      | 42      |      |
| Baseline characterisics at index pregnancy |         |         |      |
| Birth weight (g) | 3,273 (454) | 3,248 (351) | 0.76 |
| At 15 years of age |         |         |      |
| Maternal glycemic status at follow-up |         |         |      |
| AGT              | 18 (20.7%) | 21 (50.0%) | 0.001 |
| DM               | 5 (5.7%)  | 10 (23.8%) | 0.003 |
| Paternal history of DM | 4 (4.6%) | 1 (2.4%) | 0.54 |
| Mean age         | 14.8 (0.8) | 15.0 (0.8) | 0.25 |
| Male-Female      | 46.41 (33.47) | 19.23 (47.53) | 0.42 |
| Tanner stage (interquartile range) | 4 (3–4) | 4 (3–4) | 0.45 |
| Body weight (kg) | 55.7 (12.5) | 56.8 (12.0) | 0.65 |
| Average weight gain since 8-year assessment (kg/year) | 3.91 (1.22) | 4.16 (1.32) | 0.30 |
| Average weight gain since birth (kg/year) | 3.55 (0.81) | 3.59 (0.86) | 0.80 |
| Body height (cm) | 163.3 (7.6) | 162.7 (8.6) | 0.68 |
| Waist circumference (cm) | 73.3 (10.1) | 73.8 (9.9) | 0.81 |
| Hip circumference (cm) | 93.7 (8.2) | 95.1 (7.4) | 0.35 |
| Waist-to-hip ratio | 0.78 (0.05) | 0.77 (0.06) | 0.55 |
| Percentage of body fat (%) | 22.5 (7.4) | 24.4 (7.2) | 0.17 |
| BMI (kg/m²) | 20.8 (3.8) | 21.4 (3.7) | 0.40 |
| Systolic BP (mmHg) | 111 (10) | 113 (10) | 0.46 |
| Diastolic BP (mmHg) | 66 (8) | 68 (7) | 0.46 |
| Fasting PG (mmol/l) | 4.7 (0.3) | 4.6 (0.3) | 0.51 |
| Second hour PG (mmol/l) | 5.6 (1.4) | 6.0 (1.5) | 0.16 |
| HDL cholesterol (mmol/l) | 1.4 (0.3) | 1.4 (0.2) | 0.95 |
| LDL cholesterol (mmol/l) | 2.0 (0.6) | 2.1 (0.5) | 0.34 |
| Total cholesterol (mmol/l) | 3.9 (0.6) | 3.9 (0.6) | 0.84 |
| Triglyceride (mmol/l) | 1.0 (0.4) | 0.9 (0.5) | 0.48 |

Data are means ± SD or n (%). *P value calculated based on the rate of AGT (include IFG, IGT, or DM). †According to the age- and sex-specific reference range in the Hong Kong Chinese population. PG, plasma glucose.
early childhood through adolescence into young adulthood will be needed to address the possible effects of in utero environment of maternal GD and hyperinsulinemia on epigenetic programming and future cardiometabolic risk in the offspring.

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

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