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 hyperinsulinemia was associated with a 17-fold increase in metabolic syndrome and a 10-fold increase in overweight at adolescence, independent of birth weight, Tanner stage, maternal GD status, and mother's BMI.

CONCLUSIONS — In utero environment of hyperinsulinemia, 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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Previous studies suggested that maternal gestational diabetes (GD) increased the diabetes susceptibility of the offspring. However, these studies were limited by their retrospective study design and the absence of a control group for comparison (1–4). In an earlier prospective controlled study, we showed that children exposed to maternal GD had significantly higher blood pressures and lower HDL cholesterol levels than the children of mothers with normal glucose tolerance (NGT) during index pregnancy (5). Moreover, in utero hyperinsulinemia predicted children's abnormal glucose tolerance (AGT) at 8 years of age (5). We reassessed the cardiometabolic risks of the same cohort at 15 years of age.

RESEARCH DESIGN AND METHODS

Between 1992 and 1994, 942 mothers were recruited into a study to define the optimal screening and diagnostic criteria for GD in Chinese individuals (6). They were classified into NGT ($n = 808$) and GD ($n = 134$) according to World Health Organization criteria. C-peptide and insulin levels in umbilical cord blood collected at the time of delivery were measured. At 8-years' postpartum, all mothers with GD and 268 age-matched control subjects, together with their children from the index pregnancy, were invited for follow-up evaluations of their cardiometabolic status. Subjects of the present study were 164 offspring who had participated in the evaluation at 8 years of age (5).

Adolescents who consented to the study underwent an oral glucose tolerance test after an overnight fast of ≥8 h (with 75 g glucose load or at a glucose load 1.75 g/kg body weight if the subjects were <42.8 kg). Anthropometric parameters were measured in the offspring while wearing light clothing, and the percentage of body fat was assessed using a body composition analyzer (Model TBF 410; Tanita, Tokyo, Japan). Mean blood pressure (BP) was recorded after three consecutive measurements in the nondominant arm using an automated vital signs monitor (Model 53000; Welch Allyn, Beaverton, OR) with an appropriate cuff size. Their pubertal stage was assessed using a validated self-assessment questionnaire with sex-specific line drawings and supplementary explanation (7). Overweight was defined based on age- and sex-specific BMI ≥90th percentile of the local population (8). Metabolic syndrome (MetS) was diagnosed according to International Diabetes Foundation criteria with modification in waist circumference (≥age- and sex-specific 90th percentile of Chinese individuals) (9) and BP (≥90 percentile age- and sex-specific reference range of our local population) (10). The cardiometabolic risks of the mothers were assessed during the study, and the results will be reported elsewhere. The study was approved by The Chinese University of Hong Kong Clinical Research Ethics Committee.

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 χ^2 or Fisher

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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 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/m^2; $P = 0.03$) 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.

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 characteristics 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 (53:47)	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/m^2)	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
Children's glycemic status			
IFG	1 (1.1%)	0	0.77*
IGT	8 (9.2%)	4 (9.8%)	0.77*
DM	0	1 (2.4%)	0.77*
HDL-C <1.03 mmol/l	3 (3.4%)	2 (4.8%)	0.72
Triglyceride ≥1.7 mmol/l	6 (6.9%)	4 (9.5%)	0.60
Fasting PG ≥5.6 mmol/l or IGT or DM	9 (10.3%)	5 (11.9%)	0.79
Waist circumference ≥90th percentile†	29 (33.3%)	17 (40.5%)	0.43
BP ≥ 90th percentile†	8 (9.2)	4 (9.5)	0.95
Metabolic syndrome	3 (3.4%)	3 (7.1%)	0.35

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.

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

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.

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