Severe Hyperemesis Gravidarum Is Associated With Reduced Insulin Sensitivity in the Offspring in Childhood

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Background: Hyperemesis gravidarum alters maternal (and possibly fetal) nutrition throughout pregnancy, but there are no data on long-term effects on offspring metabolism. Thus, we aimed to assess whether severe hyperemesis gravidarum (SHG) affects glucose homeostasis and body composition in the offspring in childhood.

Methods: Healthy prepubertal children (aged 4–11 years) born at term were studied: offspring of mothers who were admitted to hospital with SHG (n = 36) and offspring of mothers from control pregnancies (n = 42). Primary outcome was insulin sensitivity measured using iv glucose tolerance tests and Bergman's minimal model. Other assessments included lipid and hormonal profiles and body composition using whole-body dual-energy x-ray absorptiometry.

Results: Insulin sensitivity in SHG children was 20% lower than in controls (8.49 vs 10.60 $\times$ 10^{-4}·min^{-1}·(mU/L); $P = .014$). SHG children also had higher fasting insulin (6.88 vs 5.04 mIU/L; $P = .024$) and lower IGF binding protein 1 (11.8 vs 19.0 ng/mL; $P = .004$) concentrations than controls. Baseline cortisol concentrations were 22% higher in SHG offspring (256 vs 210 nmol/L; $P = .021$). Children in both groups were anthropometrically similar.

Conclusion: Children born to mothers who experienced SHG have lower insulin sensitivity, which may increase their long-term risk of developing diabetes mellitus. Follow-up of SHG offspring is essential to determine later risk of metabolic disease. **(*J Clin Endocrinol Metab* 98: 3263–3268, 2013)**

Hyperemesis gravidarum is a severe form of morning sickness in pregnancy, involving at least 1 antenatal hospital admission before 20 weeks gestation (1, 2). The onset of hyperemesis gravidarum usually occurs at 4 to 8 weeks gestation, and in most cases the condition greatly improves by 14 to 16 weeks (2). However, some women suffer from hyperemesis gravidarum throughout pregnancy (3). Although nausea and vomiting during pregnancy is seen in 50% to 90% of pregnancies (4, 5), hyperemesis gravidarum occurs only in 0.3% to 2% of pregnancies (2, 5–7). A genetic basis to hyperemesis gravidarum has been suggested due to an apparent familial link (8), and there is a higher prevalence in certain ethnic groups (9).

Severe hyperemesis gravidarum (SHG) is usually defined as the presence of at least 1 of the following features: ketonuria, increased blood urea, increased hematocrit, and abnormal electrolytes (10). Other authors identify SHG by the presence of intractable vomiting during pregnancy associated with dehydration and electrolyte and/or

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Abbreviations: BMI, body mass index; CV, coefficient of variation; FSIGT, frequently sampled iv glucose tolerance test; HDL-C, high-density lipoprotein cholesterol; IGFBP, IGF binding protein; LDL-C, low-density lipoprotein cholesterol; SHG, severe hyperemesis gravidarum.

metabolic disturbances as well as a weight loss ≥5% (11, 12). Some women require enteral (via a nasogastric tube) or total iv nutrition (13). SHG is associated with considerable maternal stress and may lead to posttraumatic stress disorder and other psychological effects (14, 15). Previous studies have assessed a number of maternal factors potentially associated with SHG, but no associations were found with human chorionic gonadotropin, estrogen, thyroid hormones, leptin, or immunological components (16, 17).

There have been conflicting reports on the short-term effects of SHG in the offspring, which include premature birth, reduced birth weight, and increased hospital stay (7, 18). Exposure to SHG in utero has also been linked to an increased risk of psychological and behavioral impairments later in life (19). However, there are no data on possible long-term effects on offspring metabolism. We hypothesize that children born to mothers with SHG are exposed to nutritional stress in utero during early gestation, leading to programmed metabolic changes in postnatal life. Hence, we aimed to assess whether SHG affects glucose homeostasis and body composition in the offspring in childhood.

Subjects and Methods

Ethics approval

Ethics approval for this study was provided by the Northern Y Regional Ethics Committee (Ministry of Health, New Zealand). Written informed consent was obtained from parents or guardians as well as verbal or written consent from each child as was appropriate to their age.

Participants

Healthy, developmentally normal prepubertal children aged 4 to 11 years were recruited for this study in June to November 2011. Potential participants were the offspring of pregnant women admitted to the National Women's Hospital (Auckland, New Zealand) with SHG and electrolyte abnormalities (including low serum bicarbonate [with or without acidosis] and hyponatremia), identified from a database. All potential participants from the database that met our study criteria were invited to participate. Control children were born to mothers without hyperemesis gravidarum or other pregnancy-associated complications. These children were recruited via study participants, so that all participants were approximately matched for age and socioeconomic status.

All recruited children were naturally conceived, born at term (37–41 weeks gestation), from singleton pregnancies, and of birth weight appropriate for gestational age (birth weight −2 to 2 SD score [SDS]) (20). Exclusion criteria included signs of puberty (Tanner stage 2 breast development in girls and testicular volume >3 mL in boys or evidence of adrenarche), genetic syndromes, or receiving medication that could affect insulin sensitivity as well as having a first-degree relative or grandparent with diabetes, the metabolic syndrome, or any of its features other than central adiposity. Children were also excluded if born to mothers with gestational diabetes, preeclampsia, gestational or preexisting hypertension, thyroid dysfunction, chronic illnesses, or maternal drug use during pregnancy (including tobacco and alcohol).

Clinical assessments

All children were assessed at the Maurice & Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). Data on each child were collected during a single visit to the clinic. A number of neonatal parameters were recorded, including birth weight and gestational age. Birth weight data were transformed into SDS (20).

Primary outcome

Insulin sensitivity was assessed using a 90-minute modified frequently sampled iv glucose tolerance test (FSIGT), modified with insulin, and analyzed using Bergman's minimal model software (21). Tests were performed between 7:00 and 8:30 AM, after a fasting period of at least 10 hours. Three baseline samples were drawn at −20, −10, and 0 minutes. A 25% dextrose infusion (at 0.3 g/kg) started at 0 minute and lasted for 1 minute. Blood samples were drawn at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 19 minutes. Insulin (0.015 U/kg) was then iv administered as a bolus at 20 minutes, and additional samples were drawn at 22, 23, 24, 25, 27, 30, 35, 40, 45, 50, 60, 70, 80, and 90 minutes. Note that no episodes of hypoglycemia (blood glucose concentration <4 mmol/L) were recorded in any of the participants throughout the study.

Secondary outcomes

Children's heights were measured using a Harpenden stadiometer. Weight and body composition data were obtained using whole-body dual-energy x-ray absorptiometry (Lunar Prodigy 2000; General Electric, Madison, Wisconsin), specifically total body fat and abdominal adiposity (represented by the android fat to gynoid fat ratio). Height SDS were derived from Tanner/Whitehouse reference data (22), and weight and body mass index (BMI) SDS according to British 1990 standards (20, 23). Parental weights and heights were measured by the investigators in 95% of mothers and 80% of fathers, with the remaining measurements reported. Mean parental BMI was calculated as the average of maternal and paternal BMI. Midparental height was calculated using standard formulae (24). Ethnicity was recorded by self-report using a prioritized system, such that if multiple ethnicities were selected, the patient was assigned to a single category, after a hierarchical system of classification (25).

At the start of the FSIGT, baseline blood samples were drawn to measure serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), IGF-I, IGF-II, IGF binding protein (IGFBP) 1, IGFBP-3, cortisol, leptin, adiponectin, androstenedione, dehydroepiandrosterone sulfate, glucose, and insulin concentrations. Secondary outcomes from the FSIGT included acute insulin release (insulin secretory capacity), glucose effectiveness (glucose-mediated glucose uptake), and disposition index (ability of β-cells to compensate for insulin resistance).

Assays

Glucose concentrations were measured on a Hitachi 902 autoanalyzer (Hitachi High Technologies Corporation, Tokyo, Ja-

pan) by enzymatic colorimetric assay (Roche, Mannheim, Germany), with an interassay coefficient of variation (CV) of 2.1%. Insulin concentrations were measured using an Abbott AxSYM system (Abbott Laboratories, Abbott Park, Illinois) by microparticle enzyme immunoassay, with a CV of 5.7%. HDL-C, LDL-C, and total cholesterol concentrations were measured using a Hitachi 902 autoanalyzer, with CV of 11.4%, 10.1%, and 8.9%, respectively. Commercially available ELISA kits E20, E30, E01, E05, E03A, E07, and E09 (Mediagnost, Reutlingen, Germany) were used for quantitative determination of serum IGF-I, IGF-II, IGFBP-1, IGFBP-3, leptin, and adiponectin concentrations, respectively; assay sensitivities were 0.09, 0.02, 0.2, 0.1, 1.0, and 0.6 ng/mL, with CVs of 3.1%, 5.0%, 9.4%, 9.6%, 6.7%, and 3.0%, respectively. Cortisol, DHEA, and androstenedione concentrations were measured using Finnigan TSQ Quantum Ultra AM triple quadrupole mass spectrometer controlled by Finnigan Xcaliber software (Thermo Electron Corporation, San Jose, California), with mean CV of 5.8%, 18.4%, and 8.2%, respectively.

Power and sample size calculation

Power calculation was carried out a priori on the primary outcome (ie, insulin sensitivity) based on previous data on healthy prepubertal children obtained via an identical FSIGT protocol (26). This gave a sample size of 36 participants to detect an insulin sensitivity index difference of $3.6 \times 10^{-4}\cdot\text{min}^{-1}\cdot(\text{mU/L})$ between 2 groups (approximately 30%) with 90% power at 5% level of significance, assuming a SD of $4.4 \times 10^{-4}\cdot\text{min}^{-1}\cdot(\text{mU/L})$.

Statistical analyses

Sex ratio and ethnic composition data in both groups were compared with Fisher's exact tests in Minitab version 16 (The Pennsylvania State University, State College, Pennsylvania). Random-effect mixed models were used to compare the primary and secondary outcomes between SHG children and the controls. Important confounding factors were adjusted for in the analyses, including ethnicity, birth weight SDS, birth order, age, and gender. Other factors were controlled for as required, depending on the outcome response of interest: for lipids, hormones, and outcomes associated with glucose homeostasis, BMI SDS were included; and for anthropometric data, the appropriate parental factor (ie, mean parental BMI or midparental height). Multivariate analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary North Carolina). Parameters associated with glucose homeostasis were log-transformed to approximate normality. All statistical tests were 2-tailed and maintained at a 5% significance level. Age data are presented as means ± SD. Outcome data are presented as model-adjusted means (estimated marginal means adjusted for the confounding factors in the models), with associated 95% confidence intervals.

Results

A total of 300 pregnancies met our study criteria and were invited to participate. Only the first 40 respondents were enrolled, because this figure equated to the required sample size (36 participants) plus an additional 10% to account for study exclusion or failure. Subsequently, 4 children were excluded due to chronic illness (n = 1), having a sibling with type 1 diabetes mellitus (n = 1), severe attention deficit-hyperactivity disorder (n = 1), or withdrawal at clinical assessment due to fear of injections (n = 1).

As a result, 36 SHG children (18 boys) were included in the study. SHG participants and nonparticipants were of similar birth weight ($P = .29$), gestational age ($P = .10$), and sex ratio ($P = .72$), but participants were slightly younger (8.6 vs 9.2 years of age; $P = .020$). Mothers of all SHG children were admitted to hospital due to SHG in the first trimester of gestation at least once, but some mothers as many as 4 times. Median duration of hospitalization was 5 days (range 1–31 days). In 32 of the 36 pregnancies, hyperemesis persisted beyond 16 weeks gestation and continued throughout pregnancy.

Among controls, 47 children volunteered to participate, but 5 failed to meet the inclusion criteria due to being born small for gestational age, parental diagnosis with type 2 diabetes during study screening, early signs of puberty, conception after in vitro fertilization, or maternal gestational diabetes. Thus, 42 controls (27 boys) were included in the study.

Overall, participants were aged 8.8 ± 1.9 years, and most (79%) were of New Zealand European ethnicity. SHG and control children were of similar age ($P = .16$), gestational age ($P = .70$), birth weight ($P = .10$), sex ratio ($P = .25$), and ethnic composition ($P = .41$) (Table 1).

Insulin sensitivity and other parameters of glucose homeostasis

Insulin sensitivity in SHG children was 20% lower than in controls (8.49 vs $10.60 \times 10^{-4}\cdot\text{min}^{-1}\cdot(\text{mU/L})$; $P = .014$) (Figure 1). Although not statistically significant, there was indication of a 30% increase in acute insulin release among SHG children (433 vs 333 mU/L; $P = .14$) (Figure 1). SHG children displayed greater area under the curve for both glucose (9886 vs 9429 mg/dL; $P = .016$) and insulin (1752 vs 1453 mIU/L; $P = .037$) and tended to display greater peak glucose concentrations (258 vs 240

Table 1. Baseline Characteristics of Children Born From Mothers Who Suffered From SHG vs Those From Control Pregnancies[a]

	SHG	Control	*P* Value
n	36	42	
Age, y	8.6 ± 1.4	9.0 ± 2.1	.16
Gestational age, wk	39.3 ± 0.8	39.3 ± 0.7	.70
Birth weight, kg	3.41 ± 0.33	3.54 ± 0.38	.10
Sex ratio (boys)	50%	64%	.25
Ethnicity (New Zealand European)	74%	83%	.41

[a] Data are means ± SD.

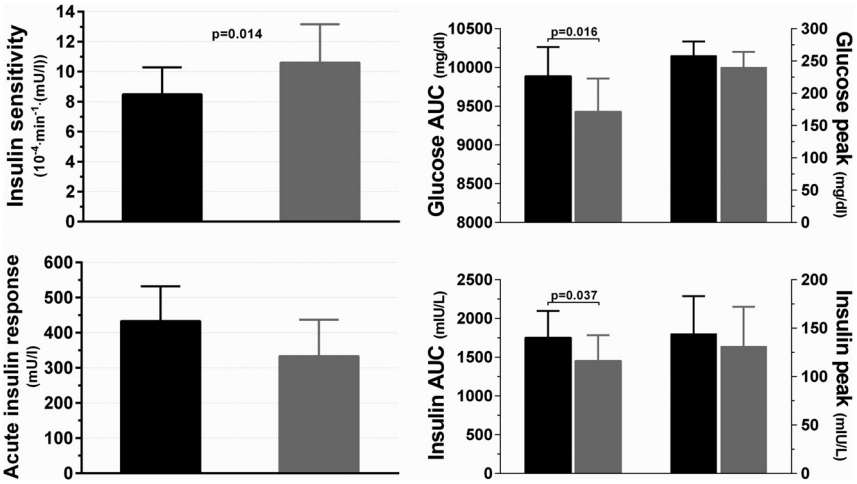

Figure 1. Insulin sensitivity and other parameters of glucose homeostasis in children born from mothers who suffered from SHG (black bars) versus those from control pregnancies (gray bars). Data are means and 95% confidence intervals adjusted for other confounding factors in the multivariate models.

mg/dL; $P = .076$) (Figure 1). SHG children also had higher fasting insulin concentrations ($P = .024$), but glucose effectiveness, disposition index, and fasting glucose concentrations were similar between groups (Table 2).

Other secondary outcomes

Baseline cortisol concentrations were 22% higher in SHG children than in controls ($P = .021$). Furthermore, SHG children had lower IGFBP-1 (−38%; $P = .004$) and lower IGFBP-3 (−14%; $P = .014$) concentrations compared with controls (Table 2). However, SHG and control children were anthropometrically similar, as were their lipid profiles (Table 2). There were also no differences in other hormone concentrations measured, including leptin ($P = .39$), adiponectin ($P = .46$), dehydroepiandrosterone sulfate ($P = .96$), or androstenedione ($P = .63$) concentrations (data not shown).

Discussion

This study provides the first evidence of long-term adverse metabolic outcomes in the offspring of mothers who suffered from SHG, manifested as lower insulin sensitivity. Importantly, the magnitude of this reduction (20%) is similar to that seen with medications used to treat diabetes in adults, such as metformin (27). There have been no studies examining the long-term consequences of reduced insulin sensitivity in childhood. However, longitudinal studies in adults show that a reduction in insulin sensitivity is associated with increased risk of developing type 2 diabetes mellitus, hypertension, coronary heart disease, stroke, and cancer many years later (28, 29).

Table 2. Secondary Outcomes Among Children Born From Mothers Who Suffered From SHG vs Those From Control Pregnancies

	Hyperemesis	Control	*P* Value
n	36	42	
Anthropometry			
Height SDS	0.61 (0.31–0.91)	0.36 (0.04–0.68)	.09
BMI SDS	0.22 (−0.19 to 0.64)	0.40 (−0.01 to 0.82)	.47
Android fat to gynoid fat ratio	0.60 (0.53–0.68)	0.64 (0.56–0.72)	.48
Total body fat, %	21.9 (18.8–25.0)	21.5 (18.3–24.6)	.82
Lipid profile			
Total cholesterol, mmol/L	3.90 (3.62–4.18)	3.89 (3.60–4.19)	.96
HDL-C, mmol/L	1.27 (1.15–1.40)	1.35 (1.21–1.48)	.35
LDL-C, mmol/L	2.34 (2.08–2.60)	2.15 (1.87–2.43)	.25
Total cholesterol to HDL-C ratio	3.24 (2.92–3.57)	3.04 (2.69–3.38)	.32
Glucose homeostasis			
Glucose effectiveness, 10^{-2}/min	2.80 (2.16–3.44)	2.75 (2.08–3.41)	.90
Disposition index	3095 (2430–3941)	2898 (2251–3731)	.67
Fasting insulin, mIU/L	6.88 (5.56–8.50)	5.04 (4.04–6.28)	.024
Fasting glucose, mg/dL	4.76 (4.63–5.88)	4.71 (4.58–4.84)	.55
Hormone concentrations			
Baseline cortisol, nmol/L	256 (224–292)	210 (184–241)	.021
IGF-I, ng/mL	181 (156–207)	183 (157–209)	.88
IGF-II, ng/mL	651 (610–693)	668 (624–711)	.54
IGFBP-1, ng/mL	11.8 (7.9–15.6)	19.0 (15.1–22.8)	.004
IGFBP-3, ng/mL	2955 (2657–3254)	3435 (3122–3749)	.014

[a] Data are means and 95% confidence intervals adjusted for other confounding factors in the multivariate models.

Our study shows that SHG children appear to have an isolated abnormality of reduced insulin sensitivity, so that overall glucose disposal seems normal as indicated by the disposition index. The higher fasting insulin concentrations in SHG children were associated with lower serum IGFBP-1 concentrations. Insulin resistance leads to a compensatory increase in portal insulin secretion, which suppresses IGFBP-1 concentrations (30). Hyperinsulinemia and low IGFBP-1 are also associated with increased likelihood of developing cardiovascular disease (31).

It is well established that adverse events early in life are associated with long-term changes that may lead to later metabolic and cardiovascular disease (32, 33). Dutch Famine studies have shown an increased risk of glucose intolerance in adulthood among those exposed to famine in any stage of gestation (34, 35). In addition, the Dutch Famine cohort displays an atherogenic lipid profile and higher risk of coronary artery disease and breast cancer in adult life (34). In our study, SHG led to hospitalization in early gestation in all pregnancies, but vomiting continued throughout pregnancy in most cases. Thus, we speculate that in our SHG cohort, nutritional compromise would have been greater in the first trimester of pregnancy, with some amelioration in later pregnancy leading to birth weight appropriate for gestational age. There are similarities between our cohort and the Dutch Famine cohort who were exposed to famine in early gestation, who were also born of normal birth weight (36). Importantly, both groups show adverse changes in glucose regulation manifest as hyperinsulinemia (during an oral glucose tolerance test) among Dutch Famine survivors (36) and reduced insulin sensitivity in SHG children. These observations highlight the importance of early gestation in the development programming of metabolism.

The mechanisms underpinning the changes observed in our SHG cohort are unknown, but possibly similar to those affecting Dutch Famine survivors exposed to undernutrition in early gestation. Interestingly, periconceptional exposure to the Dutch Famine was associated with hypomethylation of the *igf*2 gene in later adult life (37). Thus, the study of Heijmans et al (37) raises the possibility that epigenetic modification of gene expression may be a possible mechanism programming metabolism in our SHG cohort.

We also observed that SHG children had higher baseline cortisol concentrations than controls. This has been shown to occur in child and adult cohorts that faced a suboptimal intrauterine environment such as those born of low birth weight (38, 39). Adults who were born of low birth weight had elevated baseline serum cortisol concentrations, which were associated with insulin resistance (40). Although early morning cortisol is commonly used as a measure of cortisol secretion, it is less precise than assessment of circadian cortisol rhythm. Nonetheless, our findings suggest that programming of the hypothalamus-pituitary-adrenal axis due to an adverse environment in utero may be an alternative explanation for the observed reduction in insulin sensitivity in SHG children. Importantly, this programming may occur in the absence of a reduction in birth weight. For example, an unbalanced maternal diet (high-meat and low-carbohydrate) in human pregnancy is associated with epigenetic changes in genes controlling glucocorticoid action in subjects born at term and of normal birth weight (41, 42). Furthermore, these epigenetic changes were noted in midadult life and were associated with increased adiposity and higher blood pressure (41, 42).

In conclusion, our study shows that children born to mothers who suffered from SHG have lower insulin sensitivity than those from control pregnancies. These children may be at an increased risk of developing insulin resistance and associated diseases later in life, such as type 2 diabetes. Our findings need to be corroborated in larger studies, and SHG cohorts should be assessed in adulthood to adequately identify any associated long-term health risks. Furthermore, future studies are necessary to establish the underlying causes and mechanisms of the observed reduction in insulin sensitivity in SHG children.

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A.A., W.S.C., P.L.H., F.H.B., and B.E.C. conceived and designed the study. A.A. recruited and performed the tests with assistance from J.B. and P.S. A.A. and J.G.B.D. collected and compiled the data, which were analyzed by J.G.B.D. A.A., J.G.B.D., and W.S.C. wrote the manuscript with input from other authors. All authors have approved the submission of the final version of this manuscript.

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