Effects of Maternal Surgical Weight Loss in Mothers on Intergenerational Transmission of Obesity

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Background and Objectives: By studying cardiometabolic risk factors in children born after maternal biliopancreatic diversion bariatric surgery (AMS) compared with those in children born before maternal surgery (BMS), we tested the hypothesis that significant maternal weight loss may modify obesity-related factors transmitted via the intrauterine environment.

Design: Anthropometry and fasting blood levels were studied in 49 mothers who had lost 36 ± 1.8% body weight sustained for 12 ± 0.8 yr and their 111 children (54 BMS and 57 AMS) aged 2.5–26 yr.

Results: AMS children had lower birth weight (2.9 ± 0.1 AMS *vs.* 3.3 ± 0.1 kg BMS, $P = 0.003$) associated with a reduced prevalence of macrosomia (1.8 AMS *vs.* 14.8% BMS, $P = 0.03$) with no difference in underweight. At the time of follow-up, AMS children exhibited 3-fold lower prevalence of severe obesity (11 *vs.* 35%, $P = 0.004$), greater insulin sensitivity (homeostasis model assessment of insulin resistance index 3.4 ± 0.3 *vs.* 4.8 ± 0.5, $P = 0.02$), improved lipid profile (cholesterol/high-density lipoprotein cholesterol 2.96 ± 0.11 *vs* 3.40 ± 0.18, $P = 0.03$; high-density lipoprotein cholesterol 1.50 ± 0.05 *vs.* 1.35 ± 0.05 mmol/liter, $P = 0.04$), lower C-reactive protein (0.88 ± 0.17 *vs.* 2.00 ± 0.34 μg/ml, $P = 0.004$), and leptin (11.5 ± 1.5 *vs.*19.7 ± 2.5 ng/ml, $P = 0.005$) and increased ghrelin (1.28 ± 0.06 *vs.*1.03 ± 0.06 ng/ml, $P = 0.005$) than BMS offspring (AMS *vs.* BMS, respectively, for all).

Conclusions: This unique study of children aged 2.5–26 yr born before and after maternal antiobesity surgery demonstrated improvements in cardiometabolic markers sustained into adolescence, attributable to an improved intrauterine environment. **(*J Clin Endocrinol Metab* 94: 4275–4283, 2009)**

Chronic overnutrition resulting in obesity is associated with insulin resistance, dyslipidemia, atherosclerotic vascular disease, and chronic low-grade inflammation. It is a major contributor to causes of death in industrialized nations, currently spreading globally. Women are particularly susceptible to developing obesity and have been demonstrated to transmit the disease and its comorbidities to their offspring (1). Insulin resistance during pregnancy increases the risk of life-long obesity and comorbidities in the offspring (2), indicating potential intrauterine imprinting.

The most effective treatment for severe obesity is weight-loss surgery (3). Biliopancreatic diversion (BPD) is one of the most effective operations: it significantly reduces the morbidity and mortality associated with severe obesity by inducing significant, long-term weight loss,

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-0709 Received April 1, 2009. Accepted August 4, 2009.
First Published Online October 9, 2009

Abbreviations: AMS, After maternal surgery; ASP, acylation-stimulating protein; BF%, body fat percentage; BMI, body mass index; BMS, before maternal surgery; BPD, biliopancreatic diversion; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; WC, waist circumference; WC/HT, WC to height ratio.

ameliorating type 2 diabetes, and correcting many features of the metabolic syndrome (4).

Since 1984, BPD has been our obesity operation of choice (5–7). The duodenum and proximal small intestine are closed to food, diverting bile, and pancreatic secretions to the distal small bowel resulting in decreased fat absorption (8, 9) and major changes in the secretion of gastrointestinal peptides (10–12). Superior outcomes of diversionary procedures such as gastric bypass (13, 14) and BPD (13, 14) are related to altered hormonal signals associated with obesity and food intake. Adipokines [such as acylation-stimulating protein (ASP) and adiponectin] as well as inflammatory peptides [C-reactive protein (CRP) and IL-6] and satiety-related hormones (leptin and ghrelin) play important roles in the pathophysiology of obesity, insulin resistance, dyslipidemia, and chronic low-grade inflammation (15).

In a pilot study, we found children born after their mother's BPD weight loss surgery had significantly lower prevalence of obesity than their siblings born to severely obese mothers before BPD surgery (16). However, the study was limited in the absence of metabolic data. The present study of offspring detects persistent differences in anthropometry, blood lipids, glycemia, and metabolic hormones regulating central, adipose tissue and gut function in relation to mothers' pre- and postoperative status.

Subjects and Methods

Study design, patient recruitment, and sample collection

A cross-sectional study was used to evaluate children born to mothers who had undergone bariatric weight loss surgery. Based on follow-up records of 2054 women who had BPD between 1984 and 2005, 161 gave birth to 245 children. We contacted women to participate based on the following criteria: 1) residing within about 200–250 km of Québec City; 2) had children currently between ages 2.5 and 25 yr old; 3) all mothers with children born both before and after surgery (42 women available); and 4) additional mothers with children born either before maternal surgery (BMS) or after maternal surgery (AMS), matched for age and sex. Subjects were recruited between July 2007 and January 2008, and all mothers (n = 49), BMS (n = 54), and AMS (n = 57) children with complete data (including blood samples) were included in the analysis. The children were separated into two groups according to whether they were born before their mother's bariatric surgery (BMS) or after their mother's bariatric surgery (AMS). Most were singleton births, with three sets of BMS twins and two sets of AMS twins. There were 25 mothers with siblings born both before and after surgery (37 BMS and 38 AMS). No intervention, surgical or otherwise, was performed on the children, and no child had any debilitating disease. Maternal presurgical data were obtained from the bariatric surgery database at Hôpital Laval. In the present study, 13% of the women had BPD with distal gastrectomy (6) and 87% had BPD with sleeve gastrectomy and duodenal switch (5).

Mothers and children attended Hôpital Laval, their doctor's office, or a regional hospital for assessment. Anthropometric values were obtained; body fat percentage using bioelectrical impedance (Tanita; Arlington Heights, IL), was assessed at Hôpital Laval (n = 58 participants). Mothers reported data by personal interview regarding pregnancies (length of gestation, gestational weight gain, complications, cesarean sections); offspring perinatal health (stillbirth, malformation, birth weight and length, breast-feeding); and food-related issues (preoccupation with weight, diet, change in family meal quality or quantity). Study procedures were approved by the Ethics Committee of Hôpital Laval and appropriate patient consent was obtained from all subjects.

Plasma analyses

Fasting blood samples were drawn into EDTA-containing tubes. The clinical biochemistry laboratory measured fasting plasma glucose, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). The research laboratory measured insulin, adiponectin, leptin, and ghrelin using radioimmunological assays (Millipore, Bedford, MA). CRP was measured using a commercially available ELISA (Millipore). Only CRP values under 10 μg/ml were included in the analysis (17). ASP was measured using an in-house ELISA method as previously reported with the following modification: standards (including the blank), samples, and controls were diluted in a 1% solution of BSA-PBS instead of PBS alone (18).

Definition of obesity

Prevalence of obesity in children was adjusted for age and gender and categorized based on body mass index (BMI; kilograms per square meter) percentile using charts from the National Health and Nutrition Examination Survey 2000 (19). For offspring younger than 20 yr, underweight was defined as BMI at the fifth percentile or less, normal as fifth to 84.9th percentile, overweight as 85–94.9th percentile, obesity as 95–97.9th percentile, and severe obesity as 98th percentile or greater. For children older than 20 yr, underweight was defined as BMI of 18.5 kg/m^2 or less, overweight as 25–29.9 kg/m^2, obesity as 30–34.9 kg/m^2, and severe obesity as 35 kg/m^2 or greater. Owing to the relatively small number of offspring, we combined underweight and normal-weight children with BMI percentiles less than 85 and overweight and obese children in the 85th to 98th percentile into two groups, N and O, respectively. Children with a BMI greater than the 98th percentile were termed severely obese, constituting a third group (SO). We also evaluated body size according to BMI z-score using charts from the Centers for Disease Control and Prevention (20), waist circumference (centimeters) to height (centimeters) ratio (WC/HT) standardized according to the American Academy of Pediatrics (21), and percent body fat (22).

Statistics

Continuous variables were compared using two-tailed *t* test or one-way ANOVA with Newman-Keuls *post hoc* test. Categorical variables were compared by χ^2 or Fisher exact test. To relate parameters with z-score in BMS or AMS children, respectively, multiple regression analyses were performed using two independent variables. The first variable, z-score, was defined as quantitative and the second variable, BMS or AMS status, was

qualitative. Interaction effect was introduced in the statistical model to evaluate statistically significant differences between regression lines. Multiple regression using best subset analysis was also used to evaluate the independent contribution of individual factors. For all analyses, $P < 0.05$ was considered statistically significant. Statistical analysis was done using SigmaStat 3.5 (Systat Software Inc., Chicago, IL) and GraphPad Prism (GraphPad Software Inc., La Jolla, CA).

Results

Mothers after BPD had reduced weight and improved metabolic profile

Mothers after BPD surgery were 41.2 ± 0.8 yr of age and 12.1 ± 0.8 yr postoperative, with significantly lower body weight, BMI, glucose, and lipids compared with before surgery (supplemental Table S1). We also measured the following parameters at the time of the study only (after BPD): adiponectin (20.8 ± 1.4 μg/ml), ASP (39.1 ± 6.0 nM), CRP (1.16 ± 0.29 (μg/ml), ghrelin (0.65 ± 0.04 ng/ml), insulin (12.1 ± 0.91 μU/ml), homeostasis model assessment of insulin resistance (HOMA-IR; 2.58 ± 0.23), leptin (13.37 ± 1.44 ng/ml), waist circumference (WC) (95.4 ± 2.7 cm), hip circumference (111.1 ± 2.9 cm), and waist to hip ratio (0.87 ± 0.01). All plasma values were comparable with ranges we reported previously in post-bariatric surgery women (13). None of the parameters correlated with the number of years since surgery, indicating stable metabolic changes over time. There were no significant changes in dietary habits after surgery compared with before surgery (self-reported, data not shown).

Improved pregnancy outcome after BPD

BPD reduced the number of pregnancy complications: gestational diabetes mellitus, gestational hypertension, and preeclampsia occurred in 7.7, 19.6, and 26.9% of pregnancies, respectively, before BPD, with no occurrences in post-BPD pregnancies (supplemental Table S2). Only four women (all before BPD) had known diabetes. There was a reduction in vomiting (15.4% before BPD *vs.* 1.9% after BPD, $P = 0.03$) and pregnancy-related hospitalization (30.0% before BPD *vs.* 7.7% after BPD, $P = 0.008$). As expected, there was a greater number of primipara among pre-BPD compared with post-BPD pregnancies, but no difference in complications for primipara. Incidence of anemia during pregnancy (7.5% before BPD *vs.* 16.4% after BPD, P = NS) and pregnancy duration were not different. BPD significantly reduced prepregnancy weights of the mothers. Gestational weight gain was significantly less after (6.6 ± 8.9 kg) compared with before BPD (13.4 ± 12.3 kg; $P < 0.0001$). There were no differences in number of miscarriages or stillbirths in pre-BPD *vs.* post-BPD pregnancies (data not shown).

Effects of maternal biliopancreatic diversion weight loss surgery on offspring

Children were classified as BMS or AMS (Table 1). There was no difference in gender distribution and no difference in age between boys and girls within each group (BMS boys 16.3 ± 0.9 yr *vs.* girls 15.8 ± 0.9 yr P = NS; AMS boys 10.4 ± 0.7 yr *vs.* girls 11.0 ± 0.8 yr, P = NS). Any differences when genders were analyzed separately are noted in the text. Analyses were done with the entire group (siblings and nonsiblings); however, analysis of siblings only yielded similar results (not shown).

Perinatal parameters: AMS children had reduced birth weight

At birth, AMS children weighed less than BMS children, with no difference in length (Table 1). Macrosomia (birth weight >4 kg) was reduced from 14.8% in BMS children to 1.8% in AMS children ($P = 0.03$, χ^2). Excluding children born with macrosomia from the analyses presented below did not change the results (data not shown). Prevalence of low birth weight (<2.5 kg, BMS 11.1% *vs.* AMS 17.5%) and duration of breast-feeding were not significantly different. There were no significant correlations between birth order or maternal age at birth and any of the birth data, anthropometric, or plasma variables presented below (data not shown).

AMS children had reduced BMI z-score *vs.* BMS children

BMS children were significantly older than AMS children; however, both prepubertal and postpubertal children were represented in both groups (Table 1). BMS children weighed more and were taller than AMS children (data not shown). Using age- and gender-normalized parameters, AMS children had a lower BMI percentile and z-score than BMS children, with no difference in height percentile. Results were the same when comparing BMS boys with AMS boys, although there was no difference in BMI percentile or z-score between BMS and AMS girls (data not shown).

There was a trend toward lower body fat percentage (BF%) (BMS *vs.* AMS, $P = 0.08$) and a decreased WC in AMS children but no significant difference in waist to hip ratio. However, the WC/HT ratio, an age-normalized parameter, was significantly reduced in AMS children, suggesting a less central distribution of body fat. This was significantly different for BMS boys *vs.* AMS boys, with no difference in girls (data not shown).

TABLE 1. Anthropometric and plasma profile of children born BMS *vs.* AMS

	BMS (n = 54)	AMS (n = 57)	*P* value[a]
Male/female	26/28	24/33	NS
Birth weight (kg)	3.3 ± 0.1	2.9 ± 0.1	0.003
Birth length (cm)	50.0 ± 0.7	49.1 ± 0.4	NS
Macrosomia	8 (14.8%)	1 (1.8%)	0.03
Low birth weight	6 (11.1%)	10 (17.5%)	NS
Age (yr) (range)	16.0 ± 0.6 (6.8–25.5)	10.7 ± 0.5 (2.4–20.8)	<0.0001
BMI percentile (%)[b]	79.4 ± 3.4	68.4 ± 4.0	0.04
Height percentile (%)[b]	50.0 ± 3.8	50.3 ± 3.7	NS
Z-score[b]	1.28 ± 0.17	0.82 ± 0.15	0.05
Weight (kg)	74.5 ± 4.5	46.5 ± 3.5	<0.0001
BF% (%)[c]	29.7 ± 2.3	24.1 ± 2.1	0.08
WC (cm)	90.7 ± 3.1	73.0 ± 2.5	<0.0001
WHR	0.90 ± 0.01	0.90 ± 0.01	NS
WC/HT ratio	0.56 ± 0.02	0.52 ± 0.01	0.01
Triglyceride (mmol/liter)	1.12 ± 0.11	0.88 ± 0.06	0.07
Cholesterol (mmol/liter)	4.30 ± 0.12	4.21 ± 0.10	NS
LDL-C (mmol/liter)	2.43 ± 0.09	2.31 ± 0.09	NS
HDL-C (mmol/liter)	1.35 ± 0.05	1.50 ± 0.05	0.04
TC/HDL-C	3.40 ± 0.18	2.96 ± 0.11	0.03
Insulin (μU/ml)	21.1 ± 1.8	15.1 ± 1.5	0.01
Glucose (mmol/liter)	5.08 ± 0.06	4.86 ± 0.05	0.008
HOMA-IR	4.82 ± 0.46	3.40 ± 0.34	0.02

NS, Not statistically significant; WHR, waist to hip ratio.

[a] Results are expressed as average ± SEM or proportion and analyzed by *t* test (continuous variables) or χ^2 (proportion); [b] results represent age- and gender-normalized parameters; [c] BF% is evaluated in children older than 6 yr; BMS, n = 31 (15 boys, 16 girls); AMS, n = 27 (12 boys, 15 girls).

Severe obesity was reduced 3-fold in AMS children *vs.* BMS children

The proportion of N, O, and SO children was evaluated using BMI percentile. There was an increased proportion of SO children in the BMS group, with 35.2% SO BMS children *vs.* only 10.5% SO AMS children ($P = 0.004$) (Table 2). Classification using alternate parameters such as z-score greater than 2, WC greater than the 90th percentile, or BF% greater than 30% yielded similar proportions (results not shown). BMS children had spent 60.3 ± 4.3% of their life in a postmaternal BPD environment (Table 2). There was no difference in percent life span in post-BPD among the three BMS weight categories. None of the birth data, current anthropometric, or plasma variables correlated with percent of time after BPD.

Blood lipids were disproportionately decreased in AMS children *vs.* BMS children

AMS children had lower TC to HDL-C ratio ($P = 0.03$) and higher HDL-C ($P = 0.04$). There was a trend toward lower triglyceride (TG) in AMS children ($P = 0.07$), with no differences in LDL-C or TC.

There were important relationships between body size and blood lipids (Fig. 1). TG, LDL-C, and TC to HDL-C ratio all were higher and HDL-C was lower from N to O to SO for BMS children. A similar relationship was seen with TC in BMS children ($P = 0.0004$, ANOVA, $P < 0.05$ *post hoc* for N *vs.* O, N *vs.* SO, and O *vs.* SO). Among AMS children, only TG and TC to HDL-C ratio were higher, whereas HDL-C decreased ($P = 0.04$, $P = 0.0001$, and $P = 0.01$, respectively). There was a trend for lower LDL-C but no difference in TC (data not shown).

There were significant correlations between BMI z-score and plasma TG, HDL-C, and TC to HDL-C ratio in BMS and AMS children (r = 0.59, −0.60, and 0.64 for BMS, and r = 0.36, −0.44, and 0.47 for AMS, respectively, all $P < 0.05$) and LDL-C (r = 0.38, $P = 0.004$) in BMS children only (supplemental Table S3). The slopes of TG and TC to HDL-C to BMI z-score were reduced in AMS compared with BMS children, (supplemental Table S3 and supplemental Fig. S1), such that at any given BMI (age and gender normalized), the TG and TC to HDL-C values were lower.

Markers of insulin resistance were reduced in AMS *vs.* BMS children

All indices of insulin resistance, including insulin ($P = 0.01$), glucose ($P = 0.008$), and HOMA-IR ($P = 0.02$) were decreased in AMS children (Table 1). When evaluated across body size categories (Fig. 2), in BMS children insulin was higher in SO ($P < 0.0001$, ANOVA) as was HOMA-IR ($P = 0.0001$, ANOVA). In AMS children, insulin was higher in SO ($P < 0.0001$, ANOVA), and HOMA-IR was higher in O and SO ($P = 0.01$, ANOVA). There was no significant difference in glucose between body size groups, despite a significant difference between

TABLE 2. Evaluation of body size distribution in BMS and AMS children

	BMS (n = 54)				AMS (n = 57)			
	Underweight/ normal	Overweight/ obese	Severely obese	ANOVA *P* value	Underweight/ normal	Overweight/ obese	Severely obese	ANOVA *P* value
n (%)	26 (48%)	9 (16%)	19 (35%)		32 (56%)	19 (33%)	6 (11%)	
Male/female	11/15	4/5	11/8	NS	15/17	8/11	1/5	NS
Age (range)	15.1 ± 0.9 (8.2–25.5)	14.0 ± 1.2 (8.2–19.1)	18.3 ± 1.0 (6.8–25.3)	0.03	9.6 ± 0.7 (2.4–17.0)	12.2 ± 0.8 (3.9–18.5)	12.2 ± 1.9 (8.4–20.8)	0.05
BMI (%)[a]	59.1 ± 4.4	94.5 ± 0.9	100.0 ± 0.0	<0.0001	47.3 ± 4.4	92.8 ± 1.0	100.0 ± 0.0	<0.0001
Height ((%)[a]	40.2 ± 4.2	69.1 ± 8.4	54.3 ± 7.2	0.02	44.1 ± 4.2	56.8 ± 7.4	61.7 ± 11.4	NS
Z-score[a]	0.21 ± 0.14	1.63 ± 0.08	2.58 ± 0.15	<0.0001	0.00 ± 0.14	1.59 ± 0.08	2.61 ± 0.14	<0.0001
Time in post-BPD environment (%)[b]	61.7 ± 6.3	57.7 ± 11.8	59.7 ± 7.1	NS				

Results are expressed as average ± SEM or as proportion and analyzed by one-way ANOVA (continuous variables) or χ^2 (proportion). NS, Not statistically significant.

[a] Results represent age and gender normalized parameters.

[b] Represents the percentage of the number of years since maternal weight-loss surgery to the BMS children's age.

FIG. 1. Blood lipids in children born BMS and AMS divided according to body weight classifications. *White bars*, N; *grey bars*, O; *black bars*, SO. One-way ANOVA with Newman-Keuls *post hoc* test was performed comparing parameters according to body weight classifications within each group. A, Plasma TGs were increased in SO BMS children ($P < 0.0001$, *post hoc*, $P < 0.05$ for N *vs.* SO and O *vs.* SO). TG increased among N, O, and SO AMS children ($P = 0.04$, *post hoc*, P = NS). B, LDL-C was higher in SO BMS children ($P = 0.0006$, *post hoc*, $P < 0.05$ for N *vs.* SO and O *vs.* SO). Among AMS children there was a trend for lower LDL-C among N, O, and SO ($P = 0.06$, one-way ANOVA, *post hoc*, P = NS). C, HDL-C decreased in O and SO BMS children ($P < 0.0001$, *post hoc*, $P < 0.05$ for N *vs.* SO and N *vs.* O) and AMS children ($P = 0.01$, *post hoc*, $P < 0.05$ for N *vs.* O and N *vs.* SO). D, TC to HDL-C ratio was higher in SO BMS children ($P < 0.0001$, *post hoc*, $P < 0.05$ for N *vs.* SO and O *vs.* SO). O and SO AMS children had a higher TC to HDL-C ratio ($P = 0.0001$, *post hoc*, $P < 0.05$ for N *vs.* O, N *vs.* SO and O *vs.* SO). Values presented as mean ± SEM.

BMS and AMS children (Fig. 2). Insulin and HOMA-IR correlated with BMI z-score comparably in both BMS and AMS (supplemental Table S3).

Adipokines and inflammatory factors

There was no overall significant difference in adiponectin (BMS 15.0 ± 1.0 μg/ml *vs.* AMS 15.0 ± 1.0 μg/ml, P = NS) or ASP (BMS 56.7 ± 9.1 nM *vs.* AMS 46.6 ± 7.8 nM, P = NS). CRP was lower in AMS children (BMS 2.00 ± 0.34 μg/ml *vs.* AMS 0.88 ± 0.17 μg/ml, $P = 0.004$).

When separated according to body size, adiponectin was lower in SO BMS children ($P = 0.002$, ANOVA, N *vs.* SO, $P < 0.05$, *post hoc*) (Fig. 3A). There was a trend for lower adiponectin with increasing body weight class among AMS children ($P = 0.06$, ANOVA). ASP was higher in SO children in BMS ($P = 0.003$, ANOVA, N *vs.* SO and O *vs.* SO, $P < 0.05$, *post hoc*) and AMS children ($P = 0.02$, ANOVA, N *vs.* SO and O *vs.* SO, $P < 0.05$, *post hoc*) (Fig. 3B). Both BMS and AMS children had increases in CRP relative to body size ($P = 0.03$, BMS, $P = 0.04$, AMS, Fig. 3C). Interestingly, adiponectin, ASP, and CRP all correlated strongly with BMI z-score in BMS children, with no significant correlations in AMS children (supplemental Table S3).

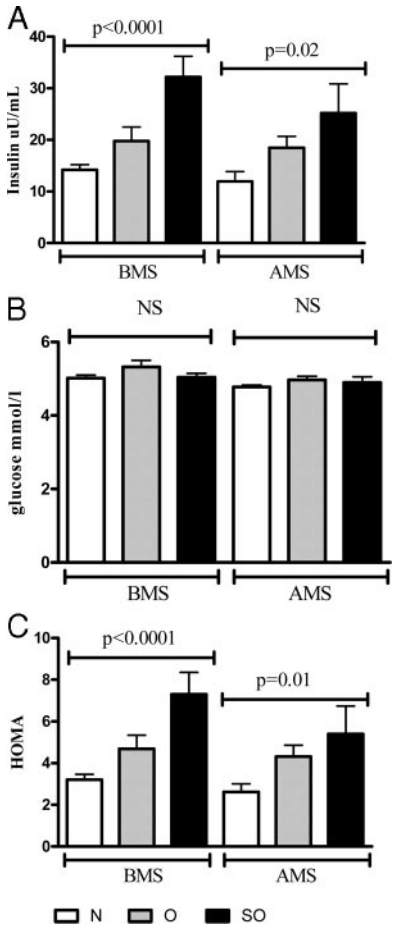

FIG. 2. Markers of insulin resistance in children born BMS and AMS divided according to body weight classifications. *White bars*, N; *grey bars*, O; *black bars*, SO. One-way ANOVA with Newman-Keuls *post hoc* test was performed within each group. A, Fasting plasma insulin (microunits per milliliter) was increased in SO BMS children ($P < 0.0001$, *post hoc*, $P < 0.05$ for N *vs.* SO and O *vs.* SO) and AMS children ($P = 0.02$, *post hoc*, $P < 0.05$ for N *vs.* SO and O *vs.* SO). B, Fasting plasma glucose (millimoles per liter) was not different among BMS children or AMS children. C, HOMA-IR was higher in SO BMS children ($P < 0.0001$, *post hoc*, $P < 0.05$ for N *vs.* SO and O *vs.* SO). HOMA was higher in O and SO AMS children ($P = 0.01$, *post hoc*, $P < 0.05$ for N *vs.* O and N *vs.* SO). Values presented as mean ± SEM.

Satiety-related factors

Ghrelin was higher in AMS children (BMS 1.03 ± 0.06 ng/ml *vs.* AMS 1.28 ± 0.06 ng/ml, $P = 0.005$) and leptin was lower (BMS 19.7 ± 2.5 ng/ml *vs.* AMS 11.5 ± 1.5 ng/ml $P = 0.005$). Ghrelin was lower in O and SO BMS children ($P = 0.002$, ANOVA, N *vs.* O and N *vs.* SO, $P < 0.05$, *post hoc*) and lower in O AMS children ($P = 0.02$, ANOVA, N *vs.* O, $P < 0.05$, *post hoc*) (Fig. 3D). Ghrelin correlated negatively with z-score in BMS, with a weaker association in AMS (supplemental Table S3). Leptin was higher in SO BMS children ($P < 0.0001$, ANOVA, N *vs.* SO and O *vs.* SO, $P < 0.05$, *post hoc*) and higher in O and SO AMS children ($P < 0.0001$, N *vs.* O, N *vs.* SO and O *vs.* SO, $P < 0.05$ *post hoc*) (Fig. 3E) and correlated strongly with BMI z-score.

Multiple regression analysis

Because both BMI z-score (supplemental Table S3) and age (supplemental Table S4) correlated with many of the parameters analyzed, we performed a best subset multiple regression analysis to evaluate factors that contributed strongly and independently (Table 3). Parameters included were group (BMS/AMS), age, gender, and age-gender-normalized factors (weight category, BMI percentile, z-score, and WC/HT ratio). Interestingly, overall, body size parameters were the strongest predictors of variation; age contributed strongly and negatively only to the variance in ghrelin, with minor effects on TG (positive) and adiponectin (negative).

Discussion

Our results have three major implications by demonstrating 1) the importance of the intrauterine environment in the transmission of obesity and metabolic derangements; 2) the potentially epigenetic nature of severe obesity, which might provide encouragement to patients who are often blamed; and 3) the importance of providing special perinatal weight control in severely obese women as a tool to curb the present obesity epidemic (23, 24).

The etiology of obesity has been under intense scrutiny for the past several decades, yet the large amount of research has yielded little practical advice to those who are overweight (25). Emerging results, including data presented in this paper, provide further insight into the causes of obesity and offers potential preventative measures.

Obesity clusters within families and recent data show that this is not just due to traditional genetic transmission or similar familial environments but may also be due to epigenetic factors (26). The presence of obesity and accompanying metabolic derangements, especially insulin resistance, during pregnancy have been shown to transmit or imprint characteristics in offspring in numerous animal studies (27–29). Evaluating humans presents ethical and practical difficulties resulting in fewer available data. To our knowledge, our paper is the first to evaluate dramatic maternal weight loss and metabolic improvements on anthropometric and metabolic parameters in children.

Our population of children was not a randomly selected group: they were all born to severely obese and overweight mothers, even those born after maternal BPD. Whereas the mothers lost a clinically significant amount of weight after BPD, the average BMI postoperatively (30.7 ± 0.9 kg/m^2) was still within the obese category (25). What is striking is that the insulin, glucose, and lipid parameters and adipokine levels reached to ranges for healthy lean individuals (13, 15) and improvements persisted over time. These metabolic changes translated into

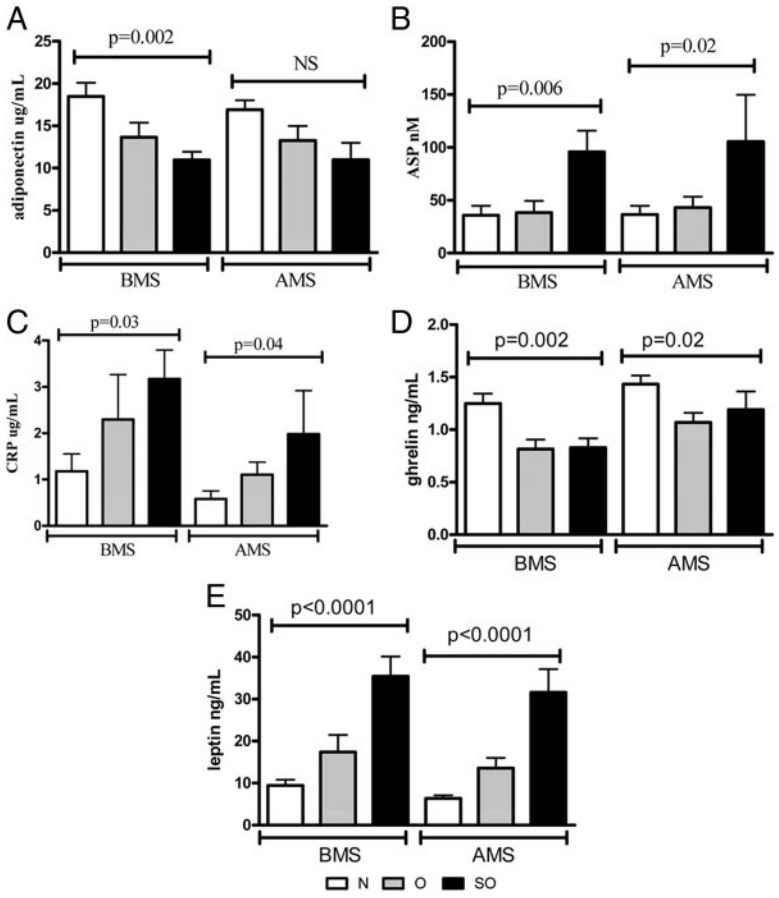

FIG. 3. Adipokines and inflammatory factors in children born BMS and AMS divided according to body weight classifications. *White bars*, N; *grey bars*, O; *black bars*, SO. One-way ANOVA with Newman-Keuls *post hoc* test was performed within each group. A, Adiponectin (micrograms per milliliter) was lower in SO BMS children ($P = 0.002$, *post hoc*, $P < 0.05$ for N *vs.* SO). There was no difference in adiponectin among N, O, and SO AMS children. B, Acylation stimulating protein (ASP; nanomolar) was higher in SO BMS children ($P = 0.006$, *post hoc*, $P < 0.05$ for N *vs.* SO and O *vs.* SO) and AMS children ($P < 0.02$, *post hoc*, $P < 0.05$ for N *vs.* SO and O *vs.* SO). C, CRP (micrograms per milliliter) was higher in SO BMS children ($P = 0.03$, *post hoc*, $P < 0.05$ for N *vs.* SO) and increased among N, O, and SO AMS children ($P = 0.04$, *post hoc*, $P =$ NS). Values presented as mean ± SEM. D, Fasting plasma ghrelin (nanograms per milliliter) was lower in O and SO BMS children ($P = 0.002$, *post hoc*, $P < 0.05$ for N *vs.* O and N *vs.* SO). Ghrelin was lower in O AMS children ($P = 0.02$, *post hoc*, $P < 0.05$ for N *vs.* O). E, Fasting plasma leptin (nanograms per milliliter) was higher in SO BMS children ($P < 0.0001$, *post hoc*, $P < 0.05$ for N *vs.* SO and O *vs.* SO). O and SO AMS children had higher leptin ($P < 0.0001$, *post hoc*, $P < 0.05$ for N *vs.* O, N *vs.* SO and O *vs.* SO).

a large impact on offspring both metabolically and in prevalence of obesity.

The 3-fold decrease in the presence of severe obesity, as defined by age- and gender-adjusted parameters, in AMS children was striking. Whereas BMS children were older, both younger and older children were represented in the three body weight categories. In addition, we also confirmed changes in body weight status using several different age- and gender-adjusted anthropometric parameters and found similar results. Furthermore, whereas many of the parameters correlated both with age as well as body size (as evaluated by BMI z-score), multiple regression analysis indicated that the body size parameters played a much stronger predictive role.

Importantly, these differences were present right from birth: AMS children had a lower birth weight. Macrosomia was reduced, but prevalence of low birth weight was unchanged. Whereas initial studies on *in utero* environment observed that low-birth weight babies were more likely to become obese and insulin resistant as adults (30, 31), macrosomia is also related to increased obesity risk and insulin resistance (2). One of the greatest risk factors for macrosomia is gestational diabetes mellitus (2). These insightful observational human studies led to mechanistic animal studies showing that DNA modification during development alters future gene expression both centrally and peripherally and affects food preference, satiety, energy expenditure, spontaneous activity, and substrate storage *vs.* oxidation (26–29, 32). These mechanisms likely contribute to the changes noted in our study.

In addition to the dramatic anthropometric changes, numerous metabolic improvements in AMS children were noted including markers of insulin sensitivity. Dyslipidemias are an obesity comorbidity, and exposure time to deleterious lipid levels has an important impact on cardiovascular disease development (33). Not only did AMS children have improvements in lipid parameters including HDL-C and TC to HDL-C ratio, the lower TG and TC to HDL-C levels in SO AMS children compared with SO BMS children were improved more than could be explained based on body size. We conclude that severe obesity is higher in BMS children and that body weight or size differences alone were insufficient to explain the differences in insulin resistance and dyslipidemia between AMS and BMS children.

Obesity is a disease comprised of well-established facets (excess adipose tissue, defective insulin signaling, atherosclerosis) and more newly recognized facets (inflammation, altered adipose tissue function) (34). Measurements of clinically nontraditional markers involved in inflammation, energy substrate oxidation and storage, and hunger/satiety signals support our hypothesis that AMS children have a more favorable metabolic profile. AMS children had lower CRP, suggesting they have less chronic low-grade inflammation than is associated with obesity and insulin resistance (35). Higher leptin levels in BMS

TABLE 3. Best subset regression analysis of contributing factors

Dependent variable	R^2	Independent variables
TG	0.454	WC/HT, gender, age
LDL-C	0.278	WC/HT, BMI percentile
HDL-C	0.286	z-score
TC/HDL-C	0.562	WC/HT (BMI percentile = z-score)
HOMA	0.296	WC/HT
Glucose	0.105	Group, BMI percentile
Insulin	0.323	WC/HT, gender
Adiponectin	0.235	Weight category, age, group, WC/HT
ASP	0.129	Weight category, z-score
CRP	0.155	WC/HT
Ghrelin	0.220	Age, weight category, WC/HT (BMI percentile = z-score)
Leptin	0.694	WC/HT, sex, group, z-score

R^2 for the predictive model of the dependent variable was calculated using best subset multiple regression analysis. The following independent variables were considered: group (BMS or AMS), weight category (normal, overweight/obese, severely obese), age, gender, and age-gender-normalized parameters (BMI percentile, z-score, and WC/HT ratio). Independent variables are reported in the table in their order of predictive value if they significantly ($P < 0.05$) and independently contributed to the regression model. Where indicated, BMI percent and z-score contributed equally but mutually exclusively.

children also support a leptin-resistant state, common in obesity and insulin resistance (15). Furthermore, ghrelin, which decreases with obesity, was higher in AMS children relative to BMS (36).

Notwithstanding these striking results, the limitations of the study should be acknowledged. The groups of BMS and AMS children were comprised of both boys and girls and covered a wide age range. Furthermore, due to the sample size, partitioning into various gender- and age-matched groups was not practical. Analysis based on body size, using age- and gender-normalized BMI percentile or z-score, was chosen as the preferred analysis, and any differences according to age or gender were reported. In addition, we performed multiple regression analysis to better evaluate the impact of all parameters, including age. Furthermore, due to the nature of cross-sectional studies, direct cause and effect cannot be proven. Finally, we cannot specifically define the contributions that genetic and familial environment had *vs.* the impact of the *in utero* environment. We limited the influence of genetics and familial environment on our results by including as many siblings as possible.

These data have several important clinical implications. Severely obese women should be encouraged to lose weight before becoming pregnant; during pregnancy they should be encouraged to modify their weight gain. For those women interested in both a surgical treatment and having children, we believe surgery should be performed first. Second, we have shown that by reducing the exposure of fetuses to an obesigenic *in utero* environment, there is a dramatic decrease in the presence of severe obesity and accompanying metabolic disturbances in children. Because obese children often go on to become obese adults (37), exposing them to greater cumulative damage from years of metabolic derangements, these data emphasize how critical it is to prevent obesity and treat it effectively to prevent further transmission to future generations.

Acknowledgments

We appreciate the technical assistance of Mélanie Cianflone for manuscript editing and preparation.

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This work was supported by Grant MOP-64446 from the Canadian Institutes for Health Research (CIHR). K.C. is a Canada Research Chair in Adipose Tissue. J.S. is supported by a CIHR doctoral scholarship.

Disclosure Summary: The authors have nothing to disclose.

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