Influence of Maternal Obesity on Insulin Sensitivity and Secretion in Offspring

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OBJECTIVE — The purpose of this study was to clarify the effects of maternal obesity on insulin sensitivity and secretion in offspring.

RESEARCH DESIGN AND METHODS — Fifty-one offspring of both sexes of obese (Ob group) and 15 offspring of normal-weight (control group) mothers were studied. Plasma glucose, insulin, and C-peptide were measured during an oral glucose tolerance test (OGTT). Insulin sensitivity was calculated using the oral glucose insulin sensitivity index, and insulin secretion and β-cell glucose sensitivity were computed by a mathematical model. Fasting leptin and adiponectin were also measured. Body composition was assessed by dual-X-ray absorptiometry.

RESULTS — No birth weight statistical difference was observed in the two groups. Of the Ob group, 69% were obese and 19% were overweight. The Ob group were more insulin resistant than the control group (398.58 ± 79.32 vs. 513.81 ± 70.70 $ml^{-1} \cdot min^{-1} \cdot m^{-2}$ in women, $P < 0.0001$; 416.42 ± 76.17 vs. 484.242 ± 45.76 $ml^{-1} \cdot min^{-1} \cdot m^{-2}$ in men, $P < 0.05$). Insulin secretion after OGTT was higher in Ob group than in control group men (63.94 ± 21.20 vs. 35.71 ± 10.02 $nmol \cdot m^{-2}$, $P < 0.01$) but did not differ significantly in women. β-Cell glucose sensitivity was not statistically different between groups. A multivariate analysis of variance showed that maternal obesity and offspring sex concurred together with BMI and β-cell glucose sensitivity to determine the differences in insulin sensitivity and secretion observed in offspring.

CONCLUSIONS — Obese mothers can give birth to normal birth weight babies who later develop obesity and insulin resistance. The maternal genetic/epigenetic transmission shows a clear sexual dimorphism, with male offspring having a higher value of insulin sensitivity (although not statistically significant) associated with significantly higher insulin secretion than female offspring.

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Type 2 diabetes is spreading out among young people as the incidence of obesity is increasing over time. This evidence has induced the American Diabetes Association (1) to include into the new classification recommendations of diabetes a form of type 2 diabetes with pubertal onset, variable insulin secretion, and decreased insulin sensitivity, strongly associated with obesity, which includes 10–20% of all diabetes in childhood and youth.

Scientists have provided a pathophysiological explanation of this phenomenon by suggesting that the development of type 2 diabetes in youth reflects the combination of insulin resistance and relative insulin deficiency. However, the limited β-cell capacity is regarded as being of "little significance" (2) in the absence of obesity.

Familial aggregation of BMI is well established in the medical literature. In a Swedish study on monozygotic twins reared in different familial contexts, within-pair correlations for BMI were 70% for men and 66% for women; these figures were quite similar for twins reared together, suggesting that familial environment did not play a relevant role in BMI in identical twins (3). Similar values for correlation coefficients (75%) were also found in a U.S. population of monozygotic twins (4).

However, epigenetics also seems to contribute, together with genetic predisposition, to the development of obesity. Studies of inheritance unequivocally show that BMI of children correlates more closely with maternal than with paternal BMI, suggesting that in addition to the genetic influences, the in utero environment may contribute to the development of obesity in offspring. In fact, overweight/obese women are more likely to give birth to heavier babies (>90th centile) than normal-weight mothers (5). Studies of inheritance clearly demonstrated a stricter correlation between a child's BMI and maternal rather than paternal BMI, suggesting that the in utero environment may contribute to the development of obesity in offspring (6,7). Gillman et al. (8) found that maternal BMI was an influencing variable in association with gestational diabetes and offspring obesity. Furthermore, Khan et al. (9–11) demonstrated that the consumption of a diet rich in saturated fat starting before conception and continuing through weaning led to increased hyperinsulinemia, adiposity, hypertension, and endothelial dysfunction in offspring at 6 months of age. Very recently, Shankar et al. (5) demonstrated that, at least in rats, maternal overweight at conception contributes to offspring obesity and insulin resistance and that programming of obesity occurs in the absence of changes in birth weights.

However, at least to our best knowledge, there is only one study (12) in the literature that investigated insulin sensitivity but not insulin secretion in young lean offspring of obese parents compared with offspring of normal-weight parents. This study (12) failed to demonstrate any significant difference between groups.

Our center follows obese subjects almost exclusively, and morbidly obese

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individuals represent >50% of the outpatient population. Recently, we have started to systematically study insulin sensitivity and insulin secretion in the offspring of obese and morbidly obese patients, after the observation that some of the young individuals with at least one parent, usually the mother, affected by obesity had impaired glucose tolerance (IGT) and/or hypertension independent of their body weight. In the present investigation insulin sensitivity, insulin secretion, and body composition were studied in offspring with a different maternal phenotype, namely normal weight or obesity.

RESEARCH DESIGN AND METHODS

— Our study population consisted of 67 offspring (39 women and 28 men) with an average age of 23.8 ± 4.50 years. To evaluate the associations of juvenile obesity and insulin resistance with the maternal degree of obesity, we sought to conduct a family-based study.

Mothers were asked details of their pregnancy and child's birth. It was not possible to obtain detailed information about weight gain during pregnancy or in early life.

Offspring of obese mothers

The Ob group consisted of 52 subjects (31 women and 21 men) who were offspring of 22 obese mothers. Maternal obesity was defined as a documented BMI of ≥30 kg/m^2 before and during pregnancy. One to three subjects from each family were included. The mean ± SD age of the parents, who did not have a history of diabetes or IGT, was 49.14 ± 3.26 years for the mothers and 51.64 ± 5.11 years for the fathers; mothers' BMI was 41.87 ± 8.62 kg/m^2 and fathers' BMI was 27.94 ± 3.01 kg/m^2.

Control group

The control subjects had to fulfill the following inclusion criteria: *1*) age from 16 to 31 years; *2*) no diabetes, IGT, or impaired fasting glucose (IFG); *3*) no first-degree relatives with a history of diabetes or obesity; *4*) no drug treatment or any disease that could potentially disturb carbohydrate metabolism; and *6*) no history of hypertension. The control group consisted of 15 offspring (8 women and 7 men) of 6 normal-weight (BMI <25 kg/m^2) mothers, who met the inclusion criteria. One to three subjects from each family were examined. The age of the parents, who did not have history of diabetes or IGT, was 48.33 ± 3.83 years for the mothers and 50.00 ± 3.03 years for the fathers; mothers' BMI was 22.69 ± 1.68 kg/m^2 and fathers' BMI was 28.49 ± 3.14 kg/m^2.

IGT was defined as 2-h postload (75 g orally) glucose between 7.8 and 11.1 mmol/l, and diabetes was diagnosed when 2-h postload glucose was ≥11.1 mmol/l or fasting glucose was ≥7 mmol/l, according to American Diabetes Association criteria. All subjects were negative for GAD autoantibody.

None of the subjects had a history of type 2 diabetes in two generations. None of the subjects had lost weight or changed his or her dietary habits during the 4–6 months preceding the study, and none was taking any medication that could influence insulin secretion or insulin sensitivity.

The study was approved by the institutional review board of the School of Medicine, Catholic University, Rome, Italy. All of the subjects gave their written informed consent before starting the study.

Experimental protocol

All subjects received a 75-g oral glucose tolerance test (OGTT). Venous blood samples were collected at 30-min intervals over 2 h for plasma glucose, insulin, and C-peptide measurements. Fasting blood samples were obtained after an overnight fast (12–14 h) to measure glucose, insulin, C-peptide, adiponectin, and leptin concentrations.

Body composition was assessed by dual-energy X-ray absorptiometry (Lunar Prodigy GE Medical Systems, Madison, WI), and fat-free mass and fat mass were computed. Height was measured in centimeters using a stadiometer. Weight was measured in kilograms using an electronic scale. Waist circumference was measured just above the uppermost lateral border of the right ileum using the National Health and Nutrition Examination Survey protocol (13). Height and weight measurements were used to calculate BMI. Normal weight was defined as BMI ≤25 kg/m^2, overweight as BMI between 25.1 and 29.9 kg/m^2, obesity as BMI between 30.1 and 40 kg/m^2, and morbid obesity as BMI >40 kg/m^2.

Analytical procedures

Plasma was immediately separated by centrifugation at 4°C and stored at −80°C until assay. The samples were not thawed until hormone assays were performed. Plasma glucose was measured by the glucose oxidase method (Beckman, Fullerton, CA). Plasma insulin was assayed by microparticle enzyme immunoassay (MEIA; Abbott, Pasadena, CA) with a sensitivity of 1 μU/ml and an intra-assay coefficient of variation (CV) of 6.6%. C-peptide was assayed by radioimmunoassay (MYRIA; Technogenetics, Milan, Italy); this assay has a minimal detectable concentration of 17 pmol/l and intra-assay and interassay CVs of 3.3–5.7 and 4.6–5.3, respectively. Plasma adiponectin levels were measured using a radioimmunoassay (Linco, St. Charles, MO) with a sensitivity of 1 μg/ml and an intra-assay CV of 6.2%. Plasma leptin was assayed by radioimmunoassay for human leptin (Phoenix Pharmaceuticals, Phoenix, AZ). Intra- and interassay CVs were 4.2 and 4.5%, respectively. The sensitivity of the method was 0.5 ng/ml.

Insulin sensitivity and β-cell function

Insulin sensitivity was calculated from the OGTT according to the method of Mari et al. (14), using the 2-h OGTT equation. This method provides an insulin sensitivity (OGIS) index that is an estimate of the glucose clearance during a euglycemic-hyperglycemic clamp, expressed in milliliters per minute per square meter of body surface area.

β-Cell function was assessed using a model describing the relationship between insulin secretion and glucose concentration, which has been illustrated in detail previously (15–17). The characteristic parameter of the dose response is the mean slope within the observed glucose range, denoted as β-cell glucose sensitivity. The dose response is modulated by a potentiation factor, which accounts for several potentiating factors (prolonged exposure to hyperglycemia, nonglucose substrates, gastrointestinal hormones, in particular gastric inhibitory polypeptide and glucagon-like peptide-1, and neurotransmitters). The potentiation factor is set to be a positive function of time and to average 1 during the experiment. Thus, it expresses a relative potentiation of the secretory response to glucose.

The model parameters were estimated from glucose and C-peptide concentrations by regularized least squares, as described previously (15,16). Regularization involves the choice of smoothing factors that were selected to obtain glucose and C-peptide model residuals with SDs close to the expected measurement

error (~1% for glucose and ~4% for C-peptide).

Basal and total insulin secretion during the OGTT were calculated from the estimated model parameters. Total insulin secretion was calculated as the integral over the 2 h of the OGTT. Insulin secretion was expressed in picomoles per minute per square meter of body surface area.

Statistical analysis

Data analyses were performed with SPSS statistical software (SPSS, Chicago, IL). Two-sided $P < 0.05$ was regarded as significant. Data are reported as means ± SD unless otherwise specified. A nonparametric Mann-Whitney *U* test was used to assess differences in subjects' variables. Pearson's coefficients were calculated to quantify the correlations among different parameters. Multivariate analysis of variance was used to assess the effect of categorical variables on insulin sensitivity and secretion. The statistical method for calculating the equation is reported on the following page. The minimal level of statistical significance was defined as $P < 0.05$.

RESULTS — Table 1 reports demographic, body composition, and biochemical data as well as insulin sensitivity and secretion parameters. According to their BMI, 86.67% of the control group were normal weight and 13.33% were overweight; whereas only 11.54% of the Ob group were normal weight, 19.23% were overweight, 50% were obese, and 19.23% were morbidly obese. Despite a trend toward a higher body weight in the offspring of the obese mothers, no significant difference in birth weight was observed either in men or in women, probably as a consequence of a rather large dispersion of the data (control group women 3,167 ± 230 g; control group men 3,301 ± 240 g; Ob group women 3,697 ± 605 g; and Ob group men 3,759 ± 555 g).

In the Ob group, one woman (BMI 44.39 kg/m^2) was frankly diabetic, and 8 of 52 had IGT, with a sex ratio (male/female) of 1:3 and an average BMI of 35.11 ± 11.60 kg/m^2 (minimum 20.70; maximum 51.97). Fasting glucose levels were similar in the two groups, whereas mean OGTT glucose was significantly higher in the Ob group than in the control group (6.9 ± 1.6 vs. 5.6 ± 1.2 mmol/l, $P < 0.01$).

Table 1—*Demographic, body composition, biochemical and insulin sensitivity, and secretion data of the study population, including male and female offspring of normal-weight, obese, and morbidly obese mothers*

	Control group	Ob group
n (women/men)	8/7	31/21
Age (years)		
Women	23.75 ± 2.96	23.63 ± 4.43
Men	26.00 ± 5.74	24.41 ± 4.83
BMI (kg/m^2)		
Women	21.45 ± 3.07	34.94 ± 8.53*
Men	24.80 ± 2.83	32.55 ± 5.31†
Waist circumference (cm)		
Women	69.71 ± 2.63	104.77 ± 17.04*
Men	83.13 ± 5.27	106.47 ± 10.68‡
Fat mass (kg)		
Women	12.38 ± 2.73	29.67 ± 11.52*
Men	16.26 ± 2.55	31.51 ± 8.77*
Fat-free mass (kg)		
Women	44.21 ± 7.26	64.65 ± 12.99*
Men	57.03 ± 6.22	69.61 ± 8.08‡
Adiponectin (μg/ml)		
Women	13.62 ± 6.40	8.57 ± 3.81§
Men	10.04 ± 2.87	6.53 ± 3.41§
Leptin (ng/ml)		
Women	9.24 ± 5.45	26.52 ± 19.04‡
Men	6.16 ± 2.79	11.51 ± 2.88‡
Mean glucose (mmol/l)		
Women	5.33 ± 1.30	6.91 ± 1.69‡
Men	5.98 ± 1.17	6.82 ± 1.35
Mean insulin (pmol/l)		
Women	351.05 ± 168.42	589.37 ± 472.17
Men	206.71 ± 85.59	575.07 ± 300.45*
Fasting insulin secretion (pmol · min^{-1} · m^{-2})		
Women	88.70 ± 29.76	118.80 ± 45.91
Men	72.21 ± 23.55	126.80 ± 47.97§
Total insulin secretion (nmol/m^2)		
Women	40.97 ± 18.95	54.70 ± 23.78
Men	35.71 ± 10.02	63.94 ± 21.20‡
OGIS (ml · min^{-1} · m^{-2})		
Women	513.81 ± 70.70	398.58 ± 79.32*
Men	484.242 ± 45.76	416.42 ± 76.17§

Data are means ± SD. *$P < 0.0001$; †$P < 0.001$; ‡$P < 0.01$; §$P < 0.05$ compared with normal-weight offspring.

Ob group subjects were more insulin resistant than control group subjects (410 ± 91 vs. 500 ± 60 ml^{-1} · min^{-1} · m^{-2}, $P < 0.001$). However, whereas men compensated for insulin resistance by significantly increasing insulin secretion both at fasting and after the OGTT, insulin secretion in Ob group women was not statistically different from that in control group women (Table 1).

In the control group, multiple regression analysis with the OGIS index as the dependent variable and constant, BMI, fat mass, fat-free mass, waist circumference, sex, basal insulin secretion, total insulin secretion, adiponectin, and leptin as independent variables (model $R^2 = 0.47$, $P = 0.028$) showed that the best predictor of insulin sensitivity was the total insulin secretion after the OGTT. In contrast, in the Ob group the best predictors of insulin sensitivity were total insulin secretion after the glucose challenge, sex, and circulating leptin levels, as summarized in Table 2.

β-Cell glucose sensitivity (picomoles per minute per square meter per millimolar) was not statistically different between groups or between sexes (237.64 ± 173.39 in control group women and 123.70 ± 32.10 in control group men;

Table 2—*Multiple regression analysis in offspring of obese mothers*

Model	B coefficient	SEM	*P* value	Partial correlations
Constant	552.05	108.88	<0.0001	
Sex	84.44	31.10	0.011	0.46
BMI	−2.92	4.08	NS	−0.14
Fat mass	−2.490	2.395	NS	−0.20
Fat-free mass	−1.370	2.741	NS	−0.10
Waist circumference	1.393	1.250	NS	0.21
Adiponectin	4.780	3.136	NS	0.28
Leptin	1.843	0.758	0.022	0.42
Basal insulin secretion	0.276	0.415	NS	0.13
Total insulin secretion	−2.866	0.615	<0.0001	−0.67

Dependent variable: insulin sensitivity (OGIS); predictors: constant, BMI, fat mass, fat-free mass, waist circumference, sex, basal insulin secretion, total insulin secretion, adiponectin, and leptin. Model $R^2 = 0.75$. $P < 0.0001$.

170.88 ± 105.45 in Ob group women and 177.49 ± 90.37 in Ob group men).

A multiway mixed-model ANOVA was used to analyze the effect of maternal obesity on insulin sensitivity and secretion. The equation, reported below, had the offspring phenotypes (insulin sensitivity and secretion) as dependent variables, the main effect factors of sex (male versus female) and maternity (born of normal weight or of obese mother) as fixed factors, and BMI, adiponectin, and leptin concentrations as cofactors:

$$Y = \text{intercept} + \text{BMI} + \text{adiponectin} + \text{leptin} + \beta\text{-cell glucose sensitivity} + \text{maternity} + \text{sex} + \text{maternity} \times \text{sex}$$

The null hypothesis, that the observed covariance matrices of the dependent variables, i.e., insulin sensitivity and insulin secretion, were not different between the two groups, i.e., obese versus nonobese mothers, was rejected by the model ($F = 0.885$, $P = 0.538$).

The results of the multivariate test are summarized in Table 3. Maternal obesity together with sex concurred with the BMI and β-cell glucose sensitivity to determine the differences in insulin sensitivity and secretion observed in the offspring.

No significant correlation was found between plasma leptin levels and insulin secretion, whereas leptin was negatively and significantly correlated with insulin sensitivity ($R^2 = -0.314$, $P = 0.017$). In contrast, adiponectin negatively ($R^2 = -0.303$, $P = 0.022$) correlated with the basal insulin secretion and positively ($R^2 = 0.394$, $P = 0.002$) with the insulin sensitivity.

CONCLUSIONS — At least to the best of our knowledge, this is the first report in humans focusing on the effect of maternal obesity during pregnancy on offspring insulin sensitivity and secretion. The major finding of the present study is that obese mothers can give birth to normal-weight babies who later develop obesity. In fact, obesity during pregnancy was associated with a high prevalence of overweight and obesity (overall ~88%), as well as with insulin resistance and hyperinsulinemia, but not with β-cell glucose sensitivity impairment, in young adult offspring. Our study confirms in humans the data reported in rats by Shankar et al. (5), who showed that maternal overweight at conception contributes to offspring obesity and insulin resistance in the absence of changes in birth weights. In this regard, it has been clearly demonstrated in animals that conditions such as undernutrition and high-fat feeding during gestation can predispose offspring to become obese (18,19).

As shown by a multivariate analysis of variance, maternal obesity together with offspring sex concurred to determine the differences in insulin sensitivity and secretion observed in offspring, thus highlighting a sex dimorphism of the epigenetic mechanism of transmission. A higher susceptibility of the female progeny to epigenetic insults has been already recognized in animals (20,21). To explain this sexual dimorphism, it has been hypothesized that the differential susceptibility to complex diseases, such as obesity and diabetes, in men and women is mediated by differences in the epigenetic regulation of genes induced by sex hormones (22).

Furthermore, although our population sample was small, our study design has evidenced a familial aggregation of obesity, suggesting a genetic susceptibility to epigenetic insults during pregnancy. Thus, the present results might be useful in designing a larger-scale family-based epidemiological study.

There is a wide acceptance of the notion that children born to overweight mothers are at higher risk of becoming overweight themselves (5–8). However, the question of the role played by the degree of overweight-obesity of the mothers in this offspring predisposition or its effect on offspring insulin sensitivity and secretion was not specifically addressed in previous studies.

Controversial results have been reported in the few available reports regarding insulin sensitivity and/or secretion in children from obese probands, and the majority of the studies were retrospective investigations. Two-thirds of subjects who later developed type 2 diabetes followed a lower birth weight-postnatal

Table 3—*Multivariate tests in the general linear model with insulin sensitivity and secretion as dependent variables*

Effect	Hotelling's *T*-square coefficient	*F*	*P*
Intercept	256.82	90.87	<0.0001
BMI (kg/m^2)	20.99	7.44	0.002
Adiponectin (μg/ml)	0.85	0.30	NS
Leptin (ng/ml)	2.28	0.79	NS
β-Cell glucose sensitivity (pmol · min^{-1} · m^{-2} mol^{-1} · l^{-1} ·)	19.63	6.94	0.002
Maternal obesity	4.94	1.75	NS
Sex	0.91	0.33	NS
Maternal obesity × sex	9.88	3.50	0.039

catch-up growth pattern, whereas one-third showed larger birth size followed by poor growth in stature (23). In another investigation (24), childhood-onset type 2 diabetes was associated with either low birth weight or high birth weight. Ong et al. (25) reported that insulin secretion was reduced in children with low birth weight, irrespective of whether they subsequently developed overweight or insulin resistance, suggesting a possible programming of pancreatic β-cell mass and/or function in utero. However, in this latter study, insulin sensitivity was assessed using the homeostasis model and insulin secretion was estimated by the insulinogenic index. Thus, a direct measure of insulin secretion was not obtained.

Lazarin et al. (12) have investigated the role of parental influence in the development of insulin resistance, not considering, however, insulin secretion abnormalities. The authors (12) did not find any influence of familial obesity on insulin sensitivity in offspring; however, in this investigation lean offspring were considered and the fathers were obese, whereas mothers were only overweight. In our series, the mothers had different BMIs, whereas the BMI of the fathers was similar. These different results might be attributable to a maternal transmission, either genetic or epigenetic. In addition, it is interestingly to note that male offspring of obese mothers compensated for insulin resistance by increasing insulin secretion. Leptin and adiponectin circulating levels did not explain any difference in insulin sensitivity and secretion between sexes.

In summary, obese mothers can give birth to normal-weight babies who later develop obesity and insulin resistance. The maternal genetic/epigenetic transmission shows a clear sexual dimorphism, with male offspring having higher insulin sensitivity (although not statistically significant) associated with a significantly higher insulin secretion than the female offspring. Whether these results are dependent on maternal genetic transmission, for instance through mitochondrial DNA, or epigenetic phenomena occurring during fetal development, will be the focus of further studies.

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