Influence of Maternal Obesity on Insulin Sensitivity and Secretion in Offspring

GELTRUDE MINGRONE, MD, PHD
MELANIA MANCO, MD
MARIA ELENA VALERA MORA, MD
CATERINA GUIDONE, MD
AMERIGO IACONELLI, MD

DONATELLA GNILI, MD
LAURA LECESI, MD
CHIARA CHIELLINI, PHD
GIOVANNI GHIRLANDA, MD

O B J E C T I V E — The purpose of this study was to clarify the effects of maternal obesity on insulin sensitivity and secretion in offspring.

R E S E A R C H D E S I G N A N D M E T H O D S — 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.

R E S U L T S — 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·min⁻¹·m⁻² in women, P < 0.0001; 416.42 ± 76.17 vs. 494.24 ± 45.76 ml·min⁻¹·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·m⁻²·min⁻¹, 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.

C O N C L U S I O N S — 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.

T ype 2 diabetes is spreading 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
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/m² 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/m² and fathers' BMI was 27.94 ± 3.01 kg/m².

**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 5) no history of hypertension. The control group consisted of 15 offspring (8 women and 7 men) of 6 normal-weight (BMI <25 kg/m²) 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/m² and fathers' BMI was 28.49 ± 3.14 kg/m².

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/m², overweight as BMI between 25.1 and 29.9 kg/m², obesity as BMI between 30.1 and 40 kg/m², and morbid obesity as BMI >40 kg/m².

**Analytical procedures**
Plasma glucose was measured by the glucose oxidase method (Beckman, Fullerton, CA). Plasma insulin was assayed by microparticle enzyme immunoassay (MELA; 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- 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.
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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 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-tailed 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, 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/m²)              |               |          |
| 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 ± 23.35  | 126.80 ± 47.97§ |
| Total insulin secretion (nmol/m²) | |        |
| Women                    | 40.97 ± 18.95  | 54.70 ± 23.78 |
| Men                      | 35.71 ± 10.02  | 63.94 ± 21.20* |
| OG1S (ml · min⁻¹ · m⁻²)  |               |          |
| Women                    | 513.81 ± 70.70 | 398.38 ± 79.32* |
| Men                      | 484.24 ± 45.76 | 416.42 ± 76.178 |

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 · 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 OG1S 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 R² = 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.
Effect
Multivariate tests in the general linear model with insulin sensitivity and secretion

Table 3—two groups, i.e., obese versus nonobese secretion, were not different between the
two groups, i.e., obese versus nonobese

The null hypothesis, that the observed co-
correlation matrices of the dependent vari-
ables, i.e., insulin sensitivity and insulin
secretion, were not different between the
two groups, i.e., obese versus nonobese

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

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

The null hypothesis, that the observed co-
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ables, i.e., insulin sensitivity and insulin
secretion, were not different between the
two groups, i.e., obese versus nonobese

CONCLUSIONS—At least to the best of our knowledge, this is the first re-
port 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 nor-
mal-weight babies who later develop obe-
sity. In fact, obesity during pregnancy was
associated with a high prevalence of over-
weight and obesity (overall ~88%), as well
as with insulin resistance and hyper-
insulinemia, 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 over-
weight at conception contributes to off-
spring obesity and insulin resistance in
the absence of changes in birth weights.
In this regard, it has been clearly demon-
strated in animals that conditions such as
undernutrition and high-fat feeding dur-
ing 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 se-
cretion observed in offspring, thus high-
lighting a sex dimorphism of the
epigenetic mechanism of transmission.
A higher susceptibility of the female prog-
eny to epigenetic insults has been already
recognized in animals (20,21). To explain
this sexual dimorphism, it has been hy-
pothesized that the differential suscepti-
bility to complex diseases, such as obesity
and diabetes, in men and women is me-
diated by differences in the epigenetic
regulation of genes induced by sex hor-
mones (22).

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

There is a wide acceptance of the no-
tion 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 de-
gree of overweight-obesity of the mothers
in this offspring predisposition or its ef-
fect on offspring insulin sensitivity and
secretion was not specifically addressed in
previous studies.

Controversial results have been re-
ported in the few available reports regard-
ing 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 fol-
lowed a lower birth weight-postnatal

### 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 $R^2 = 0.75$. $P < 0.0001$.

### 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/m²)                     | 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      | 19.63                            | 6.94    | 0.002 |
| (pmol · min⁻¹ · m⁻² · mol⁻¹ · l⁻¹ · s⁻¹) |                        |         |       |
| Maternal obesity                | 4.94                             | 1.75    | NS    |
| Sex                             | 0.91                             | 0.33    | NS    |
| Maternal obesity × sex          | 9.88                             | 3.50    | 0.039 |

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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 insulogenic 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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